WORLD CANCER REPORT 2008

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Foreword

The International Agency for Research on Cancer (IARC) was founded by Resolution of the World Health Assembly in September 1965. At this time, although data were sparse, cancer was widely considered to be a disease of westernised, high-resource, industrialised countries. Today the situation has changed dramatically, with the majority of the global cancer burden now found in low- and medium-resource countries.

The global burden of cancer has more than doubled during the past 30 years. In 2008, it is estimated that there were over 12 million new cases of cancer diagnosed, 7 million deaths from cancer and 23 million persons alive with cancer. The continued growth and ageing of the world’s population will greatly affect the cancer burden. By 2030, it could be expected that there could be 27 million incident cases of cancer, 17 million cancer deaths annually and 73 million persons alive with cancer within five years of diagnosis.

The greatest impact of this increase will fall on the low- and medium-resource countries. Such countries are, arguably, harder hit by cancer than the high-resource countries. These countries frequently have a limited healthcare budget and a high background level of communicable disease. Cancer treatment facilities are not universally available and life-saving therapies are frequently unavailable for economic reasons. Cancer, and other chronic diseases that are becoming more common, can cause devastating damage to entire families when the head of household and frequently the only source of income for a frequently an extended family, succumbs to cancer.

The rapid increase in the cancer burden represents a crisis for public health and health systems worldwide. A major issue for many countries, even among high-resource countries, will be finding sufficient funds to treat all cancer patients effectively and provide palliative, supportive and terminal care for the large numbers of cancers which will be diagnosed in the coming years.

However, there are prospects for cancer prevention in all resource settings. Tobacco smoking is the best-understood major human carcinogen. One third of cancers in high-resource countries are caused by tobacco smoking, which also causes a large proportion of deaths from other chronic diseases including vascular disease and chronic obstructive pulmonary disease. The worst of the tobacco epidemic has yet to materialise in low-resource countries. There is a 40-year temporal gap between big changes in tobacco prevalence in a population and the peak of the disease epidemic caused by this habit. Tobacco control is a major task for countries irrespective of their resource setting.

Modifiable risk factors for cancer have been identified, including alcohol consumption, excessive exposure to sunlight, lack of physical activity, overweight and obesity, dietary factors, occupational exposures and chronic infection. Effective prevention will reduce the risk of cancer, and effective screening will allow many others to be successfully treated for their disease.

In low-resource countries, many common cancers such as primary liver cancer, cervix cancer, nasopharynx cancer, Kaposi Sarcoma and stomach cancer are caused by chronic infections with different agents. In these circumstances, there are now prospects for prevention via vaccination for hepatitis B (liver cancer) and human papillomavirus (cervix cancer). The major issue in the poorest countries is delivery of the prevention action at a price that is affordable for the countries’ health systems.

Identification of risk factors for cancers is not a simple task, and delivering effective prevention can be even more difficult. Prevention research must take on a higher profile and greater importance in the broad cancer research strategy and in those cancer plans currently being developed. An additional advantage of prevention is that many key risk factors for cancer are shared with other common conditions such as vascular disease and diabetes.

A complete understanding of the mechanisms of the development of cancer is very unlikely to come about in the foreseeable future, making impossible reliance on a single approach to prevent cancer and deaths from the disease. Translational research in its broadest meaning is of paramount importance, covering the spectrum from translating cutting-edge scientific discovery into new approaches to cancer treatment to translating information about cancer risk factors into changes in population behaviour.

Priorities clearly must be identified to tackle the global cancer burden. Such priorities must include a focus on low- and medium-resource countries and the identification, delivery and evaluation of effective cancer control measures. Focus should be on the four pillars of cancer control: prevent those cancers which can be prevented, treat those cancers that can be treated; cure those cancers that can be cured; and provide palliation whenever palliation is required.

Peter Boyle
Director
International Agency for Research on Cancer
Global Cancer Control
Introduction: Needs and Prospects for Cancer Control

Cancer can quite easily be thought of as a modern disease but there are good reasons to think otherwise. Cancer is not a modern disease but has clearly existed for many centuries. It is however a more common phenomenon in man nowadays than previously. While there are reasons for an artefactual correlation, much of it buried in dissertations and pathological or the clinical aspect having existed for many centuries. It is however a more common phenomenon in man nowadays than previously.

Table 1.1.1

<table>
<thead>
<tr>
<th>Country</th>
<th>Highest Life Expectancy</th>
<th>Lowest Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andorra</td>
<td>80.6</td>
<td>39.8</td>
</tr>
<tr>
<td>Iceland</td>
<td>80.4</td>
<td>41.0</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>79.4</td>
<td>41.2</td>
</tr>
<tr>
<td>Japan</td>
<td>79.0</td>
<td>41.7</td>
</tr>
<tr>
<td>Switzerland</td>
<td>79.0</td>
<td>42.1</td>
</tr>
<tr>
<td>Australia</td>
<td>78.9</td>
<td>42.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>78.7</td>
<td>43.3</td>
</tr>
<tr>
<td>Israel</td>
<td>78.6</td>
<td>43.9</td>
</tr>
<tr>
<td>Macau</td>
<td>78.5</td>
<td>44.1</td>
</tr>
<tr>
<td>Canada</td>
<td>78.3</td>
<td>44.6</td>
</tr>
<tr>
<td>New Zealand</td>
<td>78.2</td>
<td>44.8</td>
</tr>
<tr>
<td>Singapore</td>
<td>78.0</td>
<td>44.9</td>
</tr>
<tr>
<td>Norway</td>
<td>77.8</td>
<td>45.2</td>
</tr>
<tr>
<td>Spain</td>
<td>77.7</td>
<td>46.4</td>
</tr>
<tr>
<td>Cayman Islands</td>
<td>77.5</td>
<td>46.9</td>
</tr>
<tr>
<td>Italy</td>
<td>77.5</td>
<td>47.5</td>
</tr>
<tr>
<td>Netherlands</td>
<td>77.5</td>
<td>48.1</td>
</tr>
<tr>
<td>Malta</td>
<td>77.3</td>
<td>48.1</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andorra</td>
<td>86.6</td>
<td>39.8</td>
</tr>
<tr>
<td>Japan</td>
<td>86.1</td>
<td>42.3</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>85.1</td>
<td>42.4</td>
</tr>
<tr>
<td>Spain</td>
<td>84.2</td>
<td>43.5</td>
</tr>
<tr>
<td>Switzerland</td>
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<td>42.7</td>
</tr>
<tr>
<td>France</td>
<td>84.1</td>
<td>43.8</td>
</tr>
<tr>
<td>Australia</td>
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<td>44.2</td>
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<tr>
<td>Italy</td>
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</tr>
<tr>
<td>Iceland</td>
<td>83.3</td>
<td>46.1</td>
</tr>
<tr>
<td>Virgin Islands (US)</td>
<td>83.3</td>
<td>46.6</td>
</tr>
<tr>
<td>Sweden</td>
<td>83.0</td>
<td>47.3</td>
</tr>
<tr>
<td>Canada</td>
<td>82.9</td>
<td>47.7</td>
</tr>
<tr>
<td>Estonia</td>
<td>82.8</td>
<td>47.8</td>
</tr>
<tr>
<td>Israel</td>
<td>82.8</td>
<td>47.9</td>
</tr>
<tr>
<td>Macau</td>
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<td>48.4</td>
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<tr>
<td>Cayman Islands</td>
<td>82.7</td>
<td>49.3</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>82.7</td>
<td>49.9</td>
</tr>
<tr>
<td>Austria</td>
<td>82.6</td>
<td>49.2</td>
</tr>
</tbody>
</table>

Cancer is not a modern disease but has clearly existed for many centuries. It is however a more common phenomenon in man nowadays than previously. While there are reasons for an artefactual correlation, much of it buried in dissertations and pathological or the clinical aspect having existed for many centuries. It is however a more common phenomenon in man nowadays than previously.

Table 1.1.2

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>1848–54</th>
<th>1971</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>2901</td>
<td>13</td>
</tr>
<tr>
<td>Bronchitis, influenza</td>
<td>2239</td>
<td>603</td>
</tr>
<tr>
<td>Scarlet fever, diphtheria</td>
<td>1016</td>
<td>0</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>435</td>
<td>0</td>
</tr>
<tr>
<td>Measles</td>
<td>342</td>
<td>0</td>
</tr>
<tr>
<td>Smallpox</td>
<td>263</td>
<td>0</td>
</tr>
<tr>
<td>URT infections</td>
<td>75</td>
<td>2</td>
</tr>
<tr>
<td>Cholera, dysentery</td>
<td>1819</td>
<td>0</td>
</tr>
<tr>
<td>Typhus (pyphus)</td>
<td>950</td>
<td>0</td>
</tr>
<tr>
<td>Non-Respiratory TB</td>
<td>753</td>
<td>0</td>
</tr>
<tr>
<td>Infections in infants</td>
<td>1003</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Other infections</td>
<td>635</td>
<td>52</td>
</tr>
</tbody>
</table>

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disease. Number 38 states: breast, lung or bone cancers. are described, but no mention is made of cervix, books) suggest that cancer was able to brain. Writings from ancient India (Ayurvedic uterus treated by local vaginal application of (Translated by Professor James Breasted in tumours. There is no treatment

Priority setting requires knowledge of the cancer burden

Priority setting for cancer control and cancer screening involves assessing knowledge of the cancer burden and the local mix of predominant cancer types. Unfortunately, neither the number of new cases of cancer nor the number of deaths caused by cancer is available from many parts of the world—in 2000, less than 20% of the world’s population was covered by Cancer Registration and 35% by vital statistics schemes based on medically-certified cause of death. Furthermore, this cover- age was not spread equally over the globe. In Africa less than 13% of the population was covered by the registry; the Asian continent, with the discoveries of Roentgen and the Curies, which tumours should be gentle in case excision of the whole lesion was possible. The captured Greek physician, Democritus, was called upon by King Darius of Persia to treat Atossa, the Queen, who had a lump in Excitation died before 45 years of age and this disease worldwide. In the United Kingdom in 1880 approximately half of the popula- tion in breast cancer. little progress or mention was made of cancer and the work of Beatson on hormonal manipu- lation in breast cancer. Different forms of cancer have been recog- nized and treated for centuries, and it is common tumours that occurred in chimney sweeps. In

The abrupt rise in the number of new cases of breast cancer, colorectal cancer in particular. Changes in lifestyle habits including maternal age at first birth and decreasing parity in women, and the work of Roentgen and the Curies, which cancer differ between high-income countries in the remainder. In high-income countries, cancers of the lung, breast, prostate and colorectal cancer are caused by tobacco use and 10% by chronic infection. [24] Cancer control priorities include tobacco control, (light) screening for small tumours, and curative treatment. In low-resource and low-resource countries, cancers of the stomach, liver, oral cavity, and cervix dominate (25, 26). This pattern is chang- ing rapidly, with large increases in many parts of the world where lung, breast and colorectal cancer have been historically uncommon. Although the proportion of the world’s population that is low-resource countries appears to be attributable to chronic infection, but 12%, is currently caused mainly by tobacco, and this proportion is growing (26). Cancer control priorities in these countries include large increases in tobacco use and tobacco. In Africa less than 13% of the population was covered by the registry; the Asian continent, with the discoveries of Roentgen and the Curies, which cancers of the stomach, liver, oral cavity, and colorectal cancer differ between high-income countries and medium-income countries most affected. Additionally, the proportion of the population in low and medium-income countries that will die before 65 is expected to increase by 3% to 10%. In view of the strong association between cancer death and its treatment effect (29). Information nowadays taken for granted (half of smokers die at a smoking-related death in middle age; less than 20% of a non-smok- er’s lifetime risk of dying from smoking-related diseases causally linked to cigarette smoking, even if a smoker stops smoking in middle age the risk to start smoking continues to rise). Cancer control priorities include tobacco control, (light) screening for small tumours, and curative treatment. In low-resource and medium-resource countries, cancers of the stomach, liver, oral cavity, and cervix dominate (25, 26). This pattern is chang- ing rapidly, with large increases in many parts of the world where lung, breast and colorectal cancer have been historically uncommon. Although the proportion of the world’s population that is low-resource countries appears to be attributable to chronic infection, but 12%, is currently caused mainly by tobacco, and this proportion is growing (26). 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increasingly focus on (expensive) new technologies and drugs to treat cancer, and many seek to help provide basic diagnostic and treatment facilities in low-income countries.

Many middle-income countries have diagnostic and treatment structures in place but face severe economic pressure to upgrade equipment and to pay for the new drugs used to treat cancer. Many hospitals need to be upgraded to high-income country standards and there is a need to accelerate training, particularly in the complement of specialized oncologists, radiotherapists, oncology nurses and all other medical, paramedical and technical personnel necessary. The situation in two middle-income countries, Hungary and Turkey, is summarised in the boxes in this chapter.

The first big step towards cancer prevention and control worldwide is to understand the magnitude and nature of the cancer burden in different regions of the world and then move towards an understanding of avoidable causes and other priorities. Recent increases in data availability in low-income countries allow a better, although still imperfect, picture of the global cancer burden.

Evolution of the global cancer burden

Around the year 2000, less than 20% of the world’s population was covered by cancer registration, and estimates were based on medically certified deaths. However, this is not equally spread over the globe in Africa less than 1% of the population was covered by a death certificate scheme, in Asia only 8.5% of the population is covered, and 53% of the population of Latin America is covered. The corresponding population coverage for cancer incidence statistics is 8% in Africa, 75% in Asia and 15% in Latin America.

In the absence of data from large portions of the population, it is necessary to make estimates, the methods used to compute these are described in detail in GLOBOCAN 2002 [31]. In summary, incidence and mortality rates were calculated from the simple average of those of neighbouring countries as described in GLOBOCAN 2002 [31].

Global Cancer Burden

It has been estimated that 58.8 million people died in 2004 [36]. Half of these deaths involved people aged 70 years and older and 10.7 million deaths in people aged 5-69 years. Deaths from cancer represent around one in eight of all deaths, although there will be more people who will have died with cancer although it was not the direct cause of death.

Mortality data provide important information but are restricted to giving insight into the absolute lack of health in any population. Cancer incidence data have the substantial advantage of providing a clearer picture of the cancer problem and how a key role to play in service planning and related activities. It is also clear, at least in qualitative terms, that the cancers which are common in certain parts of the world are not so common in others. It is essential to have estimates of the cancer incidence and mortality in different types in different parts of the world.

WHO African Region (AFRO)

The estimated population of the AFRO Region in 2008 was 812 million (404 million men and 408 million women), most of whom are young (Figure 1.1.2a). The effectiveness of national population censuses in several African countries is not reliable, and a very small proportion of the total population of the AFRO Region is covered by medically certified causes of death (7.2% of the population) or is covered by population-based cancer registries which provide incidence data (8.3% of population). The estimates of population and cancer burden for AFRO have a large measure of imprecision present.

It is estimated that there were 667,000 incident cases of cancer in 2008 (314,000 in men and 3.53 million in women) and 518,000 deaths from cancer (approximately 252,000 in men and 266,000 in women) (Figure 1.1.1b). In men, the commonest cancer, and the commonest cause of cancer-related mortality, was prostate cancer, which is an undoubted consequence of the HIV/AIDS epidemic, followed by cancers of the liver, prostate and oesophagus. In women, the commonest cancers were breast cancer and cervical cancer. Breast cancer was second most common in incidence and mortality, followed by liver cancer and Kaposi sarcoma (Figure 1.1.1b).

WHO Region of the Americas (AMRO/PAHO)

Each country in the Region of the Americas (AMRO/PAHO) has a national census. In North America (United States of America and Canada) the entire population is covered by a national death certificate scheme and 90% of the population by population-based cancer registration. In Central and Latin America, 95% of the population is covered by a national mortality scheme and 17% by population-based cancer registration. Estimates will be better in North America than in Central and Latin America.

The estimated population of the AMRO/PAHO Region was 831 million in 2000, with marginally more women than men (Figure 1.1.2b). The population pyramid demonstrates a population that contains a large number of men and women, quite dissimilar to the young population of the AFRO Region (Figure 1.1.2a).

There were an estimated 2,617,000 incident cases of cancer in 2008, 1,338 million in men and 1,279 million in women. Overall, there were an estimated 1,258,000 deaths from cancer in 2008. In men there were an estimated 651,000 deaths from cancer and 607,000 cancer deaths in women. Prostate cancer was the commonest incident cancer in men although there were more deaths from lung cancer (Figure 1.1.2c). Lung cancer was the second commonest incident form of cancer in women, followed by cancer of the colorectum, stomach and liver.
lymphoma (Figure 1.1.2a). In women, breast cancer was the commonest incident form of cancer; although, as in men, there were more deaths from lung cancer. Lung cancer was the second commonest form of cancer in women followed by colorectal cancer, cervix cancer and cancer of the corpus.

There are substantial differences between North America (United States and Canada) and Central and South America. The population pyramids of these regions are remarkably different. In North America (total population 346 million) there is a clearly ageing population (Figure 1.1.3a) while in Central and Latin America (total population 577 million) there is a young population (Figure 1.1.3b).

In North America there were an estimated 1,606,000 incident cases of cancer (849,000 in men and 757,000 in women) and 669,000 deaths from cancer (349,000 in men and 320,000 in women) in 2008. Prostate cancer clearly predominates incidence, followed by lung cancer, colorectal cancer, bladder cancer, melanoma and lymphoma (Figure 1.1.3d). Lung cancer is the commonest form of death from cancer, followed by prostate cancer and colorectal cancer (Figure 1.1.3d). In women, breast cancer is the commonest incident form of cancer, followed by cancer of the lung, colorectal cancer and cancer of the corpus (Figure 1.1.3d). Lung cancer is the commonest cause of cancer death in women, followed by breast cancer and colorectal cancer (Figure 1.1.3d).

In the southern part of the PAHO Region (Central and South America and the Caribbean) in 2008 there were 1,011,000 incident cases of cancer (489,000 in men and 522,000 in women) and 589,000 cancer deaths (302,000 in men and 287,000 in women). In men the commonest incident form of cancer is prostate cancer followed by lung cancer, stomach cancer and colorectal cancer (Figure 1.1.3d). Lung cancer is the most frequent cancer cause of death followed by prostate, stomach and colorectal (Figure 1.1.3d). In women, the commonest form of cancer is breast cancer followed by cervix cancer and colorectal cancer.
cancer, colorectal cancer, stomach cancer and lung cancer. Breast cancer, cervix cancer, stomach cancer, lung cancer and colorectal cancer are the commonest forms of cancer death (Figure 1.1.3d).

**WHO South East Asia Region (SEARO)**

The effectiveness of national population census in several Asian countries is uncertain, and only a small proportion of the total population of the SEARO Region has mortality data available or is covered by population-based cancer registries which provide incidence data. When considering the estimates of population and cancer burden for SEARO, these observations must be taken into account while also noting that the overall burden and the cancer pattern is dominated by India, which comprises 67% of total population of the Region.

It is estimated that the population of the SEARO Region in 2008 was 1.768 billion, with a slight predominance of men than women. The population pyramid demonstrates a young population (Figure 1.1.4a).

It is estimated that in 2008, there were 1 589 000 incident cases of cancer (758 000 in men and 831 000 in women) and 1 072 000 deaths from cancer (approximately 557 000 in men and 515 000 in women) (Figure 1.1.4b). In men, the commonest cancer was lung cancer, followed by oral cancer, pharyngeal cancer, colorectal cancer, liver cancer and lymphatic malignancy (Figure 1.1.4b). Lung cancer was the commonest form of cancer deaths in men (Figure 1.1.4b). Oral cavity and pharynx are combined, then this site is the predominant site of incident cancer and cancer death in men. In women, cervix cancer and breast cancer were the commonest incident and fatal forms of cancer (Figure 1.1.4b). The different case mix between men and women results in more deaths in men than in women, based on fewer incident cases.

**WHO Eastern Mediterranean Region (EMRO)**

As in SEARO and WPRO, the effectiveness of national population census in several countries is uncertain, and only a small proportion of the total population of the EMRO Region has mortality data available or is covered by population-based cancer registries which provide incidence data. When considering the estimates of population and cancer burden for EMRO, these observations must be taken into account.

The estimated 2008 population of the EMRO Region was 561 million, with a slight predominance of men over women. The population pyramid demonstrates a young population (Figure 1.1.5a).

It is estimated that in 2008, there were 467 000 incident cases (228 000 in men and 239 000 in women) and 323 000 deaths from cancer (approximately 228 000 in men and 153 000 in women) (Figure 1.1.5b). In men, the commonest cancers were lung cancer and bladder cancer, although there were more deaths from lung cancer (Figure 1.1.5b). In women, breast cancer was the commonest incident and fatal form of cancer, with a considerable margin from cervix cancer (Figure 1.1.5b).
The population of the WPRO Region in 2008 was estimated to be 1.780 billion, with marginally more men than women (Figure 1.1.6a). The population pyramid demonstrates an ageing population with a bulge in the numbers in middle age (Figure 1.1.6a).

It is estimated that in 2008 there were 3.689,000 incident cases of cancer (2.213,000 in men and 1.476,000 in women) and 2.575,000 deaths from cancer (approximately 1.629,000 in men and 946,000 in women) (Figure 1.1.6b). In men, the commonest incident cancer was stomach cancer, closely followed by lung cancer and liver cancer, and then oesophagus cancer and colorectal cancer (Figure 1.1.6b). Lung cancer, liver cancer, stomach cancer and oesophageal cancer were the commonest forms of cancer death in men (Figure 1.1.6b).

WHO European Region (EURO)

National censuses of the population in countries of the EURO Region provide fairly good data. In addition, 98.3% of the population of the Region is covered by mortality statistics and 36.5% of the population is covered by population-based cancer registration.

The population of the EURO Region in 2008 was estimated to be 891 million, with marginally more women than men (Figure 1.1.7a). The population pyramid demonstrates an ageing population with a bulge in the numbers in middle-age and decreasing numbers of births in younger age categories (Figure 1.1.7a).

It is estimated that in 2008 there were 3.422,000 incident cases of cancer (1.821,000 in men and 1.601,000 in women) and 1.847,000 deaths from cancer (approximately 1,034,000 in men and 813,000 in women) (Figure 1.1.7b). In men, the commonest incident cancer was lung cancer followed by prostate cancer, colorectal cancer, bladder and stomach cancer (Figure 1.1.7b). Lung cancer, colorectal cancer, prostate cancer and stomach cancer were the commonest forms of cancer death in men (Figure 1.1.7b). In women, breast cancer was the commonest incident form of cancer, followed by colorectal cancer, lung cancer, corpus cancer and stomach cancer (Figure 1.1.7b). Breast cancer was also the commonest cause of death in women, followed by colorectal cancer, lung cancer and stomach cancer (Figure 1.1.7b).

Countries of Central and Eastern Europe have experienced an ongoing economic transition for over a decade. It was decided to restrict attention to the countries of the WHO EURO Region that were outside the European Union and the European Economic Area. This provided a sub-region with a total population of 413 million. The population pyramid demonstrates a reduced number of births in recent years and a marked predominance of women at older age groups (Figure 1.1.8a).

There were an estimated 1.049,000 incident cases of cancer in 2008 (523,000 in men and 526,000 in women) and 644,000 cancer deaths (359,000 in men and 285,000 in women) (Figure 1.1.8b). The commonest incident form of cancer in men were lung cancer, stomach cancer, colorectal cancer, prostate cancer and bladder cancer (Figure 1.1.8b). Lung cancer, stomach cancer and colorectal cancer were the commonest forms of cancer death (Figure 1.1.8b). In women, breast cancer was the commonest form of cancer followed by colorectal cancer, stomach cancer, cervix cancer and corpus cancer (Figure 1.1.8b). Breast, colorectal and stomach cancer were the commonest forms of cancer death in women (Figure 1.1.8b).
Worldwide

Globally, there were an estimated 12.4 million incident cases of cancer in 2008 (6.72 million in men and 5.77 million in women) and 7.6 million deaths from cancer (4.29 million in men and 3.78 million in women). Over half of the incident cases occurred in residents of four WHO regions with a large proportion of countries of low- and middle-income—AFRO, EMRO, SEARO and WPRO (Figure 1.19). Globally, lung cancer was the commonest incident cancer and cause of cancer-related mortality in men, while the most common incident cancers and cause of cancer-related death was breast cancer.

The global cancer burden: Factors driving the increase

There are three clear scenarios under which the global cancer burden could increase over time. First of all, the increase in the world’s population anticipated from 6.1 billion in 2000 through 6.7 billion in 2008 to attain 8.3 billion by 2030 will lead to an increase in the cancer burden even if the age-specific rates remain constant. Secondly, given the very large increases in cancer risk with age, if the population size and the age-specific rates remain constant, then the burden will increase if the population ages. Figure 1.110 clearly shows that the world population will age considerably by 2030 as well as increasing significantly.

Aging is a major issue for the future cancer burden. Aging has proceeded more gradually in more developed countries than in less developed countries, allowing these nations time to adjust to this structural change. Japan is the major exception, doubling its percentage of population age 65 or older in just 26 years. Other countries in East and Southeast Asia (especially China, South Korea, Taiwan and Thailand) are on a similarly rapid trajectory, fuelled by dramatic and relatively recent drops in fertility. It took 115 years for the proportion of France aged 65 and over to double from 7% (1865) to 14% (1980). In Singapore it will take an estimated 19 years for the proportion of the population to double from 7% (2000) to 14% (2019) (figure 1.111).

In China, due to vast improvements in health and longevity at birth has increased by two thirds, from 40.8 to 71.5 years, between 1955 and 2005. The percentage of elderly people (over 65) in China is projected to triple from 8 percent to 24 percent between 2006 and 2050. Because chronic health problems become more common in old age, China’s population aging has led to increases in the country’s prevalence of chronic disease and disability (37,38).

The third element that can lead to an increase in the cancer burden, even when the population size remains constant and the age distribution remains unchanged, is an underlying increase in the incidence rates. In France, cancer incidence rates increased by 1.3% per annum between 1978 and 2000 (19,21) in the Indian cancer registries, between 1983 and 1997; the incidence rate increased at an annual rate of 0.5% per annum. In China (Qidong), between 1973 and 1997, the incidence rate increased at an annual rate of 1.4% per annum. In Latin American registries between 1985 and 1997 the incidence rate increased at an annual rate of 1.0% per annum (39,46).

The growth and ageing of the world’s population and the continual increase in the underlying incidence rates in low- and middle-income countries will contribute to increases in the global cancer burden. The global cancer burden under a range of scenarios of percentage increases is presented in Table 1.1.3. It is clear that population growth and aging contribute much more to the future cancer burden than an underlying increase in the incidence rates (Table 1.1.3). Under the zero increase in cancer incidence scenario, the global burden will increase from 10.9 million in 2002 to nearly 20 million in 2030. Similar figures and conclusions are available for mortality data (Table 1.1.4).

By extrapolation of these data, taking into account demographic changes and factors in a yearly increase in cancer incidence of 1%, it could be expected that by 2030 there will be approximately 26.4 million incident cases of cancer and 17.0 million cancer deaths a year (Table 1.1.4). The extrapolations made are likely to produce conservative estimates of the cancer burden.
the proportion of cancer caused by tobacco use and 10% by chronic infection. In high-resource countries, cancers of the lung, breast and colorectal cancer are of greater importance; a third of cancers are caused by tobacco use and 10% by chronic infection. In low-resource countries, cancers of the stomach, liver, oral cavity and pharynx dominate; a third of cancers are caused by tobacco use and 10% by chronic infection. In the world, the assumption of the same percentage increase in death rate could be questioned. For example, if the overall increase in incidence is driven by forms of cancer for which the case fatality rate is low, then the mortality rate may not rise so quickly. The other hand, if the increase in incidence is driven by forms of cancer for which fatality is high, then the increase in mortality may be greater than that in incidence. Assuming the same change in mortality rates as incidence is in many respects the optimal course, although the estimates of the burden of cancer deaths may be less reliable than those of the global burden.

The growth and ageing of the population of low- and middle-income countries together with westernisation of lifestyle and the rapid growth of tobacco smoking, are contributing to dramatic changes in the burden of cancer. Changes in lifestyle habits (including adoption of a more sedentary lifestyle, weight gain and obesity) and sociocultural changes (notably increasing age at first birth and decreasing parity in women) are leading to large increases in breast and colorectal cancer in particular. In view of the substantial delays—about 40 years—between changes in smoking prevalence in populations and changes on the burden of cancer. Changes in population will greatly affect the future cancer burden. Given these demographic changes (Figure 1.1.3), and factoring in an annual increase in cancer incidence and mortality of 1%, by 2030 it could be expected that there will be 26.4 million incident cases of cancer and 17.0 million cancer deaths annually (Tables 1.1.3 and 1.1.4). An annual increase at 1% per annum in the incidence rate seems reasonable, and may well be conservative.
Both sexes

Women

Men

Annual Percentage Change

-1.50% 7,183 5,893 13,076

-1.25% 7,712 326 14,038

-1.00% 8,277 6,791 15,068

-0.75% 8,883 7,267 16,171

-0.50% 9,531 7,819 17,351

-0.25% 10,225 8,388 18,614

0.00% 10,968 8,997 19,965

0.25% 11,762 9,649 21,411

0.50% 12,611 10,346 22,957

0.75% 13,500 11,091 24,611

1.00% 14,491 11,888 26,380

1.25% 15,530 12,760 28,270

1.50% 16,640 13,651 30,291

Table 1.1.2: Number of new cancer cases (millions) expected globally in 2030.

For comparison purposes, there were 10.9 million cancer cases in 2002.

Table 1.1.3:

<table>
<thead>
<tr>
<th>Region</th>
<th>2008</th>
<th>2030(^a)</th>
<th>2030(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>7.6</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Searo</td>
<td>1.6</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Wpro</td>
<td>2.6</td>
<td>4.4</td>
<td>6.4</td>
</tr>
<tr>
<td>eMro</td>
<td>0.9</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>paHo</td>
<td>2.3</td>
<td>3.4</td>
<td>4.5</td>
</tr>
<tr>
<td>aFro</td>
<td>1.8</td>
<td>2.6</td>
<td>3.4</td>
</tr>
<tr>
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<td>3.4</td>
<td>4.1</td>
<td>5.5</td>
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<tr>
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<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>PAHO</td>
<td>2.6</td>
<td>4.8</td>
<td>6.4</td>
</tr>
<tr>
<td>SEARO</td>
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<td>3.8</td>
<td>5.2</td>
</tr>
<tr>
<td>WYMO</td>
<td>3.7</td>
<td>6.1</td>
<td>8.1</td>
</tr>
<tr>
<td>WORLD</td>
<td>12.4</td>
<td>20.0</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Table 1.1.4: Number of cancer deaths (millions) expected globally in 2030.

For comparison purposes, there were 6.7 million cancer deaths in 2002.
In theory, therefore, the large majority of human cancers have not yet been clearly identified. A prerequisite of cancer prevention lies in identifying the determinants of cancer risk. Cancer control embraces a number of important elements with the aim of reducing the incidence of cancer. The cancer death rate is significantly reducible mostly due to cancer-related mortality either by finding disease at an earlier stage and at times uncoordinated package, and many details will be presented in individual sections below.

Cancer would be an even more economic problem if it were not for the fact that half of the people who develop cancer die from their disease. Thus the concept of Cancer Control has been developed to attack the cancer problem at various points:

(i) Primary Prevention
The most obvious ways to prevent people dying from cancer are either to find cures for different forms of the disease or to find ways to stop the development of clinical cancer in the first instance. At present, cancer prevention involves determining the causes of cancer (risk determinants) among those factors shown to be associated with the development of the disease by epidemiological studies (risk factors). Avoiding a changing exposure to risk determinants would result in a reduction in cancer risk.

The evidence that cancer is preventable is compelling. Different populations around the world experience different levels of different cancer risk. Thus, prevention in the context of cancer is an important area of public health.

(ii) Secondary Prevention
It is very frequently the case that the probability of successful treatment of cancer is increased, sometimes very substantially, if the cancer can be diagnosed in an early stage. Awareness of the significance of signs and symptoms is important, but too often cancers that exhibit symptoms and that could have been diagnosed at an earlier time are frequently applied to the situation where tests are used to indicate whether a generally asymptomatic individual has cancer or is having a cancer. Detecting cancers at an early, asymptomatic stage could lead to decreases in the mortality rate for cancer. Awareness of the background to cancer deaths can be explained by known risk factors (22), it is thought that risk determinants exist for about one half of cancers. Thus, primary prevention in the context of cancer is an important area of public health.

The American Cancer Society has established a goal of reducing cancer mortality in the United States by 25% and cancer incidence by 50% by 2015. This would be consistent with an arm’s-length appearance in addressing the cancer problem. Cancer death rates have decreased by 18.4% among men and 10.3% among women since the early 1990s.

The Annual Report to the Nation on the Status of Cancer, 1973-2005, 2nd Edition was a joint report of the National Cancer Institute (NCI), the American Cancer Society, the American Cancer Society, and the North American Association of Central Cancer Registries (NAACR) [22]. It is thought that risk determinants exist for about one half of cancers. Thus, primary prevention in the context of cancer is an important area of public health.

Acutely obvious is the term screening efficacy is a challenge. Although all of the avoidable causes of cancer have not yet been clearly identified (e.g. in France), one third of cancer deaths can be explained by known risk factors (22), so. If you fail to stop, do not smoke in the presence of non-smokers.

Any recommendation made to reduce cancer occurrence should not be one that could lead to an increased risk of other diseases. The recommendations that comprise the revised European Code Against Cancer should, if followed, lead to improvements in other aspects of general health (Table 1.1.8). It is also important to recognize from the outset that each individual has choices to make about their lifestyle, and it would be possible to lead in their risk of developing cancer. These choices, and the rationale underlying their recommendation, are presented below.

The Code initially contained ten points (64) but was increased to eleven points for the third version (65). If followed, this would lead to reductions in cancer incidence and/or mortality. The first three points are very important, while the others are not necessarily in order of importance in terms of how many cases of cancer could be prevented.

1. do not smoke, if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.

It is estimated that 25-30% of all cancers in developed countries are tobacco-related. From the results of studies conducted in Europe, Japan and North America, between 87 and 91% of lung cancers in men, and between 37 and 85% of lung cancers in women, are attributable to cigarette smoking. For both sexes combined the proportion of cancers arising in the oropharynx, larynx and laryngeal and oesophageal attributable to the effect of tobacco, either acting singly or in conjunction with the consumption of alcohol, is between 43 and 60. A large proportion of cancers of the bladder and pancreas, and a proportion of cancers of the stomach are related to alcohol intake (67). The role of alcohol in cancer causation is well established.

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1. Do not smoke. If you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.

2. Avoid obesity.

3. Eat a variety of vegetables and fruits every day: eat at least five portions daily. Limit your intake of foods containing fats from animal sources.

Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards; three smoke is inhaled, and both cigar and pipe smoke cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx and oesophagus.

Worldwide, it is estimated that smoking killed four million people each year in the 1990s and that altogether some 60 million deaths were caused by tobacco in the second half of the 20th century. In most countries, the worst consequences of the tobacco epidemic are yet to emerge, particularly among women in developed countries and in the populations of developing countries.

This first point of the European Code Against Cancer is referred to the most important cause of cancer (AS) and should be viewed as containing three distinct messages.

Many aspects of general health can be improved and many cancer deaths prevented, if we adopt healthier lifestyles!

1. Do not smoke. If you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.

2. Avoid obesity.

3. Eat a variety of vegetables and fruits every day: eat at least five portions daily. Limit your intake of foods containing fats from animal sources.

4. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a woman or one drink per day if you are a man.

5. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a woman or one drink per day if you are a man.

6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn, the sun activity must not be taken throughout life.

7. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and radiation protection offices.

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to the development of regulatory regimes and guidance. The message in this item of the code relates to the responsibility individuals who should adopt scientific consensus evaluations into European Union law, and control compliance with these regulations and procedures. Follow all health and radiation protection offices.

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to the development of regulatory regimes and guidance.
role in preventing cancers than individual measures of protection. Apart from individual lifestyle choices, there are public health programmes that could prevent cancer. There is evidence that improving the probability that a cancer may be cured.

Early detection is an important factor in reducing the death rate from cancer, whether it is achieved by personal actions or through participation in population-based programmes. Among cancer patients initially diagnosed in the United States, different visual body signs or symptoms that could easily be observed by anyone and that are possibly related to cancer is important. It is unequivocally established that cancer survival is better for cancers detected at an earlier stage, advanced form of the disease. Thus the earlier in the process that a cancer can be diagnosed and treated then the better this for the patient. Much effort has gone into cancer screening and the development of methods for finding cancers at an earlier stage in their develop and increasing prospects for cure. It is possible to make recommendations based on the available evidence.

8 Women from 25 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with EU guidelines for quality assurance in mammography screening.

The effectiveness of screening for cervical cancer has never been demonstrated in a randomised trial. There is evidence, however, that if a substantial proportion of women aged 10–15 years is lost due to breast cancer diagnosis before the age of 80 years are attributable to cases presenting symptomatically at age 35–49 years, frequently an age of considerable social responsibility.

Mammographic screening is only one step in the total management of the woman with breast cancer. As has been shown from long-term established programmes in the United Kingdom, Sweden, Finland and the Netherlands, recognition of the importance of the multidisciplinary team in the assessment of mammographic abno-Malpattern spread into the lymphatic system, leading to the development of integrated multi-
The Programme of Action on Cancer Therapy (PACT), established by the International Atomic Energy Agency (IAEA) and partners, aims principally to ensure effective and sustainable cancer care in low-resource and medium-resource countries. The programme is important for cancer control because, in cancer-stricken households, communities and countries alike, cancer could become a major impediment to socioeconomic development in low-income and economically emerging nations.

Current Opportunity

The timing is now right to address this growing cancer burden, part of the overall medical attention to chronic diseases and a neglected development goal [26,74,76]. The WHO Resolution on Cancer Control (WHC.42-18) [77] provides a strong impetus for countries to develop programmes aimed at the prevention, up-to-date treatment, and control of cancer. Although this is a strong incentive, there is an overwhelming need for leadership and coordination in this area. Compared to other global health communities, the global cancer community is diffuse and often ineffective.

This has important implications for public health as well as other elements of health services around the world. The absence of a specific MDG to address cancer control has led to cancer control taking on something of a neglected and urgent need for leadership and coordination in this area. Compared to other global health communities, the global cancer community is diffuse and often ineffective.

Priorities must be realistic and achievable, and include a focus on low-resource and medium-resource countries and the identification, delivery, and assessment of effective cancer care interventions. Depending on resources and competing health priorities, all steps must be taken to prevent those cancers which are preventable, to treat those cancers which are treatable, and to cure those cancers which are curable, and to provide palliation and supportive care to patients throughout their cancer trajectory.

In the chapters that follow in this volume, current knowledge of cancer causes and prevention prospects will be outlined to serve as a basis for cancer control planning and prioritization in regions at different resource settings.
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69. 66: 1 191-1308.

70. 2: 115-152.

71. 28: 115-152.

72. 63: 1291-1298.

73. 35: 1199-1203.

74. 19: 631-640.

75. 1: 183-187.

76. Fifty-eighth World Health Assembly  (2005).

77. 370: 1881-1882.


80. 1312-1325.

81. 14: 1312-1325.

82. Cancer Control in Turkey. Editor: Prof Dr A Murat Tuncer. Department of Cancer Control, Turkish Republic Ministry of Health, Ankara, 2008

83. Cancer Control in Turkey. Editor: Prof Dr A Murat Tuncer. Department of Cancer Control, Turkish Republic Ministry of Health, Ankara, 2008

84. Cancer Control in Turkey. Editor: Prof Dr A Murat Tuncer. Department of Cancer Control, Turkish Republic Ministry of Health, Ankara, 2008

85. Cancer Control in Turkey. Editor: Prof Dr A Murat Tuncer. Department of Cancer Control, Turkish Republic Ministry of Health, Ankara, 2008

86. 1: 183-187.

87. 18: 606-615.

88. 14: 1312-1325.

89. 2: 115-152.

90. 18: 591-604.

91. 2: 115-152.

92. 18: 591-604.

93. 18: 591-604.

94. 18: 591-604.

95. 18: 591-604.
Cancer Nomenclature

Neoplasia (Greek for “new growth”) is the abnormal and uncontrolled proliferation of cells in a tissue or organ. Most neoplasms proliferate to form distinct masses (tumours). Malignant neoplasms show a great degree of anaplasia and have the properties of invading neighboring structures and an ability to spread through the lymphatic system and bloodstream to other organs. The term cancer is largely synonymous with neoplasm and is used as a general term for many diseases that are characterized by uncontrolled, abnormal growth of cells. Most frequent are carcinomas, malignant tumours that arise from epithelial cells in skin, the gastrointestinal tract and other internal organs. Sarcomas are derived from soft tissues (muscle, blood vessels, adipose tissue) and bone. Gliomas result from the transformation of glial cells in the central nervous system.

The WHO and IARC contribute significantly to cancer control worldwide by providing reliable cancer statistics that are a basis for the identification of cancer risks, time trends in cancer incidence and public health resource allocation. The basis of this must be a statistical classification of disease and pathology.

WHO Classification of Tumours

Cancer is typically diagnosed by pathologists on histological sections routinely stained with hematoxylin and eosin (H&E) as well as by immunohistochemistry. More recently, tumours have also been characterized by their genetic profiles, which complement histopathology and are increasingly used to predict prognosis and response to therapy.

To ensure an international standard for histopathological classification, the WHO publishes the book series WHO Classification of Tumours (WHO Blue Books). Since its initiation in 1957, the objectives of the WHO Classification have remained the same, i.e. to establish a classification and grading of human tumours that is accepted and used worldwide. IARC has been publishing the Blue Book series since 2000. Reflecting the recent rapid progress in genetics and our understanding of molecular mechanisms of cancer development, the 3rd edition (2000–2005) contains not only the histopathological classification, but includes genetics, genetic susceptibility, and concise sections on epidemiology, clinical signs and symptoms, imaging, prognosis and predictive factors.

Inclusion of new entities is a very important function of the WHO Classification. Entities are characterized by distinctive morphology, location, age distribution and biological behavior, and not simply by an unusual histopathological pattern, whereas histological variants are defined as being reliably identified histologically and having some relevance for clinical outcome, but are still part of a previously defined entity. Once an entity or new variant is included in the WHO Classification, a morphology code of the International Classification of Diseases for Oncology (ICD-O) is assigned, which is used by cancer registries worldwide and forms the basis for the generation of histopathologically stratified data on cancer incidence. The cancer registry data provide essential data for the IARC book series Cancer Incidence in Five Continents (Figures 1.2.1 and 1.2.2) [2].

Tumour Grade and Stage

In the clinical setting, tumour grade and tumour stage are important additional factors that influence the choice of treatment, and allow a prediction of prognosis. Histological grade combines histological parameters, in particular the degree of dysplasia, that reflect the aggressiveness of a tumour. Grade is rated numerically (e.g. grade 1–4) or descriptively (“high-grade” or “low-grade”). The higher the numeric grade, the less differentiated the tumour cells are, a low-grade cancer is usually well-differentiated.

The TNM classification system, developed and maintained by the International Union Against Cancer (UICC) is the most widely used tool for classifying the extent of cancer spread. This classification is based on the extent of the primary tumour [T], the absence or presence of regional lymph node metastases [N], and the absence or presence of distant metastases [M] [3].

REFERENCES

Summary

- In 2008, there were 12.4 million new cancer cases and 7.6 million cancer deaths worldwide.
- Lung cancer burden, in terms of incidence and mortality, is among the highest in the world.
- More than half of cancer cases and 60% of deaths occur in the less-developed countries.
- There are striking variations of cancer patterns by site from region to region.
- Future cancer burden will be influenced by trends in the elderly population of both the less-developed and more-developed areas.
- The role of prevention in cancer control programmes (tobacco control, vaccination, screening) will increase in the coming decades.

Estimating the burden of cancer in terms of incidence (number of new cases occurring) and mortality (number of deaths occurring) is necessary to establish priorities for cancer control. Overall in 2008, based on the most recently available international data [1,2], there were an estimated 12.4 million new cases and 7.6 million deaths. The most common cancer in the world in terms of incidence was lung (15.2 million cases), breast (1.3 million cases) and colorectal cancers (1.4 million cases), whereas lung cancer was also the most common cancer diagnosed in the more-developed regions recently (643,000 cases, 20.2% of the total of new cases), but only sixth in the less-developed countries (197,000 cases, 5.6%), whereas lung cancer ranks first (538,000 cases, 13.3%). In women, breast cancer is by far the most frequent cancer worldwide, with an estimated 715,000 new cases diagnosed in the more-developed regions (56.5% of the total) and 577,000 in less-developed countries (18.8%).

Worldwide Cancer Burden

Table 1.3.1 Estimated (2008) and projected numbers (millions) of cancer cases and deaths, all cancers, both sexes, by region and Development Status. (IARC Region No. 160, Lyon, International Agency for Research on Cancer.)

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases 2008</th>
<th>Deaths 2008</th>
<th>Cases 2030</th>
<th>Deaths 2030</th>
<th>Cases 2050</th>
<th>Deaths 2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>12.4</td>
<td>7.6</td>
<td>20.0</td>
<td>12.9</td>
<td>26.4</td>
<td>17.0</td>
</tr>
<tr>
<td>Africa (AFRO)</td>
<td>0.7</td>
<td>0.5</td>
<td>1.2</td>
<td>0.9</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Europe (EUC),</td>
<td>3.4</td>
<td>1.8</td>
<td>4.1</td>
<td>2.6</td>
<td>5.5</td>
<td>3.4</td>
</tr>
<tr>
<td>East Mediterranean (EMRO)</td>
<td>0.5</td>
<td>0.3</td>
<td>0.9</td>
<td>0.6</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Pan-American (PAHO)</td>
<td>2.6</td>
<td>1.3</td>
<td>4.8</td>
<td>2.3</td>
<td>6.4</td>
<td>3.1</td>
</tr>
<tr>
<td>South-East Asia (SEARO)</td>
<td>1.6</td>
<td>1.1</td>
<td>2.8</td>
<td>1.9</td>
<td>3.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Western Pacific (WPRO)</td>
<td>3.7</td>
<td>2.6</td>
<td>6.1</td>
<td>4.4</td>
<td>8.1</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Figure 1.3.1 shows the magnitude of the more common cancers in terms of incidence and mortality, for men and women in the more-developed (Europe, North America, Australia) and less-developed (New Zealand and Japan) and the less-developed countries of the world. Overall, 53% of the total number of new cancer cases and 60% of the total number of deaths occur in the less-developed countries. In men, prostate cancer is now the most common form of cancer diagnosed in the more-developed regions recently (634,000 cases, 20.2% of the total of new cases), but only sixth in the less-developed countries (197,000 cases, 5.6%), whereas lung cancer ranks first (538,000 cases, 13.3%). In women, breast cancer is by far the most frequent cancer worldwide, with an estimated 715,000 new cases diagnosed in the more-developed regions (56.5% of the total) and 577,000 in less-developed countries (18.8%).

Figure 1.3.2 summarises these results and illustrates the striking variations among regions (as classified by the WHO) in the patterns of cancer occurrence. Figure 1.3.3 shows the cancer incidence by site with the 20 registries with the highest and lowest rates in the Cancer Incidence in Five Continents Volume IX [4].

In 2008, the world population was estimated at around 6.7 billion, and it will reach about 9.3 billion by 2050 [5]. A 3.8% increase in the population of the less-developed countries is expected between 2008 and 2030, while the population growth of the more-developed regions will be limited to 2%. Cancer affects mainly older age groups, and within the same period, the proportion of people over age 65 is projected to increase from 5.3% to 9.8% and from 14.6% to 22.6% in less developed and more developed areas respectively. We have already noted that there are slightly more cancer cases and deaths occurring in less-developed than in more-developed countries, and since the biggest changes in the world’s demography will take place in the developing areas, the future cancer burden will be more evident in these countries, and will be influenced by the elderly populations of both the more developed and less developed areas.

Figure 1.3.3 shows the incidence and mortality of the most common cancers in males and females in more-developed and less-developed countries.

REFERENCES

Fig. 1.3.3 Cancer incidence by site with the 20 registries with the highest and lowest rates.
Fig. 1.3.3 (Cont.)

Fig. 1.3.3 (Cont.)
Cancer Control in Low-Resource Environments

The burden of cancer in low-resource environments is growing, and threatens to exact a heavy toll in morbidity, mortality and economic cost in these countries in the next 20 years. The expected public health dimensions of the cancer epidemic in low-resource countries demand a widespread effective international response. The good news is that the majority of cancers in low-resource environments are preventable, and the efficacy of treatment can be improved with early detection. Currently there is enough knowledge to implement, based on evidence-based practices in cancer prevention, screening/early detection, treatment and palliation. The information is available to put into place one third of new cancers and increase survival for another one third of cancers detected at an early stage. To achieve this, knowledge must be translated into action.

In the developed countries, great strides have been made over the past half century in translating knowledge into action but the same is not true in low-resource environments where cancer is generally low or absent on the health agendas.

The WHO, in response to the looming pandemic, has intensified its fight against worldwide wide with many promising avenues for sustainable change. In 2005, the World Health Assembly called on WHO (WHA 58) to meet the “global challenge of cancer”. This resolution pro-vides the foundation for what is envisaged as a global strategy to accelerate the translation of knowledge into effective and efficient public health measures for cancer.

In low-resource environments, there is no doubt that this will be an enormous endeavour, requiring comprehensive policies and strategies to mobilise resources in prevention, early detection, diagnosis, treatment, rehabilitation and palliation. These strategies may entail the application of all available tools and resources for the application of these tools, an additional third of new cases can be prevented. For those with early stage cancer, there are effective strategies that can increase survival. For those with advanced and disseminated cancer, understanding of palliative care could also alleviate a great deal of suffering and improve the quality of life for cancer patients and their families.

The WHO, in response to the looming pandemic, has intensified its fight against worldwide cancer with many promising avenues for sustainable change. In 2005, the World Health Assembly called on WHO (WHA 58) to meet the “global challenge of cancer.” This resolution provides the foundation for what is envisaged as a global strategy to accelerate the translation of knowledge into effective and efficient public health measures for cancer.

The World Health Organization (WHO) is a specialized agency of the United Nations that is concerned with international public health.

4. Diagnosis and Treatment
Diagnosis requires clinical assessment through use of modalities such as endoscopy, cytology, imaging and histopathology. Appropriate services to combat cancer and return the patient to normal health include surgery, radiotherapy, chemotherapy or a combination of these. Optimal treatment can improve cancer survival significantly. Unfortunately, diagnosis of cancer in low-resource environments is too frequently made in advanced stages.

WHO initiatives toward a unified cancer control strategy
Over the years the WHO, in addition to producing publications on cancer control, has put forth several initiatives that can be considered milestones in the effort to put knowledge into action. These include a major international treaty on tobacco, global strategies on diet and physical activity, planning and implement- ing cervical cancer prevention and control pro- grammes, and several guidelines on national cancer control programmes.

1. Tobacco Treaty – The Framework Convention on Tobacco Control (FCTC)
Tobacco consumption in low-resource environ- ments is increasing. The devastation that will be caused by the increase in tobacco consumption is enormous. If no interventions are put in place, this will place a mammoth burden on healthcare systems in low-resource environments.

Tobacco is the single greatest preventable cause of cancer in the world, causing 80-90% of all lung cancers and 30% of all cancers in the developing countries. Under the current patterns of use, world tobacco-related deaths will continue to rise on a trajectory that will reach 500 million by 2050 [7]. Interventions that decrease the number of new smokers by half would lower that mortality to 340 million. While smoking rates have fallen in developed countries, tobacco multinationals have continued their efforts toward promotion of new...
A healthy diet of fresh fruit and vegetables can reduce risk for many cancers.


Cervical cancer is one of the most important health problems for adult women in developing countries [8]. Cervical cancer is the second most common cancer among women worldwide.

There are 409,000 new cases diagnosed annually and 234,000 deaths in the developing world from cervical cancer [9]. The natural history burden of disease, together with the proven impact of effective screening and early treatment programmes, makes this an essential area for action on [10].

Several notable resources from WHO have assisted in guiding the development and implementation of cervical cancer control programmes. An expert consultation initiated by WHO in 2001 resulted in the report Cervical Cancer Screening in Developing Countries [11]. This report documents guidelines on the importance of a position on cytology screening in mid-income countries with specific recommendations supporting the use of flexible and mobile technology, and the need to develop referral mechanisms for cervical cancer prevention and control. Detailed information on guidelines for cervical cancer prevention and control is available in the WHO publication Comprehensive Cervical Cancer Control: A Guide for Essential Practice [12].

4. Social and cultural barriers to cancer care

In some low-resource countries, non-economic barriers impede early detection and effective management of cancer. These include a host of cultural and traditional beliefs and taboos that can vary between different regions of the same country, religions and cultures. Failure to recognize and address these misbeliefs and taboos can result in the failure of any cancer screening programme. It is also relevant to note that many health workers, including nurses and doctors, cannot provide appropriate care for patients until they have received appropriate training and have the necessary equipment.

5. Conclusion

Cervical cancer is preventable. If detected and treated in the early stages, this is not a fatal disease. The responsibility of the WHO, the United Nations, the World Bank, national governments, regional bodies, non-governmental organisations (NGOs) and the private sector is to work together to provide effective practical solutions to the problem of cervical cancer control around the globe.
and including a message of empowerment for patients to take charge of their own health.

Several parties can help overcome social barriers to cancer care. A potentially very effective way of promoting public participation is by involving the public itself or trusted community religious leaders to give the public a sense of ownership.

6. Poor resource allocation in cancer services in low-resource countries

Setting priorities for health care in general, and cancer care specifically for, is particularly difficult in limited-resource environments in light of the meagre resources set aside for health services. By creating evidence-based guidelines that simplify health care interventions into specific levels and through programmatic proposals based on cost-neutral implementation strategies, ministries of health can be offered realistic options for planning the delivery of cancer services within their public health system.

7. Lack of collaboration with other sectors and organisations

Improving a healthcare system so that it can deliver better cancer care can be accomplished if multiple sectors and organisations act in collaboration. A good example is that of the IAEA/PACT programme. The Programme of Action for Cancer Therapy (PACT) was created within the International Atomic Energy Agency (IAEA) in 2004 to build on the Agency’s experience in radiation medicine and technology with a vision of enabling developing countries to introduce, expand or improve their cancer care capacity and services in a sustainable manner. PACT does this by integrating radiotherapy into a comprehensive cancer control programme that maximises therapeutic effectiveness and impact. PACT integrates and aligns cancer prevention, screening and early detection, treatment and palliative care activities. Based on the WHO guidelines, PACT also addresses other challenges, such as long-term support for the continuing education and training of cancer care professionals in developing countries.

8. Limited use of information technology and other creative approaches

Overcoming cancer care constraints and obstacles in low-resource countries requires novel thinking and creative approaches. This is important because low-resource countries have limited availability of trained human resources and adequate facilities for prompt cancer diagnosis. The use of commonly available communication technology to transmit images to facilities in developed countries, for example, the use of telemedicine, would be very helpful in low-resource countries.

Conclusion

Low-resource countries face numerous challenges in designing and implementing programmes to improve cancer care. Although financial constraints are one obvious barrier to improving cancer services, low-resource countries face a variety of other barriers, such as lack of scientific and epidemiological information to guide resource planning, shortage of trained professionals to provide necessary clinical care, competing health care crises, political insecurity or wars, or combinations thereof that divert attention from long-term healthcare issues, and social/cultural factors that obstruct the timely and effective delivery of care.

In particular, efforts aimed at early cancer detection are impeded by public misconceptions about cancer that make patients reluctant or unwilling to seek care when they notice early symptoms. The World Health Organization has provided the framework for cancer control and improving outcomes for patients with cancer in low-resource countries and has also stressed the importance of alliances and working together with other organisations working in the cancer field. The International Atomic Energy Agency has established a Programme of Action for Cancer Therapy (PACT) and so far has six PACT model demonstration sites project in Tanzania, Sri Lanka, Vietnam, Albania, Nicaragua and Yemen.

REFERENCES

One of the most striking innovations in cancer therapy has been the combination of chemotherapy with surgery or radiotherapy. This approach, often referred to as multimodal therapy, exploits the synergistic effects of these treatments to achieve better outcomes than each modality alone.

Chemotherapy and surgery are often used in combination. For example, in the treatment of colorectal cancer, chemotherapy is given before surgery to shrink the tumour and make it more surgically accessible. After surgery, chemotherapy is continued to prevent recurrence.

Chemotherapy and radiotherapy are also used together. Radiotherapy is typically used to treat localised tumours, while chemotherapy is used to treat metastatic disease or to prevent recurrence.

The combination of chemotherapy with targeted agents or immunotherapy is a rapidly evolving field, with promising results in a variety of cancers. These approaches complement each other and target different aspects of cancer biology, leading to improved outcomes.

One of the key challenges in the development of new cancer therapies is the rapid emergence of resistance. Therefore, it is crucial to develop strategies that can overcome resistance and prolong the effectiveness of treatment.

In summary, the combination of chemotherapy with other modalities represents a promising strategy for cancer treatment. However, further research is needed to identify optimal treatment combinations and to develop effective strategies to overcome resistance. This requires a multidisciplinary approach involving oncologists, surgeons, radiologists, and basic scientists with expertise in cancer biology.
for cancer patients with advanced colorectal cancer without treatment is approximately six months, but rises to 20–24 months for patients who receive sequential chemotherapy [7]. Adjuvant therapy (six months of chemotherapy following surgical resection of the primary cancer) has increased the cure rate for both breast and colorectal cancer by around 10% [8]. This is a story of steady progress rather than the ‘breakthroughs’ which we see so heavily promoted in the media, but which are now reflected, for breast and bowel cancers, in improvements in population-based national cancer survival statistics.

**Novel agents**

The past decade has seen a remarkable increase in the translation of basic scientific knowledge into novel treatments, particularly in the field of growth factor signalling [9]. This knowledge has been translated into novel treatments, particularly in the field of growth factor signalling [9].

**Table 1.5.1**

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumour type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: Tumours for which there is evidence that the use of a single or a combination of drugs used alone or with other therapeutic modalities will result in cure as defined by a normal lifespan in the majority of patients.</td>
<td></td>
</tr>
<tr>
<td>Category 2: Tumours where the average survival is prolonged when chemotherapy is used as an adjuvant to local surgery or radiotherapy in the early stages of disease.</td>
<td></td>
</tr>
<tr>
<td>Category 3: Tumours where there is evidence that a single drug or a combination of drugs will produce clinically useful responses in more than 20% of patients.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.5.2**

<table>
<thead>
<tr>
<th>Alkylating drugs</th>
<th>Cytoxic antibiotics</th>
<th>Antimetabolites and related therapy</th>
<th>Vinca alkaloids and etoposide</th>
<th>Other antiangiogenesis drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Bleomycin</td>
<td>Cytarabine</td>
<td>Vinblastine and vincristine</td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Daunorubicin</td>
<td>Fluorouracil</td>
<td>Cisplatin</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Dactinomycin</td>
<td>Mercaptopurine</td>
<td>Cyclophosphamide</td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expensive, costing up to $100 000 per year for individual patients, putting it currently beyond the cost-effectiveness model employed by the UK’s National Institute for Clinical Excellence.

**Inhibition of angiogenesis**

Microtubulostats can grow to a size of 1-2 mm in diameter, but to advance further, require establishment of their own blood supply. The tumour signal their lack of oxygen by releasing vascular endothelial growth factor (VEGF), which stimulates the growth and invasion of new blood vessels into the tumour nodule, greatly accelerate its proliferative capacity (Figure 1.5.3). The most successful means of blocking angiogenesis has come from the development of monoclonal antibodies which bind to and inactivate VEGF, which is a target for therapeutic intervention, blocking the possibility of apoptotic cell death. These innovative cancer medicines pose an enormous challenge to the oncology community given the potential of new targets, novel agents and the potential they have to be combined with conventional chemotherapy and with other translation inhibitors. It will require a huge number of empirical clinical trials, or a change in trial paradigm in which we try to select patients with tumour-associated biomarkers which we are entering a period when sophisticated molecular tools—e.g. DNA signatures, specific DNA mutations, and patterns of phosphorylation of specific proteins—will give us the technical capacity to deliver on the potential of personalised medicine, saving patients from the needless toxicity of reactive drugs, and allow healthcare systems the possibility of targeting expensive new cancer drugs to the subpopulation of patients who will benefit most [11].

**Medical oncology in the developing world**

As has been emphasised elsewhere [Chapter 11], the increasing incidence of cancer in the developing world presents an extraordinary challenge to the healthcare systems of these emergent nations. While realising that there are many competing priorities (cancer screening, early detection and prevention, palliative care etc.), this does not detract from the requirement

![VEGF and other signals promote the angiogenic switch in tumours](image-url)
to treat patients who present with established cancer. These nations suffer from a relative paucity of treatment facilities, few accredited oncologists and limited access to the appropriate drugs, coupled to the fact that patients tend to present with advanced disease. Given the background of intercurrent illness (e.g., HIV/AIDS) and malnutrition, dose adaptation from conventional cytotoxic drug regimens is often required. There is a large survival gap comparing outcomes between high-resource and low-resource nations, especially when comparing the potentially chemosensitive cancers. Survival rates for childhood cancers can be more than twenty times better in developed healthcare systems. As previously described, research has yielded steady improvements in outcome from novel agents, but at a hugely increased cost. This must be set against a context of the per-capita total healthcare expenditure of approximately $8 per annum in Kenya [12]. It would seem rational to create a prioritised list of essential anticancer drugs, striking a balance between efficacy, tolerability and cost. WHO has published a cancer formulary, identifying drugs that are generic, relatively cheap and moderately effective. As national cancer plans are developed by individual countries, priority should be given to those tumours which may be curable, perhaps focusing on paediatric cancers and on prevalent tumours where chemotherapy can offer useful palliation and prolongation of life, e.g., breast and cervical cancer, by far the two most common cancers of women in Africa, accounting for about 60% of disease burden.

REFERENCES

Since then, surgery has become a potent tool in the treatment of cancers of the larynx, oesophagus, skin ulcers and chronic infections like pneumonia. Surgery has a well-defined role in the prevention of cancer and between 23-54% of lifetime risk of ovarian cancer. Prophylactic mastectomy and surgical oophorectomy are among established methods of reducing risk [3]. Several high-penetrance genetic risk factors for colorectal cancer have been identified, and their presence is an indication for increased frequency of screening and in some cases prophylactic resection of the colon and rectum [4,5]. Surgical intervention in inherited neoplasms (EN) involving organs such as the oral cavity, urinary bladder, breast, uterine cervix and esophagus also leads to substantial reduction in invasive cancer risk [5].

Surgery in cancer screening and prevention

Surgery has a well-defined role in the prevention of cancer. Surgery is now used within the context of multidisciplinary management of cancer patients, where it plays a role as one of the components of modern cancer management.

Surgery for cancer screening and prevention

Figure 1.6.1: Baseline Cancer Management, Policies of Surgery of the University of Tokyo, Japan

The role of the surgeon in cancer diagnosis is very important because this is often the first step for many patients, and the choices made by the surgeon may have significant and far-reaching effects on the treatment and outcome for the individual patient. Careful history-taking and clinical examination remains the bedrock upon which a sound diagnosis is based. This includes evaluation of the presence of risk factors, clinical stage of disease, presence of co-morbid factors, family history of cancer, psycho-social status of the patient and the patient’s expectations from treatment. Clinical intervention also provides an opportunity for the clinician to educate the patient about the disease and treatment options, ascertain the patient’s treatment preferences and learn the patient know-about follow up and patient care. The key steps in getting a tissue sample for diagnosis is to do this and obtain tissue that will help the pathologist contribute to the management of the patient, the surgeon must select the appropriate biopsy method, decide on need for ancillary imaging facilities, ensure that the tissue is properly fixed and gets to the pathologist on time, and that the results are obtained promptly from the pathologist. Surgical intervention includes treating the patient about the illness starts informing the patient, correctly assessing the patient, taking appropriate management and offering support and other interventions designed to maintain and improve quality of life.

Surgery for palliative care

Surgical palliation is designed to relieve symptoms for patients beyond cure when non-surgical measures are not feasible, not effective or not expedient. It encompasses all treatment options that are designed to enhance quality of life rather than cure the malignancy [17]. The aim of comfort and control of cancer-related symptoms can be achieved by offering palliative care, which may involve a combination of different treatments such as pain relief, psychosocial care, nutritional support, and in some cases, surgical procedures. Palliative care is designed to maintain and improve quality of life.

Future of surgery in cancer management

In the future, surgery in cancer management will continue to play an important role in the multidisciplinary treatment of cancer. Further clarification of the genetic risk situations, such as peritonitis, which may occur on account of progression of cancer, can be treated as a complication of chemotherapy, for example, in gastrentestinal lymphomas. Cancer can also be treated as a complication of therapeutic treatment, for example, in gastrentestinal lymphomas. Cancer can also be treated as a complication of therapeutic treatment, for example, in gastrentestinal lymphomas. Cancer can also be treated as a complication of therapeutic treatment, for example, in gastrentestinal lymphomas.

Factors that influence outcome of treatment

Outcome of cancer surgery depends on several factors, including the patient’s general health, the type of surgery performed, the skill and experience of the surgeon, the availability of resources, and the patient’s compliance with post-surgical care.

Conclusion

Surgery plays an integral role in the multidisciplinary management of cancer patients, and Surgeons have access to other individuals at risk for a range of skin lesions (MENS) Types 2A and 2B. MENS arises as a result of autosomal dominant germ line mutations in RET proto-oncogene, and all the mutations develop MTC. To prevent MTC, prophylactic total thyroidectomy is done before 5 years of age in MENS 2A and during the first year of life in MENS 2B. Germ line mutations in BRC A1 and BRC A2, present in 150 to 1 in 800 North Americans, is associated with about an 80% lifetime risk of breast cancer and between 23-54% lifetime risk of ovarian cancer. Prophylactic mastectomy and surgical oophorectomy are among established methods of reducing risk [3]. Several high-penetrance genetic risk factors for colorectal cancer have been identified, and their presence is an indication for increased frequency of screening and in some cases prophylactic resection of the colon and rectum [4,5]. Surgical intervention in inherited neoplasms (EN) involving organs such as the oral cavity, urinary bladder, breast, uterine cervix and esophagus also leads to substantial reduction in invasive cancer risk [5].

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The role of the surgeon in cancer diagnosis is very important because this is often the first step for many patients, and the choices made by the surgeon may have significant and far-reaching effects on the treatment and outcome for the individual patient. Careful history-taking and clinical examination remains the bedrock upon which a sound diagnosis is based. This includes evaluation of the presence of risk factors, clinical stage of disease, presence of co-morbid factors, family history of cancer, psycho-social status of the patient and the patient’s expectations from treatment. Clinical intervention also provides an opportunity for the clinician to educate the patient about the disease and treatment options, ascertain the patient’s treatment preferences and learn the patient know-about follow up and patient care. The key steps in getting a tissue sample for diagnosis is to do this and obtain tissue that will help the pathologist contribute to the management of the patient, the surgeon must select the appropriate biopsy method, decide on need for ancillary imaging facilities, ensure that the tissue is properly fixed and gets to the pathologist on time, and that the results are obtained promptly from the pathologist. Surgical intervention includes treating the patient about the illness starts informing the patient, correctly assessing the patient, taking appropriate management and offering support and other interventions designed to maintain and improve quality of life.

Surgery for palliative care

Surgical palliation is designed to relieve symptoms for patients beyond cure when non-surgical measures are not feasible, not effective or not expedient. It encompasses all treatment options that are designed to enhance quality of life rather than cure the malignancy [17]. The aim of comfort and control of cancer-related symptoms can be achieved by offering palliative care, which may involve a combination of different treatments such as pain relief, psychosocial care, nutritional support, and in some cases, surgical procedures. Palliative care is designed to maintain and improve quality of life.

Future of surgery in cancer management

In the future, surgery in cancer management will continue to play an important role in the multidisciplinary treatment of cancer. Further clarification of the genetic risk
of cancer and identification of populations at risk may increase the role of surgery in prevention. Future advances include expanded use of laparoscopic and other minimally invasive techniques, robotic surgery, image-guided interventions and telemedicine. In developing countries, surgical services, though grossly inadequate, remain the most widely used treatment for solid tumours [18]. Efforts at improving availability and consideration of alternative models for delivery of surgical treatment for cancer patients are needed [19].

Radiotherapy has been developing as a clinically essential part of the armamentarium against cancer since the last decade of the nineteenth century, when Röntgen invented a means of generating X-rays. The scientific basis has been explored and explained through radiobiology and its associated sciences. The clinical foundation of radiotherapy has expanded through high-quality clinical trials. The economic and social justification for radiotherapy is defined by tumour cancer service and public health reviews.

A little over 50% of all patients who develop cancer will require radiotherapy at some time during their illness. This percentage will vary from one tumour type to another. About 70–83% of breast cancer patients would be expected to undergo radiotherapy (2) while only 1% of patients with diagnose cancer will require such intervention (2). Service needs depend, therefore, on the disease type and the patient community. It is also affected by the extent of disease at presentation. Where the disease burden is such that the norm at presentation is more locally advanced disease, indications for a given treatment intent and duration will differ from situations where early presentation, for example through screening, is a common practice.

Radiotherapy may be applied with different intents which vary with the disease type and its extent. Palliative radiotherapy, delivered often in a few (one to five) radiation exposures and using extreme, often single field techniques, will be offered to improve quality of life and relieve symptoms in advanced metastatic disease. It is particularly effective in the palliation of both bone metastases and dysphonia from obstructive lungs tumours, dysphagia from obstructive oesophageal cancer, bleeding from advanced pelvic malignancies, coughing and headache and symptoms of raised intracranial pressure from brain secondary tumours, superior vena cava obstruction and early presentation of malignant spinal cord compression.

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Linear energy transfer (LET) radiation such as neutron therapy have either proved ineffective, too toxic or logistically too complex. The effect of radiation may be increased by the use of concomitant chemotherapy as used increasingly in oesophageal, head and neck, cervix and rectal cancers. Concomitant radiation and targeted therapies—such as cetuximab in head and neck cancer—is also being used in selected patients.

Altered fractionation of radiotherapy has been explored for a number of tumours. In head and neck cancer, twice-daily treatment has been found more effective than daily treatment. For non-small cell lung cancer Continuous Hypofractionated Accelerated RadioTherapy (CHART) given in three fractions per day over twelve consecutive days (no weekend break) has been shown to be superior to single daily (Mon–Fri) treatments over six weeks. Acute toxicity with these combinations and other alterations from standard therapy may be more severe.

Stereotactic aimed and delivered small beams have been used for both malignant and benign intracranial lesions for many years. Astro-cerebral malformations may be thrombosed with single high-dose treatments, known as stereotactic radio-surgery if a fractionated course is given it is stereotactic radiotherapy. These stereotactic techniques are being explored in extracranial sites such as head and neck and also lung (for small peripheral lesions) and intra-abdominally for liver metastases. These require significant modification of a linear accelerator and special immobilisation techniques. It is also essential where organ and hence tumour movement is marked with respiratory movements to deliver the radiation beam only in specific parts of the respiratory cycle. Respiratory gating is now available as an add-on to modern linear accelerators. Systems to confirm tumour position radiologically before and during treatment are also essential, and modern linear accelerators can be equipped with on-board kilovoltage or cone-beam CT imaging devices.

In addition there are megavoltage treatment units with built in CT scanner capability (Tomotherapy®) or which have high precision stereotactic treatment capability (Cyberknife®).

In the last decade the value of heavy particle irradiation with protons or heavy ions has been investigated following the development of particle generators delivering manipulateable and often multiple beams. These therapies have a proven role in the management of some orbital tumours and, for example, bone of skull sarcomas. Due to very high cost low such installations exist, but as the cost is falling and as the clinical role is becoming further defined, national services are being proposed.

**Overview**

Radiotherapy has seen a technology avalanche in the last twenty years that has offered the same level of exciting prospects that the quantum leap from kilovoltage to megavoltage equipment encouraged sixty years ago.

Equipment costs have risen, as has demand on staff and the need for improved quality assurance and safety. However, as the range of treatments has correspondingly increased, toxicity has decreased. Thus, what were common side effects, such as 3–4% incidence of acute pneumonitis and unacceptable levels of radio-neocrotic fractures of rib and even the low but dreadful incidence of radiation-induced bronchiolitis pulmonary from breast radiotherapy technique and noted too often until the 1980s, are now rarities.

While the cost of radiotherapy has slowly risen over the last twenty years, these costs remain lower per episode of care than for other modalities, the mean cost for ‘standard treatment’ delivering 21 fractions being estimated at €3239 across three European and one Canadian study [3]. However, while radiotherapy technology has changed beyond recognition and hence requires a greater initial capital outlay, high quality radiotherapy demands no more than a functioning megavoltage unit-cobalt or linear accelerator—with facilities for adequate beam shaping, a process to image the area of interest to determine field placement, a basic planning computer system and, of course, trained and dedicated medical, physics and technology staff committed to safety. High quality but basic and hence low-cost equipment is now being produced by major equipment manufacturers for lower-resource nations. These developments may allow the introduction of low-cost sustainable radiotherapy services where none or few exist currently.

Radiotherapy is part of the multimodality and multidisciplinary management of patients with cancer. It is essential for good cancer care, chemotherapy and surgery cannot effectively replace it. Where it is not available 50% of cancer patients are being denied appropriate care.

**References**


Principles of Supportive and Palliative Care

Summary

- Every cancer service requires an active and resourced Supportive and Palliative Care Service (spawning university teaching hospitals to community care) that is engaged in a timely way for patients and their families.
- Supportive and Palliative Care Services should be developed in parallel with cancer services (in high-resource and low-resource countries).
- Opioids, together with other key medications for symptom control, need to be more systematically available around the world.
- People with advanced cancer should have access to supportive and palliative care services long before their terminal phase. "Terminal care" represents a small fraction of the illness trajectory for which supportive and palliative care services are configured.
- The definition of supportive and palliative care is needed to meet the complexity of their needs, take forward an agenda of research to refine clinical practice and service provision, and educate existing practitioners (for whom supportive and palliative care was not part of their training) and those still in training.

Impact of cancer around the world

Cancer continues to be a major cause of human suffering everywhere. The diagnosis of cancer is strongly associated with premature death in the mid- to long-term. Despite continuing significant advances in understanding modifiable risk factors, prevention programmes, early detection of some cancers or precancerous conditions and rapid advances in the treatment of many previously universally fatal cancers, for many people the whole world, cancer will cause premature death. For others, active cancer will be present at the time of their death although, not directly causing it, and for a third group of people, cancer will have been diagnosed and treated at some earlier time in life sometimes with long-term consequences.

Premature death from cancer affects all age groups. Very poor five-year survival persists for many cancers, including lung and unknown primary, even in high-resource countries.

In low-resource countries, cancers associated with infectious diseases (hiv-related cancer, hepatitis B and C, nasopharyngeal carcinoma) continue to cause premature mortality that has significant consequences for families and for communities in which they live. The increasing contribution to premature death because of likely factors such as tobacco use has not peaked in many countries.

In parallel with therapies designed to improve cancer or survival rates is a process of optimizing a person’s function while having therapy and subsequently in line with the resources available [1]. Such needs to be planned in a national framework that reflects the resources, practices and beliefs of the country [2]. Wherever people are on their disease trajectory there is a need to address symptom control. This happens in tandem with disease modification therapy [3].

Like any area of clinical practice, much of the work in palliative and supportive care is needed to be achieved by a wide range of health professionals. For a number of people, involvement of health professionals who work at the interface of symptom control, psychosocial care and how to optimise a person’s function. Such processes and activities are needed to train specialists in supportive and palliative care. The model also acknowledges that many people do not need to access specialist services the current care of family and health professionals is meeting their needs.

Informed decisions include all the reasonable options, including not having any therapy aimed at changing the course of the disease at any given time. For most of the palliative care phase, there will be decisions that need to reflect the patient’s and family’s values. These decisions will arise because the course of the illness (either as a direct result of the cancer, the treatment of cancer or inter-current co-morbid illness) can potentially be modified. Equally, there is a time when changes in the course of the illness are no longer possible.

How do we need specifically identified supportive and palliative care services? In low-resource settings it includes the direct effects of the cancer and the short- and long-term effects of its treatment, co-morbid illnesses that can be affected by the palliative challenge to the body of cancer. (Benefit and burden) from the specific involvement of the health care professionals serving them. This includes outcomes for the person with cancer [6] and their caregivers, while in the role and after they have relinquished the role. Caregiver outcomes can be seen to relate to metrics associated with widely reported health outcomes – survival, impaired health states, health service utilisation, mental health and physical functioning.

The evidence base for supportive and palliative care

What is the evidence base of net benefit (bennett and burgess) from the specific involvement of specialist supportive and palliative care services for people with more complex needs from cancer? There are four levels at which such a conversation could occur:

- The person with cancer;
- Family caregivers;
- Health service providers; and
- Whole populations.

If you treat the disease, it is win or lose. If you treat the person, you always win.

Patric Adams

If you treat the disease, it is win or lose. If you treat the person, you always win.
No single systematic review has brought together the many aspects of care across time covered by supportive and palliative care services. The net impact of supportive and palliative care services is a cumulative effect from each aspect of assessment and care.

At a community level, end-of-life care is valued for the continuity of care, reducing burden for caregivers, avoiding hospitalisation, and ensuring the final weeks of life are spent at home. Similarly, supportive care for patients with advanced cancer or chronic illness has been shown to:

- improve survival having relinquished the role [22];
- reduce hospital stays [17-23];
- decrease costs when compared to conventional care [17-23]; and
- substantially influence the likelihood that place of death is that of the patient’s choosing [26].

Importantly, there is often a perception that referral to a hospice/palliative care service will compromise care in a way that may shorten prognosis. Although this could not be tested with randomised controlled trials, it is noteworthy that in at least one large population-based study, prognosis was longer for each of the 16 diagnoses that were studied, 12 of which were advanced cancers [27].

Systematic reviews of the impact of specialised palliative care services suggest benefit in a number of domains [28-30]: pain and symptom control [31]; satisfaction with services, reduced hospital bed days and overall costs [32] and potential benefits for caregivers [33]. It has been more difficult to access people who have not accessed services [34-36] explore the wide regional variation in referral and access patterns [37], or account for the variations in time from referral to death in different health systems but similar burdens of cancer [28-38-40].

Delivering supportive and palliative care services around the world

What are the supportive and palliative care services offered around the world? There is wide variation in the availability and structure of services around the world. These reflect:

- local philosophy relating to health service resource distribution;
- funding models within health systems (user pays versus universal health care);
- service development philosophies (supportive and palliative care services will be developed when all other oncology services are fully established compared with parallel growth of both);
- the availability of trained staff;
- the overall competing demands for health resources (or in many cases for any resources);
- community beliefs and values surrounding the inpatient and dying;
- and the background disciplines (anaesthesiology, psychiatry, surgery, oncology, family medicine, other branches of internal medicine) people providing specialised supportive and palliative care.

Despite these wide variations, there is evidence of strong growth of supportive and palliative care services around the world, of the qualified staff to provide care and further develop services and of increasing infrastructure in research and education [41-44].

There are data to demonstrate that a start has been made in developing services in every region of the world. The capacity building to provide comprehensive supportive and palliative care around the world includes:

- providing the skills for all healthcare professionals to optimise care for people wherever they are in the cancer trajectory (living with cancer, having survived cancer with no known disease, or facing premature death because of cancer);
- employing care staff who will take responsibility for providing care for people with more complex needs, service planning, seeking funding, research and education; and
- making available key medications, including opioids for pain.

In high-resource countries, there are still cancer care services and facilities that refuse to invest in either the staff to provide supportive and palliative care, or the inpatient beds for acute symptom assessment units. Without these resources, cancer services cannot claim to be comprehensive. These centres often have limited links to the community care needed by people as they become more frail.

In resource-challenged countries, issues include workforce, competing demands for scarce health resources and the predictable supply of medications used in symptom control, especially opioids for analgesia [45-46]. The continuing struggle to provide predictable access to therapeutic opioids is an indication of health and regulatory systems around the world that needs urgent and effective action [47].

In recognition of the need for models of sustainable practice, the World Health Organization has collaborating centres in places such as Jordan and Spain [48,49].

The Future

As mapped by the World Health Organization, there is much that needs to be done in every country around the globe to improve access to specialist supportive and palliative care at every level of the health system from university teaching hospitals (which should all have acute inpatient symptom assessment units) to community-based care, continued development of the clinical workforce at all levels and in all disciplines, improved infrastructure (most notably equitable access to opioid analogues) and community care that can support people who want their care to be at home [2]. This is a challenging agenda, but much has been achieved since the publication of the first IARC World Cancer Report in 2003 [50].

| Fig. 1.8.1 | Supportive and palliative care services should be developed in parallel with cancer services |
## REFERENCES


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Psycho-oncology is a subspecialty of oncology that focuses on the psychological, social, and emotional aspects of cancer care. It is particularly important in Western countries where it is integrated into oncology. The psycho-oncology field promotes a multidisciplinary approach and offers evidence-based interventions to enhance health promotion and disease prevention. It addresses not only the physical aspects of cancer care but also psychosocial needs and deficiencies in care, such as lack of attention to cancer patients' social factors.

Psycho-oncology concerns the facilitation of patients' and families' coping, treatment adherence, and thus call for different priorities of interventions. It improves healthcare outcomes by providing treatment to prevent, control or relieve symptoms, including hormonal therapy, have physical side-effects, which may be short-term or time-limited, or chronic and persistent, and develop or worsen after treatment has ended. Decreased performance status and physical functioning may also emerge; in the survivorship phase, patients may experience problems in returning to work, feeling marginally or even stigmatized as a result of having been affected by cancer.

The global care approach is particularly relevant in the field of cancer. Cancer and its associated conditions may significantly damage patients' quality of life. Complementary to therapy for cancer, the care provided in oncology must include the management of diverse symptoms, treatment side effects and sequelae, as well as psychosocial distress and needs that grow in that context.

A dimension of quality of life is the psychological well-being, which may be considerably affected by the diagnosis of cancer and the therapeutic process. Patients as well as their family members are confronted with a number of distressing emotions and experiences, including the fear of death and uncertainty about the nature, evolution and prognosis of the disease. Individuals affected by cancer have to face a reduced ability to control their life, increased dependency on others, and disequilibrium in familial, professional and social life. Unmet psychological conditions may further damage quality of life as well as increase medical costs by longer hospital stays or in higher rates of utilization of primary care medical services [1,2].

Psycho-oncology addresses the psychosocial distress of patients and their family members, and thus the continuum of care, from prevention and early detection through treatment and survivorship to palliative and end-of-life care [3]. Psychosocial interventions in oncology include the facilitation of patients' and families' coping, relief of psychological distress and also address the wellbeing of oncology professionals. The psycho-oncology discipline also strives to contribute to the World Health Organization efforts in the psychosocial care of cancer patients, providing not only knowledge but also strategies and principles that may be used in the global cancer literature to mean health status, physical functioning, severity of symptoms, psychosocial adjustment, well-being and satisfaction with life. Broad quality of life domains have been described, comprising the physical, psychological, economic, spiritual and social domains.

Psycho-oncology: a subspecialty of oncology that has developed rapidly over the past 30 years with the recognition of the psycho-social impact of cancer and its treatment and the need to foster global, holistic care of the person confronted with this disease. Global care refers to the consideration of the multi-dimensional aspects of health, i.e. the physical health, mental health, social well-being and role functioning. Human aspects of care have been underscored in the face of increasing emphasis on bio-technological aspects of medicine, especially in Western countries.

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General distress

7.1% adjustment disorder
22% anxiety disorder
11.5% major depression
35.1% post-traumatic stress disorder
37.3% major depressive disorder
16% anxiety and depressive disorders
47.2% for anxiety, 7.8% and 57% for depression

n=4496
n=190
n=107
n=127
n=212
n=1277
n=222
n=117
n=3307
n=142
n=204

14% for anxiety disorder
16% for depression
11.5% for anxiety
7.1% for depression
35.1% for post-traumatic stress disorder
37.3% for major depressive disorder
16% for anxiety and depressive disorders
47.2% for anxiety, 7.8% and 57% for depression

Secondary analysis

Studies conducted in recent decades have revealed that pathological levels of distress were more prevalent in patients with cancer than in the general population [15]. One third of all cancer patients experience prolonged high levels of distress that contribute to ongoing adjustment difficulties and can potentially interfere with treatment compliance [16]. As presented in Table 1.9.1, among mood and anxiety disorders, figures range from 6.3% and 47.2% for anxiety, 7.8% and 57% for depression, and 7.1% and 48.4% for general distress and are found in North America [17] as well as in Europe [18], European countries [19-23], the middle East [24,25], South Africa [26], South America [27] and Asia [28], and across the trajectory of the illness—from the time of the diagnosis of treatment to termination of treatment, survivorship, or recurrence and palliation [20,29]. Post-traumatic stress disorders as a result of the stress event that represents confrontation with a life-threatening illness such as cancer are also found in the cancer setting, with prevalence rates at 15% to 25% in breast cancer patients, post-surgery and 16% at 6 months [22]. In advanced cancer, about half of patients express some level of suffering, with physical symptoms, psychological distress and existential concerns contributing to the prediction of this experience [30]. Acute confusional states are less common in patients with cancer overall but develop frequently in advanced cancer, and are a leading source of distress for family caregivers [31]. Patients become restless, suspicious and confused, with impaired concentration, memory and orientation in time and space. Opioid analogues essentially, but also other psychoactive agents, cause symptoms of encephalopathy are common causes.

Predictors of psychological disturbance in cancer patients have been highlighted including medical (e.g. staging of disease, physical or psychological symptoms), individual (e.g. gender, past history of psychiatric disorder, personality), contextual (e.g. patients, and caregivers, current concerns) [1,17,20,32]. Potential predictors are not very useful clinically as they only partly explain the development of psychological disturbances. There is meanwhile a consensus to consider the systematic screening of these disturbances as useful in order to allow early treatments of these conditions [33,34].

Couple and family issues. Cancer is a familiar affair and not the patient's problem alone [35]. The effect of cancer on family members, in turn, may affect the patient's adjustment to illness. The well-being of close relatives is also a cancer especially since contexts of scarce psychosocial resources lead to reliance of this only source of support to patients. Marital relationships may be altered, especially in those suffering from breast cancer. In contrast, whereas good marital relationship may buffer the stress of cancer, and are associated with less distress in the patient. An insufficiently recognised complication of cancer is sexual functioning [36]. Sexual problems can be a consequence of cancer-related interventions (surgery, radiation, chemotherapy), neurological and physical damage following certain treatment such as disfiguring surgery, ostomy, surgically induced nerve damage, radical pelvic irradiation, side-effects of chemotherapy, or hormone therapy treatment for prostate cancer such as prostatectomy or hormone therapy can diminish a man's self-esteem as a sexual partner [37]. Body image and sexual problems were experienced by a substantial proportion of women in the early months after diagnosis of breast cancer and were associated with wanting cosmetic procedures to reconstruct, hair loss from chemotherapy, concern about weight gain or loss, poorer mental health, vaginal dryness and partner’s dissatisfaction contributing to patients’ feelings [38]. Breast cancer susceptibility testing offers the potential for early detection of breast cancer, since a positive test result points to the need for increased surveillance, i.e. regular mammography or magnetic resonance imaging (MRI) or indicates the possibility of reducing cancer risk through chemoprevention and risk-reducing surgery. A positive test may also lead to psychological benefits in reducing the individual’s uncertainty and doubt. However, cancer-susceptibility testing also encompasses limitations and potential risks, depending on the test result. The test result may be 1) positive in an unaffected, at-risk individual when a disease-related mutation has been identified in the family, 2) positive in a breast cancer patient when she is the first identified mutation carrier in a family, 3) negative when a disease-related mutation has been identified in the family or, 4) inconclusive at uncertain risk [39]. A positive test result may lead to heightened anxiety about being a cancer carrier or induce guilt about possible transmission of genetic risk to children. Mutation carriers may be confronted with the medical and psychological risks of increased screening or surgical prophylactic interventions or of potential insurance,
Psychosocial issues in oncology professionals

Management of psychosocial issues

Interventions targeted at health care professionals

In the context of cancer care, the relationship between patients and healthcare providers and the standards of cancer care are of crucial importance. Inadequate explanations may lead to patients being confused about their diagnosis, prognosis and potential therapeutic options, thereby harming dissatisfaction and psychological distress. This can affect attitudes towards treatment, mortality, and the performance of cancer survival outcomes. However, there is information that needs to be conveyed to patients including disclosure of a diagnosis or explaining a negative treatment outcome, often involving the presence of distress. The presence of distress constitutes one of the most important tasks of healthcare providers, particularly in the presence of distress.

The care of patients with cancer may be particularly stressful. In particular, dealing with cancer patients’ psychosocial issues entails an emotional burden that can lead to burnout. A high level of morbidity and mortality, confronting death, treatment with limited efficacy that are powerful but toxic or maladaptive, difficult therapeutic decisions, medical or nursing staff conflicts, patient or family emotional or behavioral symptoms can interfere with the stress associated to the involvement of the patient in medical care. For example, healthcare professionals may report feelings of hopelessness, anger, or occasional identification with the patient. It is therefore imperative to provide an adequate care for patients and their relatives.

Interventions have been designed to facilitate the detection of psychological and psychosocial problems through the use of quality of life questionnaires in routine oncology practice. The provision of assessment tools and guidelines for psychosocial management have been described; these are promoted in training and lead to highlighting more reliable symptoms, such as, for depression, anhedonia, guilt, suicidal thinking and hopelessness.

In the United States, through the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO), specific tools and psychological diagnoses have been used to trigger referral by the oncology staff to the psychosocial services.

In the United Kingdom, the National Institute for Health and Clinical Excellence also offers clinical guidance from a critical and comprehensive appraisal of studies assessing the effectiveness of psychosocial, supportive and palliative care services for cancer patients. Other countries with guidelines in use are Germany, Hungary, Italy, Israel, Japan and in all others, guidelines are at different stages of development. It is important to mention that a patient-centred care approach is encouraged; this entails the following specific features:

1. An individualized, bio-psycho-social attention to the patient confronting the difficulties the disease imposes in his/her daily life.
2. The consideration of a patient who is no longer a passive recipient of care, but perceived as possessing resources to deal with his/her condition, such as the capacity to understand medical information and share decision making; and
3. A patient-centred, genuine and comprehensive caring attitude.

Cancer patients generally prefer a collaborative role in deciding on a treatment plan; however, cancer patients are frequently passive, deferring to their physicians on treatment decisions. Patients are not necessarily informed about important interests, wishes regarding their involvement in shared decision-making. An uneven balance of power in treatment decision making (leaving all the decision making to the patient) may affect patients’ well-being and satisfaction. Recent systematic reviews have provided evidence for the effective role of communication in improving the quality of communication skill in the cancer setting. These must comprise the following specific features: learner-centered, skills-focused, and practice-oriented, organized.
Interventions targeted at patients or relatives improving quality of life. There is now a consid-
erable body of evidence concerning the effect-
iveness of psychological interventions and individ-
uals or families confronted with cancer [9]. Because of the various individuals’ needs and con-
texts, different types of professional psycho-
social interventions have been developed and
tested. These comprise individual interventions such as education, counselling (crisis-oriented or psychoeducational), cognitive (cognitive refra-
ing, problem solving), therapy (relaxation, hypnosis, meditation), group interventions (expressive-existential, cognitive-behavioural), or psychodynamic), and couple or family interventions. They are usually targeted to specific episodes of the illness trajectory: diagnosis/pre-treatment, treatment immediately post-treatment or during extended illness trajectory: diagnosis/pre-treatment, treatment (chemotherapy or radiotherapy), and advanced illness or death; through the bereavement period when addressed to rela-
tives [1]. More specific interventions have also been designed for particular problems (e.g., sexual dysfunction, sleep disturbance). Careful psychosocial assessment at appropriate time points in the patient’s journey may channel to specific interventions.

Cancer patients’ psychological adjustment results from the interaction between their appraisals of the stressors associated with the disease and their internal or external resources, in terms of their coping style, personality traits or available support resources. Psychological therapy in people with cancer strives at facili-
ting coping in favour of improved patient out-
comes, their quality of life and satisfaction with care, and to ensure healthcare providers’ well-being while carrying out the activities of their caring profession.

Chapter 1.9: Psycho-Oncology

Cancer and its treatment may considerably affect patients’ physical and psychosocial func-
tioning, hence overall quality of life. The psy-
cho-oncology discipline has been developed and implemented in an increasing number of countries to respond to the psychosocial needs raised in oncology at the different phases of the cancer journey, including prevention and early detection, diagnosis and care, treatment, survivorship, recurrence, terminal stages and bereavement.

Evidence-based psychosocial interventions addressing patients, families or their social milieu, psychological therapy and counseling various aspects of quality of life, Newell et al. [9] con-
cluded that group therapy, education, structured and unstructured counseling, and cognitive-behavioural therapy offer promise for many of the psychosocial outcomes explored (e.g., depression, anxiety, overall quality of life and physical symp-
toms such as fatigue or conditioned nausea).

Further studies need to address the appropri-
ateness of existing forms of psychological therapy for subgroups of patients so as to design or adapt interventions accordingly (e.g. patients from rural areas, with psychosocial problems or from varying cultural backgrounds). For example, these may either adapt patients belonging to higher socioeconomic classes [60], although cancer patients from lower socio-
-economic status have been shown to present greater morbidity and poorer perseverance with anti-tumour treatment. Psychosocial factors, like optimism, can improve patient outcomes, or negative social interaction have been shown to moderate the effect of psycho-oncological interventions, highlighting a specific group of participants more susceptible to patients with cancer who may not be open to address their distress at any time, especially as long as a treatment decision has not yet been made [64].

Conclusions and recommendations

The International Psycho-Oncology Society (IPOS) recommen
ded in 1994 to bring together investigators and clinicians dedicated to the clinical, educational and research aspects of psycho-oncology, in order to share knowledge and practice in the psycho-oncological care of cancer patients worldwide while taking into account the diversity of problems and needs accord-
ing to the cultural, economical or healthcare system background. Thanks to an initiative from the Psycho-Oncology Co-operative Research Group in Australia, a world map showing psy-
cho-oncology research groups is now available (http://www.oncologyresearch-networks.org/tools-resources/research-centres.htm).

Cross-national psycho-oncology research is now possible thanks to the international develop-
ment and validation of psychosocial tools allowing monitoring of patients’ difficul-
ties and assess interventions effectiveness [65, 66]. To evaluate the quality of cancer care pro-
vided [65]

The further mission of the IPOS is to assist the WHO in shaping priorities of action regarding the psychosocial element of national cancer control programmes [1].

Psycho-oncological care is an essential component of high-quality cancer care that should be made available across countries to improve cancer patients’ and relatives’ health outcomes, their quality of life and satisfaction with care.
Chapter 1.9: psycho-oncology

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1.10 and psychosocial distress. As a consequence, and radiation has become more aggressive few decades, whereas the cure rates have of cancer therapy, survival times for many rehabilitation in oncology summary>

Rehabilitation is an essential part of a comprehensive concept of cancer care starting from early detection of cancer, physical, social, psychological and work-related functionality after cancer treatment.

Rehabilitation programmes include an interdisciplinary and comprehensive approach providing support to patients and their families to cope with treatment sequelae and to allow them to regain quality of life and functional status.

Rehabilitation needs must be assessed individually by measuring physical performance and quality of life.

Research results provide good empirical evidence for effects of rehab programmes, especially on important outcome domains such as health-related quality of life, psychosocial status and psychiatric morbidity.

Due to early detection and improvement of cancer therapy, survival times for many types of cancer have increased over the past few decades, whereas the cure rates have improved in only a few instances. Oncological treatment including surgery, chemotherapy and radiation has become more aggressive and is often long-lasting. Cancer therapies are producing toxicities which cause substantial short- and long-term side effects, functional loss and psychosocial distress. As a consequence, in many cases cancer has to be regarded as a chronic disease involving great challenges for patient care. Many cancer patients require repeated oncologic treatment with substantial impact on quality of life and functional status. The demands on the patients and caregivers can vary depending on their extent as well as whether they are temporary or permanent. Patients themselves have higher expectations of medical treatment for participation in an active life. Against this background, cancer rehabilitation has become more important during the last decades. Today, rehabilitation is an essential part of a comprehensive concept of cancer care starting from early detection of cancer and covering the entire continuum from diagnosis to treatment, rehabilitation and aftercare including end-of-life phases.

Basic concepts and structure of cancer rehabilitation Cancer rehabilitation may be defined as a process of helping the patient to regain physical, social, psychological, and work-related functionality after oncologic treatment.

Rehabilitation as a process starts during or immediately after the end of the primary treatment to reach both secondary and tertiary prevention. Therefore, rehabilitation integrates all aspects of medical care and enables the patient to return to work and live a relatively normal life. As a comprehensive approach, it provides support to patients and their families to cope with treatment sequelae and aims to help them to become reemployed or return to their previous occupations.

Cancer rehabilitation aims at regaining or maintaining physical function and independence, normalizing daily functioning, restoring physical function and independence, and to allow them to regain quality of life and functional status.

As a conceptual basis for rehabilitation, the WHO classification of function, disability and health (ICF), former ICDH=International classification of function, impairment and disability describes how people live with health conditions [3]. ICF is a classification of health and health-related domains that describes body functions and structures, activities and participation. The domains are classified from body, individual and societal perspectives. ICF also includes a list of environmental factors. ICF is useful to understand and measure health outcomes. It can be used in clinical settings, research, health services or surveys at the individual or population level [3]. A first version of the ICF classification for breast cancer has been published [4].

Cancer rehabilitation services can be effectively introduced in a variety of settings adapted to the local situation. In most European countries as well as in the USA, rehabilitation services are mostly based in specialized rehabilitation centers and cancer hospitals offer a variety of cancer rehabilitation services to their patients. Germany provides a unique system of rehabilitation clinics delivering important rehabilitation programmes for all chronic diseases [5,6].

Rehabilitation needs There are multiple rehabilitation-related issues in different stages throughout the course of the disease. Problems during the initial phase after treatment are different from those that may arise from phases after recurrence or at the end of life [7]. Therefore, rehabilitation needs must be assessed individually [8]. The need for rehabilitation in cancer patients is assessed by instruments measuring physical performance and quality of life [9,10]. Cancer-specific scales attempt to assess how illness and treatment sequelae affect daily living. Therefore, instruments are used in clinical and research settings and are also used for evaluation of the effects of rehab programmes. Some of those scales can be used along with more in-depth interviews and case management interventions. They may also be used to document cancer-related problems, assess patient needs and provide information to enhance outcomes.

Goals and interventions Cancer rehabilitation is aimed at regaining or restoring physical function and independence, often following surgical and medical treatments. Over and above that, an important task of rehabilitation is also to prevent impairment. Although remission may be initially declared for patients with cancer, vocational reintegration is an important goal of rehabilitation especially for young patients [11]. In detail, the goals in cancer rehabilitation are:

- to cope with the physical and emotional changes,
- to improve physical condition and performance status focused on strength, endurance and mobility,
- to improve social, emotional and mental functioning;
- to identify and treat rehabilitation problems and sequelae (e.g. pain, fatigue, lack of stamina, polyneuropathy, sleeping disorders);
- to enhance self-help strategies, competence and resourcefulness in disease management;
- to improve dietary habits through nutritional counseling;
- to help the patients to become reemployed or return.

Goals are based on individual needs and, ideally, should be attainable within a reasonable amount of time. As each person with cancer has unique physical and emotional needs, each requires an individual rehabilitation plan. Patients and their family are encouraged to be active and fully-informed partners in the rehabilitation process and thereby contribute to reaching their goals.

Having completed a need and goal assessment the composition of the rehabilitation interventions is to be designed according to the patient’s current needs of recovery. Rehabilitation programmes include a wide spectrum of treatment options (Table 1.10.1).

- Medical treatment including pain management and complementary medicine
- Exercise programmes
- Physical therapy
- Diet counselling
- Pain management
- Smoking cessation education
- Psychological counselling/individually
- Physical education
- Art therapy/Occupational Therapy
- Neuropsychological training

Specialized programs have been developed for diagnostic subgroups (e.g. breast cancer, prostatic cancer), and treatment subgroups (e.g. after stem cell transplantation). For example, specialized rehabilitation programmes for breast cancer in women may focus on comprehensive management of lymphedema, exercise, diet counselling, post-operative management of breast reconstruction, psychological counselling and psychosynthesis, or aims to address body image and self-esteem. As another example, patients with brain cancer transplantation with severe fatigue and decreased physical performance often require specific training, psychological education and a prolonged period of recovery.

Psycho-oncology in rehabilitation

Psychosocial interventions are an essential part of a comprehensive rehabilitation programme. During the last few decades psychosocial intervention based on individual or group therapy have been developed [12,13], which are carried out also in rehabilitation centres. Meta-analyses and systematic reviews have proven these interventions for depression and anxiety, for quality of life, for psychosocial distress, for coping strategies, for sexual problems, and for sleep disturbance [14-17]. Psychosocially oriented group interventions in rehabilitation are mostly based on the cognitive-behavioural approach including various elements (Table 1.10.2). They encompass 8 to 12 sessions based on a structured agenda focusing on the most prominent issues of cancer patients and initiating active coping behaviours.

Cancer rehabilitation as a multi-disciplinary task Comprehensive cancer rehabilitation is provided by a multidisciplinary team of health care professionals. In almost all countries, cancer rehabilitation are all committed to help an individual return to the highest possible level of function and quality of life, and to offer the best possible quality of life. These professionals may include oncologists, psychologists, re habilitation nurses, occupational therapists, physical therapists, occupational therapists, art therapists (including music therapy, dance therapy, bibliotherapy), social workers and case managers. All of them work closely under the guidance of an oncologist. They work together very closely and should provide a regularly based interchannel through multidisciplinary case conferences throughout rehabilitation. Structured meetings as well as external supervision are elements of quality assurance of the rehabilitation.

Evaluation of cancer rehabilitation

Systematic investigation and evaluation in rehabilitation is fundamental to show the effectiveness and impact of rehabilitative inter- ventions. Compared with other research areas, only a few empirical studies have been conducted in the field of oncological rehabilitation. Some studies provide good empirical evidence for effects of rehab programmes, especially on important outcome domains such as health-related quality of life, psychosocial status, and psychiatric comorbidity [18-23]. However, some longitudinal studies showed that the effects of rehabilitation programmes could not be proven non statistically in subsequent follow-up analyses [23,24]. In some studies, scores of many outcomes measures tend to decrease to baseline level or even below [23]. Only some studies with short term follow up [20] showed that the improvements achieved in rehabilitation were still present one year after the follow up period. Factors like gender, age,
have been shown to be of prognostic relevance concerning the success of rehabilitation over time [22]. Some studies have found that specified outpatient rehabilitation programs are effective in reducing fatigue while changes in fatigue were associated with changes in physical parameters [23]. Some other studies verify the effects of exercise and training programs for cancer patients [26,27]. There is some evidence that patients prefer multidimensional programmes to programmes with only one component [28]. In the future, further research is required, especially in terms of prospective longitudinal studies to improve the effectiveness of the rehabilitation programs.

REFERENCES


[Date Accessed: November 15, 2008]
Modern Imaging in Oncology

Summary

1. Ultrasound is a safe, noninvasive imaging modality used worldwide for initial investigation of many symptomatic oncologic patients who will subsequently undergo Computed Tomography (CT) or Magnetic Resonance (MR) imaging for further, more refined assessment. Performance of ultrasound includes detection of tumors of any accessible solid organ, based on lesion morphology and on a specific gray-scale. Optimal contrast resolution is achieved in deep solid organs, such as thyroid, liver, spleen, pancreas, uterus, ovaries, and prostate, and superficial structures such as lymph nodes.

2. Ultrasound can also be used in intraoperative diagnosis because of the superb vision of tiny lesions when the probe is placed intimately close to the region of interest. Furthermore, ultrasound is the ideal mode of guidance for interventional procedures because of its real-time multiplicity. However, despite the low cost and widespread availability of this modality, its high operator-dependence makes it less suitable in routine staging of proven malignancies, search for metastases and evaluation of responses to treatment.

CT is currently used for diagnosis, staging and follow-up of almost all tumors. CT imaging is based on X-ray attenuation ([Figure 1.11.1]). The introduction of the spiral scanning mode in the 1990s allowed continuous data acquisition and improvement of dynamic contrast imaging. [Figure 1.11.2]. The advent of multichannel CT scanners in 1998 allowed much faster scanning with thinner slices (up to 0.6mm) and higher-power levels ([Figure 1.11.2], with the current most important application in cardiac imaging. However, the use of iodinated contrast medium is still frequently necessary because of the intrinsic low resolution of ultrasound to normal tissue.

Traditionally used of CT imaging, lacking of multiplanar complexity, has been enhanced by modern image-processing methods. These include multiplanar reformatting views ([MR] for sagittal, coronal and oblique visualization, ([Figure 1.11.2]), maximum-intensity projections (MPR) for displaying only structures with the maximum density within a mass, as well as vascularisation of lesions ([Figure 1.11.3]) and volume rendering (VR) reconstructions to display enhancing voxels on the edge of structures ([Figure 1.11.3]a); volume (VR) and coronal (c) images, thus making the virtual colonoscopy possible.

Because of its reproducibility, CT has also been included as a standard examination for monitoring response to therapies by the standardized criteria. The use of iodinated contrast medium is still frequently necessary because of the intrinsic low resolution of ultrasound to normal tissue.

MR imaging is based on the use of a magnetic field and high-frequency electromagnetic pulses to generate images of anatomic structures with superb soft-tissue contrast, even without the use of contrast medium. Modern MR sequences have significantly reduced acquisition times and motion artifacts.

MR does not apply ionizing radiation; therefore repeated examinations may be performed without risk of radiation damage to tissues, although frequent exposure is now being examined by an expert committee in the United Kingdom to check for any possible predisposition to cancers. Unavailability due to high costs makes MR difficult to disseminate for routine use worldwide.

Recent developments in MR imaging are Diffusion Weighted Imaging (DWI-MR) and Dynamic Contrast-Enhanced (DCE-MR). In DWI, image contrast derives from differences in water-motion of molecules ([Figure 1.11.4]), it can be performed quickly and yields insights about tumor cellularity and integrity of the vasculature ([Figure 1.11.5]). To overcome limitations between tissues are highlighted by heterogeneous contrast medium uptake and varied degree of tumor angiogenesis, while DCE-MRI is able to detect extra-colonic abnormalities. Limitations of this technique can be false negatives related to retained fluid, incomplete distention, and difficulty to demonstrate flatt lesions. The most important disadvantage of virtual colonoscopy, compared to endoscopic colonoscopy, is the lack of ability to perform biopsies and remove polyps under vision. Another advantage over CT colonography, when VC is considered as a screening modality for colorectal cancer, is the exposure to ionizing radiation. However, VC is usually performed at a low radiation dose due to the high natural contrast between the colon wall and the endoluminal gas.

Positron Emission Tomography (PET) imaging can be used for staging and assessing response to treatment, as well as described in lymphoma and melanoma patients. Advantages of PET for monitoring response to therapy rely on characteristics of post-treatment therapies as metabolically active (residual tumor) or inactive (post-therapy masses) as metastases. PET contrast agents that will further expand the range of applications of the technique are currently under evaluation.

Virtual Colonoscopy. Virtual Colonoscopy (VC) is a noninvasive CT method for detection of colorectal polyps and cancers ([Figure 1.11.5]). In contrast to endoscopic colonoscopy, if a fast, noninvasive, does not require sedation and, although the experience is still short, its rate of modality and mortality is very low.

Currently, the use of multidetector CT, the mean scan time is 4-10 seconds, and the slices of 0.6mm enable high-quality MPR (Multiphase reconstruction) and 3D reconstruction.

VC can demonstrate lesions behind haustral folds and beyond bends of the colon by providing endoluminal views of the interior of the bowel in both forward and reverse direction. It is also able to detect extra-colonic abnormalities.

Molecular imaging

Molecular imaging is based on anatomic techniques. Recently, radiological research has been focusing on complementing anatomical imaging with functional imaging. Molecular imaging in oncology encompasses new techniques and probes to study processes at the cellular and molecular levels. Molecular imaging methods can be used to stage patients, to monitor response to therapies and to provide information on bio-distribution of targeted molecules. The use of specifically targeted contrast agents along with high-resolution imaging modalities are aimed at delivering earlier diagnoses and guiding the choice of new cancer-targeted drugs.

Depending on the properties of the tracers, various aspects of cancer cells including signal transduction, apoptosis, and protein interactions can be targeted and visualized.

Several modalities can be used for molecular imaging, mainly single photon emission com-
For instance, the use of superparamagnetic iron oxide (SPIO) particles for cellular trafficking has enabled the visualisation of a single cancer cell by using a clinical MR [7]. Furthermore, positron-emitting analogues of chemotherapeutic agents, such as paclitaxel or fluorouracil, are under evaluation for assessment of a tumor’s ability to sequester the radiolabelled analogue [8] and of the consequent advantage for the patient to undergo that specific chemotherapy.

The use of radiolabelled somatostatin analogues for imaging has become the gold standard for staging of neuroendocrine tumors, because the somatostatin receptor is strongly over-expressed in most tumors, resulting in high tumor-to-background ratios. Based on this attribute, a peptide receptor radionuclide therapy with radiolabelled somatostatin analogues is emerging as a treatment modality for patients with unresectable, somatostatin-receptor-positive neuroendocrine tumors [9].

Future directions for imaging in oncology

Advances in different imaging modalities and the possibility of their integration are predicted to show better outcomes than the sum of their single parts. CT, MR, US and PET may guide high-precision radiotherapy techniques, such as intensity-modulated RT (IMRT) [10].

An additional synergy may come from fusion of PET/SPECT and CT, where the use of common detectors may be used to detect emission of gamma rays and transmission X-rays to provide better localisation of metabolic processes.

The traditional low spatial resolution of PET has been improved with co-registration and fusion of PET and anatomical images either on a software basis with CT and MR, or with integrated hardware with CT (PET-CT) (Figure 1.11.6).

Whole-body MR imaging is under evaluation as a diagnostic tool in cancer staging as an alternative to scintigraphy, in staging the skeletal spread of disease and in assessing tumor burden [11].

Whole-body MR imaging is under evaluation as a diagnostic tool in cancer staging as an alternative to scintigraphy, in staging the skeletal spread of disease and in assessing tumor burden [11].

REFERENCES

Breast Health Care Delivery in Low- and Middle-Income Countries

Summary

- Breast cancer is an international problem affecting women of all ages, races, and ethnicities, and it is the most common cancer among women, and worldwide, is the most likely reason that a woman will die of cancer.
- Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths occur in low- and middle-income countries (LMCs).
- The breast cancer burden in LMCs will continue to increase in coming years on the basis of increasing life expectancy and shifting reproductive and behavioral patterns associated with heightened breast cancer risk.
- The Breast Health Global Initiative (BHGI) has developed evidence-based, economically feasible, resource-sensitive guidelines for breast cancer early detection, diagnosis, treatment, and health care systems in LMCs.
- BHGI guidelines can provide a framework for systematic, comprehensive improvement and are intended to assist ministers of health, policymakers, administrators, and institutions in prioritizing resource allocation.
- A systematic program of research to develop appropriate readiness assessment instruments and ideally identify effective implementation strategies is needed to effectively apply BHGI guidelines in LMCs.

Among women, breast cancer is the most common cause of cancer-related death worldwide, with case fatality rates highest in low- and middle-income countries (LMCs).

Breast cancer is the most common cancer among women, comprising 23% of all female cancers that are newly diagnosed in more than 11 million women each year (1). Over 411,000 deaths result from breast cancer annually—accounting for 1.6% of all female deaths from all causes (Figure 1.12.1) (2). Projecting to 2030, the global annual burden of new breast cancer cases will be 1.5 million, and an ever-increasing majority will be from LMCs (3). Approximately 4.4 million women aged 40 years and older will be diagnosed with breast cancer every year in the last five years are currently alive, making breast cancer the single most prevalent cancer in the world (1). Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths in fact occur each year in developing rather than developed countries (3).

Healthy care disparities. Breast cancer already is an urgent public health problem in high-resource regions, and is becoming an increasingly urgent problem in low-resource regions, where incidence rates have been increasing by 2.5% per year (24). In most LMICs, breast cancer incidence rates are increasing at a more rapid rate than in areas where incidence rates are already high. Global breast cancer incidence rates have increased by about 0.3% annually since 1990; by contrast, cancer registries in China are recording annual increases in incidence of 3–4% even in the absence of population-based breast cancer screening (1). Among Asian countries with the most developed data registries, breast cancer rates in Japan, Singapore, and Korea have doubled or tripled in the past decade alone (5). In the urban areas of India, cervical cancer had the highest incidence among female cancers 15 years ago, but has now been overtaken by breast cancer as the most commonly diagnosed cancer among women (6). Despite the younger age structure of most developing countries, breast cancer already accounts for about 45% of the incident cases and 54% of the annual deaths (3).

The breast cancer burden in LMCs will predictably continue to increase in coming years on the basis of 1) increasing life expectancy and 2) shifting reproductive and behavioral patterns associated with heightened breast cancer risk. Even conservatively assuming no change in underlying age-specific rates (Figure 2), there could be a nearly 50% increase in breast cancer deaths in LMCs from 2002 to 2020 due to demographic change alone, with disproportionate shares of that increase occurring in low-resource regions, and the last five years are currently alive, making breast cancer the single most prevalent cancer in the world (1). Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths in fact occur each year in developing rather than developed countries (3).

This statistics probably underestimate the actual rising breast cancer rates, since the few data available from LMICs reveal increases in breast cancer age-specific incidence and mortality rates, especially in recent birth cohorts. This is especially true among urban women and is probably due at least in part to the adoption of Western lifestyles that tend to promote decreased parity, delayed childbirth, decreased physical exercise, and dietary habits associated with earlier menarche, all of which are associated with increasing rates of postmenopausal breast cancer (5,7).

Despite significant scientific advances in breast cancer management, most of the nations of the world face resource constraints that limit their capacity to improve early detection, diagnosis, and treatment of the disease. In LMCs, worsened cancer survival is largely due to late stage at presentation, which leads to particularly poor outcome when coupled with limited diagnosis and treatment capacity (9). Of the over 75,000 new cases presenting for treatment each year in India, between 30% and 70% have locally advanced (Stage III) or metastatic breast cancer (Stage IV) breast cancer at diagnosis (10). By comparison, 38% of European and 30% of American breast cancer cases were reported to be locally advanced at diagnosis in the EUROCARE study and SEEK cancer registry covering 1990 and 2005 (11).

Compounding the problem of late diagnosis, breast cancer case fatality rates are high because LMICs typically lack major components of health care infrastructure and resources necessary to implement improved methods for early detection, diagnosis and treatment of breast cancer (12,13). Although most LMICs have not identified cancer as a priority health care issue, because infectious diseases are a predominant public health problem, cancer care will become an important health problem over the next decades as the control of communicable diseases improves and life expectancy rises (8).

Breast health care guidelines. Evidence-based guidelines outlining optimal approaches to breast cancer detection and treatment have been well-developed and disseminated in several high-resource countries (14,15). These guidelines define optimal practice and therefore have limited utility in LMICs. Optimal practice guidelines may be inappropriate to apply in LMICs for numerous reasons, including inadequate personnel resources, limited health-care infrastructure, lack of pharmacists and critical supplies. Hence, there is a need to develop clinical practice guidelines oriented towards LMICs, specifically considering and adapting to existing health-care resources.

Co-sponsored by the Fred Hutchinson Cancer Research Center and Susan G. Komen for the Cure, the Breast Health Initiative (BHGI) strives to develop evidence-based, economically feasible and culturally appropriate guidelines for breast cancer care in nations with limited health-care resources to improve breast cancer outcomes. The BHGI held three Global Breast Health Care conferences (2002, 2006, 2012) (16) as related to breast care in LMICs. Modelled after the approach of the National Cancer Institute (NCI) and the World Health Organization, the BHGI has developed and applied an evidence-based, culturally sensitive, and cost-effective Breast Health Care guidelines.
such as providers or health units, or has focused on intention without considering self-efficacy or environment. As a conclusion, extension intention without considering self-efficacy such as providers or health units, or has focused on system readiness for innovation and for more studies evaluating implementation of specific interventions [36].

A review of available information strongly suggests a crucial role for research in applying the experience and knowledge of high-income societies to the challenges of women and breast cancer throughout the world. A recent survey of oncology experts from Latin American countries found that 84% of the surveyed experts consider clinical-epidemiologic research development on breast cancer insufficient in their country [37]. The main reasons identified were insufficient economic incentives and lack of available time.

Very little research on guideline implementation has been done in LMICs. It is necessary to see whether the basic frameworks and instruments being described in high-income countries apply in these very different environments and what adaptation is needed to make them both valid and feasible. A systematic program of research to develop appropriate readiness assessment instruments and identify effective implementation strategies is now needed in a variety of LMICs. As the adoption, implementation and maintenance of the new evidence-based principles embodied in the BHGI guidelines progresses, it is critical that careful evaluation be undertaken in the efforts to learn about effectiveness and efficiency are captured. It is precisely because resources are scarce in these countries that it is even more imperative for LMICs to adopt effective practices as quickly as possible, and that implementation approaches are designed with limited resources in mind [31].

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The common problems reported by all countries are:
- the advanced stages of diagnosis of cancer and the need for early detection programs;
- the need to improve access, availability and quality of cancer treatment centres, particularly outside of big cities;
- limited access to affordable cancer drugs;
- weak surveillance and cancer registry systems;
- inadequate opportunities for training and continuing education; and
- the need to increase the public health priority and resources for cancer in the public health agenda.

PAHO has been providing technical cooperation to countries in Latin America and the Caribbean, and responding to these problems and the needs expressed by the Ministries of Health. The main areas of cooperation have been in creating comprehensive national cancer control plans, cervical cancer prevention, tobacco control and radiotherapy services. As part of the Alliance for Cervical Cancer Prevention, PAHO has been assisting countries in improving the quality and coverage of screening programs and testing alternative screening approaches. The lessons learned from this work have culminated in the development of a Regional Strategy for Cervical Cancer Prevention and Control, which provides policy and technical guidance for comprehensive programs, and is anticipated to be presented to the 2008 PAHO Directing Council. In the sub-region of Central America, the Ministers of Health have called for the creation of a sub-regional cancer plan, which is being coordinated by PAHO through a participatory process with the Ministries of Health. This subregional plan will elevate the political and technical commitments for national cancer programmes, as well as solidify a sub-regional response for common issues on cancer prevention, early detection, treatment and palliative care. PAHO continues to evaluate and improve the quality of radiation therapy through its longstanding radiological health program.

With an aging population and corresponding rise in cancer burden in Latin America and the Caribbean, health systems will need to be equipped to control cancer. The challenges remain in having adequate resources, applying current and new knowledge and sustaining the political will to achieve effective cancer control.

Website: www.paho.org
Etiology of Cancer
Chapter 2.1: Identifying Human Carcinogens

The first step in cancer prevention is to identify the causes of human cancer. Carcinogen identification involves the scientific evaluation of epidemiological studies, animal bioassays, and mechanistic and other relevant data. Carcinogen identification is an important activity at IARC (the IARC Monograph) and at several national health agencies.

Identifying Human Carcinogens

Section 2 - etiology of cancer

Carcinogen identification programmes should avoid real or apparent conflicts of interests in order to maintain public confidence in the integrity of their evaluations.

Identifying a carcinogen involves the detection of a compound that is capable of causing cancer while an exposure to that compound is present or has occurred.

Carcinogen identification programmes are developed during an IARC meeting of experts who conduct the original scientific research. The experts are selected on the basis of knowledge, experience, and absence of real or apparent conflicts of interests. The experts work in subgroups of toxicologists and pathologists, subsections of exposure data, and several other relevant data. Each giving insight into the biology of cancer and helping to identify susceptible individuals and development stages. Carcinogen identification programmes are a worldwide scientific endeavor that has involved more than 100 scientists from more than 50 countries.

IARC Monographs are developed during an 8-day meeting whose objective is peer review and consensus. Before the meeting, each expert writes a portion of the original scientific research related to his or her area of expertise. At the meeting, each expert present their research, discuss their results, and develop a consensus subgroup draft. When the subgroup of epidemiologists has reviewed the pertinent studies of cancer in humans, they characterise this evidence with a set of standard descriptors that span a range of levels of evidence.

Limited evidence of carcinogenicity: A causal interpretation is credible, but chance, bias, or confounding cannot be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available evidence is not strong enough to rule out a causal relationship at all levels of exposure.

Evidence suggesting lack of carcinogenicity: Several adequate studies are mutually consistent in not showing a positive association at any level of exposure.

Evidence showing lack of carcinogenicity: Several adequate studies are mutually consistent in showing a positive association at any level of exposure.

For these reasons, long-term studies in experimental animals generally provide the means of assessing potential risks to humans. In these studies, exposures can be tightly controlled and confounding factors can be excluded. It is also possible to develop an organ or organ system that may be potential sites of carcinogenic activity. The use of animal studies is based on the physiological similarity that exists across mammalian species and on the plausible scientific assumption that agents causing cancer in animals will have similar effects in humans. In evaluating a body of cancer studies in experimental animals, the key scientific question is whether the results can plausibly be generalised to humans, as indicated by replication in independent studies in different experimental systems and species.

Mechanistic studies and other relevant data are used to assess the correspondence of response between animals and humans. Toxicokinetic studies allow cross-species comparisons of absorption, distribution, metabolism, and elimination. Mechanistic studies attempt to elucidate the multiple cellular processes involved in tumour development. This has the potential to improve the analysis of studies in both humans and experimental animals. To provide experimental carcinogenicity evidence using similar standard descriptors.

For example, it is often difficult to attribute causality to a single factor or to rule out small risks below a study’s level of sensitivity. In addition, cancer’s latent period implies that many years of preventative human exposure studies become available.
At the same time, another subgroup of experimental scientists reviews the mechanistic and other relevant data to characterise this evidence. Decisions about reducing exposure to suspected carcinogens are sometimes controversial, in part because the available data often cannot identify human carcinogenicity with certainty and because the costs and the benefits of exposure reduction go to different segments of society. For this reason, it is important that carcinogen identification programmes implement strong measures to avoid real or apparent conflicts of interests so that the public can have utmost confidence in the integrity of these classifications [19-20].

Table 2.1.1: Some examples of carcinogenic agents

<table>
<thead>
<tr>
<th>Some examples of carcinogenic agents</th>
<th>Some agents that are probably carcinogenic to humans</th>
<th>Some agents that are probably not carcinogenic to humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals</td>
<td>Benzene, 1,3-butadiene, formaldehyde, vinyl chloride</td>
<td>Ethylene oxide, 1,3-butadiene, formaldehyde</td>
</tr>
<tr>
<td>Complex mixtures</td>
<td>Aflatoxins, crocetin, storks</td>
<td>PCBs, crocetin, emissions from high-temperature frying</td>
</tr>
<tr>
<td>Occupations</td>
<td>Painting, chimney sweepers, coal gasification, coke production</td>
<td>Petroleum refining, handwriting</td>
</tr>
<tr>
<td>Metals</td>
<td>Arsenic and compounds, beryllium and compounds, cadmium and compounds, aluminium</td>
<td>Arsenic and compounds, beryllium and compounds, cadmium and compounds, aluminium</td>
</tr>
<tr>
<td>Particles and Fibres</td>
<td>Asbestos, crystalline silica, wood dust</td>
<td>Diesel engine exhaust</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>DES, estrogen progesterone monosulphate, thalassemia, phuselium</td>
<td>Androgenic lindane, steroids, chlorophenol</td>
</tr>
<tr>
<td>Radiation</td>
<td>Radon, solar radiation, Rn-222, Rn-220</td>
<td>Radon, solar radiation, Rn-222, Rn-220</td>
</tr>
<tr>
<td>Biological agents</td>
<td>Hepatitis B and C, human papillomaviruses type 16 and several others</td>
<td>Hepatitis B and C, human papillomaviruses type 16 and several others</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Tobacco smoke (biologically active), oestrogen, nitr, nitro-benzoic compounds, household combination of coal</td>
<td>Tobacco smoke (biologically active), oestrogen, nitr, nitro-benzoic compounds, household combination of coal</td>
</tr>
</tbody>
</table>

Tobacco Smoking

Summary

- Tobacco smoking causes 13 different cancers of the head, neck, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, esophagus, stomach, colon, rectum, urinary bladder, kidney and uterine cervix, and myocardial infarction (MI) [1]. In addition, in vitro and in vivo animal research also shows tobacco-related cancer of the lung [12]. Furthermore, the detrimental effects of tobacco use, smoking in particular, are seen in the causation of other important chronic conditions: cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and pulmonary artery/venous disease [3].

- In the year 2000, 1.42 (95% CI 1.27–1.57) million cancer deaths in adults (≥30 years) were reported worldwide due to smoking [4]. This global estimate translated into a proportion of cancer mortality attributable to smoking of 21%, representing 32% and 8% of adult cancer mortality in males and females respectively. In high-resource countries, tobacco smoking has been estimated to cause approximately 30% of all human cancers [5-7]. Table 2.2.1 shows the regional distribution of cancer mortality attributable to smoking, indicating higher values in more developed regions, where widespread consumption of cigarettes had an earlier start in the 20th century. A pronounced disparity in cancer mortality attributable to smoking is seen between males and females, reflecting substantial sex-related mortality attributable to the fact that in most countries women took up smoking a few decades after men and never reached their consumption levels.

- Lung cancer has the highest smoking-attributable fraction among all cancers, both in males and females. Lung cancer is the strongest determinant of excess lung cancer risk in smokers, with risk increasing proportionally with the number of cigarettes smoked. Tobacco smoking raises the excess risk of all histological types of lung cancer.

- Pooling estimates from a recent meta-analysis of smoking and cancer shows, persuasively, very similar risks of cancer associated with smoking in males and females.

- Tobacco smoke is the most common source of carcinogens to humans, including polycyclic aromatic hydrocarbons (i.e. benzo[a]pyrene) and tobacco-specific nitrosamines (i.e. NNK). The chronic presentation of carcinogens to the airway epithelial cells, through sustained smoking, can lead to molecular lesions which, in the presence of reduced metabolic detoxification, can diminish repair capability, overwhelming cellular defences and leading to lung cancer.

- About 1.3 billion people smoke globally, making tobacco a major avoidable cause of disease and mortality worldwide. Approximately 150 million deaths from tobacco use are projected worldwide for the year 2020, 80% of which will occur in less-developed regions. About 1.3 billion people smoke globally, achieving tobacco abstinence in the future, at reducing tobacco use. Given the number of people in the world population in 1995 (including users of chewing tobacco) and the leading cause of death attributable to tobacco smoking, the projected population of daily smokers in 2015 years of age to be 29% of the world population in 1995 (including users of cigarettes and/or bidis in South Asia). The percentage of daily smokers residing in less-developed areas of the world, with wide variations in prevalence across regions in both males and females, but with overall prevalence being higher in males (47%) than in females (11%). However, the proportion of male daily smokers 20-years of age can be significantly higher than the above average in many countries: 82% in Indonesia, 78% in the Philippines and 72% in Colombia, to illustrate a few high estimates. The percentage of daily smokers 20 years of age is lower in the European Union but with contrasting differences by sex and across countries (Figure 2.2.2). The preceding data suggest that if smoking patterns continue unabated, the habit will cause approximately 1 000 000 deaths this century, representing a tenfold increase over the previous century [12]. These data also highlight how large the number of people that would benefit from interventions aimed at reducing tobacco use. Given the number of smokers worldwide, achieving tobacco abstinence is an urgent public health priority with no geographic limits.

- World production of tobacco is approximately 6.6 million tonnes annually, with China being the leader in production (41% of total) [13].

WHO Region* Smoking-Attributable Cancer Mortality

<table>
<thead>
<tr>
<th>Region</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>133 000</td>
<td>49</td>
<td>144 000</td>
</tr>
<tr>
<td>Europe B</td>
<td>72 000</td>
<td>9 000</td>
<td>81 000</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(India and others)</td>
<td>174 000</td>
<td>16</td>
<td>190 000</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>45 000</td>
<td>2 000</td>
<td>47 000</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>131 000</td>
<td>26</td>
<td>211 000</td>
</tr>
<tr>
<td>Western Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>225 000</td>
<td>40</td>
<td>272 000</td>
</tr>
<tr>
<td>Western Pacific</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>69 000</td>
<td>18</td>
<td>87 000</td>
</tr>
<tr>
<td>Eastern Mediterranean B</td>
<td>12 000</td>
<td>7</td>
<td>16 000</td>
</tr>
<tr>
<td>Eastern Mediterranean B</td>
<td>26 000</td>
<td>3</td>
<td>29 000</td>
</tr>
<tr>
<td>Americas B</td>
<td>68 000</td>
<td>17</td>
<td>60 000</td>
</tr>
<tr>
<td>Western Pacific (China and others)</td>
<td>209 000</td>
<td>55 000</td>
<td>264 000</td>
</tr>
<tr>
<td>Africa E</td>
<td>23 000</td>
<td>5 000</td>
<td>28 000</td>
</tr>
<tr>
<td>Africa D</td>
<td>5 000</td>
<td>4 000</td>
<td>9 000</td>
</tr>
<tr>
<td>Americas D</td>
<td>2 000</td>
<td>3 000</td>
<td>5 000</td>
</tr>
</tbody>
</table>

Table 2.2.1: Estimated cancer mortality attributable to smoking by WHO Region in 2000.

* A, very low child mortality and low adult mortality; B, low child mortality and high adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.

Chapter 2.2: Tobacco Smoking - 111
Table 2.2.2 | Highest and lowest lung cancer age-standardized (world) incidence rates (per 100 000) in males and females by continent as reported in CI5, Vol IX

<table>
<thead>
<tr>
<th>Continent</th>
<th>Country/Location</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>Tunisia, Centre</td>
<td>371.9</td>
<td>2.05</td>
</tr>
<tr>
<td>Algeria</td>
<td>199.1</td>
<td>1.05</td>
<td>6.3</td>
</tr>
<tr>
<td>Zimbabwe, Harare</td>
<td>6.8</td>
<td>0.69</td>
<td>6.3</td>
</tr>
<tr>
<td>America</td>
<td>USA, New Orleans Black</td>
<td>96.6</td>
<td>3.30</td>
</tr>
<tr>
<td>North</td>
<td>USA, Kentucky</td>
<td>90.1</td>
<td>0.84</td>
</tr>
<tr>
<td>Argentina, Bahia Blanca</td>
<td>45.5</td>
<td>2.42</td>
<td>6.3</td>
</tr>
<tr>
<td>Central &amp; South</td>
<td>Brazil, Sao Paulo</td>
<td>33.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Asia</td>
<td>Turkey, Isan</td>
<td>76.5</td>
<td>0.98</td>
</tr>
<tr>
<td>China, Guangzhou City</td>
<td>71.9</td>
<td>1.19</td>
<td>6.3</td>
</tr>
<tr>
<td>Europe</td>
<td>Poland, Kielce</td>
<td>76.9</td>
<td>1.39</td>
</tr>
<tr>
<td>Croatia</td>
<td>72.1</td>
<td>0.67</td>
<td>6.3</td>
</tr>
<tr>
<td>Oceanico</td>
<td>French Polynesia</td>
<td>62.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Australia, Northern Territory</td>
<td>51.4</td>
<td>0.07</td>
<td>6.3</td>
</tr>
<tr>
<td>Lowest rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>Zimbabwe, Harare</td>
<td>9.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Algeria, Kyalanda</td>
<td>4.8</td>
<td>0.84</td>
<td>6.3</td>
</tr>
<tr>
<td>America</td>
<td>USA, California, L.A.: Hispanic</td>
<td>23.2</td>
<td>0.66</td>
</tr>
<tr>
<td>North</td>
<td>USA, New Mexico: Amer. Indian</td>
<td>12.2</td>
<td>0.91</td>
</tr>
<tr>
<td>America</td>
<td>Ecuador, Quito</td>
<td>7.9</td>
<td>0.56</td>
</tr>
<tr>
<td>Central &amp; South</td>
<td>Peru, Trujillo</td>
<td>5.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Asia</td>
<td>India, Bombay</td>
<td>9.7</td>
<td>0.23</td>
</tr>
<tr>
<td>India, Nairobi</td>
<td>7.3</td>
<td>0.45</td>
<td>6.3</td>
</tr>
<tr>
<td>Europe</td>
<td>Portugal, Porto</td>
<td>30.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Sweden</td>
<td>20.9</td>
<td>0.24</td>
<td>6.3</td>
</tr>
<tr>
<td>Oceanico</td>
<td>Australia, Capital Territory</td>
<td>25.6</td>
<td>1.77</td>
</tr>
<tr>
<td>New Zealand</td>
<td>35.3</td>
<td>0.53</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Table 2.2.3 | Summary: production, imports and exports in 2005

<table>
<thead>
<tr>
<th>Location</th>
<th>Production (tonnes / annum)</th>
<th>Import** tonnes</th>
<th>Export** tonnes</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>2 688 500</td>
<td>69 404</td>
<td>161 850</td>
</tr>
<tr>
<td>Brazil</td>
<td>889 426</td>
<td>7 900</td>
<td>616 468</td>
</tr>
<tr>
<td>India</td>
<td>550 000</td>
<td>1 152</td>
<td>251 570</td>
</tr>
<tr>
<td>Europe</td>
<td>498 916</td>
<td>126 578</td>
<td>233 177</td>
</tr>
<tr>
<td>USA</td>
<td>290 170</td>
<td>281 067</td>
<td>132 978</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>80</td>
<td>1 739</td>
<td></td>
</tr>
<tr>
<td>World</td>
<td>6 580 828</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Fig. 2.2.3 Lung cancer mortality in UK current and former male smokers by age at quitting Adapted from Peto et al., 2000
Table 2.2.4: Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco

<table>
<thead>
<tr>
<th>Substances</th>
<th>Smokeless tobacco ng/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatile aldehydes</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>70 - 100 μg</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>500 - 1400 μg</td>
</tr>
<tr>
<td>Crotonaldehyde</td>
<td>200 - 2400</td>
</tr>
<tr>
<td>N-Nitrosoamines</td>
<td>2 - 1000 ng</td>
</tr>
<tr>
<td>N-Nitrosodimethylamine</td>
<td>3 - 38 ng</td>
</tr>
<tr>
<td>N-Nitrosopyrrolidine</td>
<td>3 - 110 ng</td>
</tr>
<tr>
<td>Polonium 210</td>
<td>8 - 24 ng</td>
</tr>
<tr>
<td>Tobacco-specific nitrates</td>
<td>4 - 22 ng</td>
</tr>
<tr>
<td>N,N-Dimethylformamide (NMN)</td>
<td>45 - 58 000 ng/g</td>
</tr>
<tr>
<td>6-Methyl-N,N-dimethylformamide</td>
<td>6 - 15 000 ng/cigarette</td>
</tr>
<tr>
<td>6-Phenylimidazo[1,2-a]pyridine</td>
<td>6-10 745 ng/cigarette</td>
</tr>
<tr>
<td>6-Nitro-1,2-dimethylnitrosamine</td>
<td>200 - 2400</td>
</tr>
<tr>
<td>Tobacco-specific nitrates</td>
<td>1 - 3 ng</td>
</tr>
<tr>
<td>Metals</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>6 - 60 ng</td>
</tr>
<tr>
<td>Cadmium</td>
<td>7 - 350 ng</td>
</tr>
<tr>
<td>Polonium 210</td>
<td>0.03 - 10 μg/cigarette</td>
</tr>
<tr>
<td>Uranium 235 and 238</td>
<td>2.4 and 1.91</td>
</tr>
<tr>
<td>Arsenic</td>
<td>40 - 120 μg</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td></td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>20 - 40 ng</td>
</tr>
<tr>
<td>Benzo[a]chrysene</td>
<td>20 - 70 ng</td>
</tr>
<tr>
<td>Benzo[b]fluoranthene</td>
<td>4 - 92 ng</td>
</tr>
<tr>
<td>Chrysene</td>
<td></td>
</tr>
<tr>
<td>Benzo[k]fluoranthene</td>
<td>1.7 - 3.2 ng</td>
</tr>
<tr>
<td>Dibenz[a]anthracene</td>
<td>4 ng</td>
</tr>
</tbody>
</table>

Numbers in black derived from IARC Monographs volumes 83 and 89; numbers in red from Hoffman, Hoffman and El-Bayoumy, 2001.

Mechanisms of carcinogenesis

Tobacco smoke is the most common source of carcinogens to humans. It includes about 10^10 cancer-causing components, of which 66 are carcinogens [19,20]. Of these, polynuclear aromatic hydrocarbons and tobacco-specific nitrosamines are the most important. In addition, inducers of reactive oxygen species like NO, NO2, persulfates and nitrosamines initiate, promote or amplify oxidative DNA damage [21-23]. Chemicals such as aromatic amines, benzene and heavy metals, independent of tobacco, established as carcinogens to humans, are present in tobacco smoke as well (Table 2.2.4). Nicotine is excreted in tobacco smoke as a highly reactive entity. Nitrosation of nicotine by tobacco smoke causes the formation of N-nitrosonornicotine (NNN) and nitrosonornicotine (NNK), are carcinogens that induce the formation of adenocarcinomas [17,18].

Fig. 2.2.4: Trends in lung cancer mortality by age group and year of death in males from 1950 to 2000. Trends in standardized mortality rates are presented for death occurring in each 5 year age group with time lag of approximately 25 years. For several of the countries, data for young age groups are not available, and these decreasing trends gradually extend to older age groups (UK, USA, Italy). France, Spain and Japan, decreasing trends were observed among some older age groups but younger age groups show increasing mortality rates.
A recent meta-analysis of 177 case-control studies, 75 cohorts and 2 nested case-control studies reported in IARC Monograph 83 [1] has provided pooled estimates of the risk associated with smoking for 13 different cancer sites [24]. Accordingly, the pooled magnitude of the association in current smokers as compared to never smokers was RR = 8.90 (95% CI 6.73-12.11) for lung cancer, RR = 6.08 (95% CI 3.14-11.53) for laryngeal cancer, RR = 6.79 (95% CI 2.86-15.98) for pharyngeal cancer, 3.57 (95% CI 2.61-4.84) for the upper-digestive tract and RR = 3.43 (95% CI 2.57-4.40) for oral cancer. Table 2.2.5 shows pooled estimates from the above-mentioned meta-analysis stratifying results by sex and demonstrates very similar risks of cancer associated with smoking in males and females.

**Smoking cessation**

A benefit of quitting tobacco smoking in adulthood has been shown for lung cancer and other major cancers causally associated with the habit (Figure 2.2.3). [23] This result emphasizes the need to devise anti-smoking strategies that address avoidance of the habit among the young people as well as reduction of smoking and quitting among adults. In fact, the decline in tobacco consumption during the last 20 years among men in North America and several European countries, and which has resulted in decreased incidence of and mortality from lung cancer, has occurred primarily by increasing quitting at middle age (Figure 2.2.4). The great challenge for the control of tobacco-related cancer, however, lies today in low-income countries, in particular in China and the other Asian countries; the largest increase in tobacco-related cancers has been forecast in this region of the world [23]. Despite growing efforts from medical and public health educators and the growing involvement of non-governmental organizations, the fight against the spread of tobacco smoking among women and in low-resource countries remains the biggest and most difficult challenge of cancer prevention to face in the coming decades.

**REFERENCES**

There is no doubt that passive smoking is carcinogenic to humans. Many national and international scientific expert committees have concluded that passive smoking (also called secondhand smoke, involuntary smoking or environmental tobacco smoke) causes lung cancer in humans. Like active smoking, passive smoking has also been causally associated with a number of non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth.[1,2]

2.3 passive smoking

SUMMARY

Passive smoking causes lung cancer and non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth.

The epidemiological evidence is strongly supported by the chemistry of tobacco smoke, cancer biosystems and mechanisms of tobacco-related carcinogenesis.

Nearly half of never-smokers are exposed to tobacco smoke at home and at work, and bans and restaurants can be particularly polluted. About 10-15% of all lung cancers in never-smokers are attributed to passive smoking.

The WHO Framework Convention on Tobacco Control calls for protection from exposure to tobacco smoke.

After the introduction of strat national smoking bans, beneficial effects on the respiratory and cardiovascular system have been shown.

Case-control and cohort studies published after this comprehensive meta-analysis have further corroborated an increased risk of lung cancer for secondhand tobacco smoke exposure.[9,10] A pooled analysis of the two largest case-control studies of secondhand tobacco smoke exposure in 1200 never-smoking lung cancer patients found an increased risk of lung cancer for secondhand tobacco smoke exposure (OR = 1.01, 95% CI 0.97–1.04).[11] A meta-analysis of seven additional studies with prospectively assessed exposure to secondhand tobacco smoke in workers concluded that the evidence linking passive smoking to lung cancer is statistically significant and consistent across occupational settings.[10]

In the US, 3423 annual lung cancer deaths in never-smokers are attributed to secondhand tobacco smoke exposure. In 2002, the IARC Working Group concluded that the evidence linking passive smoking to seven cancers was significant. Since the US Surgeon General’s Report in 1994 (2), a number of studies have established a causal link between inhaled smoke and lung cancer. The proportion of lung cancer deaths attributable to secondhand smoke in the UK is 12% (see Chapter 2.3.1). In the US, 3423 annual lung cancer deaths in never-smokers are attributed to secondhand tobacco smoke exposure (RR, 0.99, 95% CI 0.93–1.05) in 2002.[9,10] A pooled analysis of the two largest case-control studies of secondhand tobacco smoke exposure in 1200 never-smoking lung cancer patients found an increased risk of lung cancer for secondhand tobacco smoke exposure (OR = 1.01, 95% CI 0.97–1.04).[11] A meta-analysis of seven additional studies with prospectively assessed exposure to secondhand tobacco smoke in workers concluded that the evidence linking passive smoking to lung cancer is statistically significant and consistent across occupational settings.[10]

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Table 2.3.1 Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes, International Organization for Standardization (ISO) a machine-smoking parameters b

<table>
<thead>
<tr>
<th>Compound</th>
<th>Regular</th>
<th>Light</th>
<th>Extra light</th>
<th>Ultra light</th>
<th>Regular/ light</th>
<th>Regular/ extra light</th>
<th>Regular/ ultra light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene (μg/cig.)</td>
<td>222.0</td>
<td>250.0</td>
<td>260.0</td>
<td>296.0*</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8*</td>
</tr>
<tr>
<td>Cadmium (μg/cig.)</td>
<td>438.0</td>
<td>484.0</td>
<td>502.0*</td>
<td>627.0*</td>
<td>0.9</td>
<td>0.9</td>
<td>0.7*</td>
</tr>
<tr>
<td>2-Naphthylamine (ng/cig.)</td>
<td>157.0</td>
<td>147.0</td>
<td>175.0</td>
<td>186.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Nickel (μg/cig.)</td>
<td>34.3</td>
<td>451</td>
<td>74.4*</td>
<td>73.0*</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5*</td>
</tr>
<tr>
<td>Chromene (ng/cig.)</td>
<td>61.0</td>
<td>62.0</td>
<td>121*</td>
<td>82.9*</td>
<td>1.0</td>
<td>0.5</td>
<td>0.7*</td>
</tr>
<tr>
<td>Arsenic (μg/cig.)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>d-Dibenz[a]anthracene (μg/cig.)</td>
<td>22.1</td>
<td>19.5</td>
<td>21.0</td>
<td>21.2</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Formaldehyde (μg/cig.)</td>
<td>378.0</td>
<td>326.0</td>
<td>416.0</td>
<td>431.0</td>
<td>1.2</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>1,3-Benzanthracene (μg/cig.)</td>
<td>196.0</td>
<td>185.0</td>
<td>264.0</td>
<td>299.0</td>
<td>1.1</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Benzo[a]pyrene (ng/cig.)</td>
<td>48.8</td>
<td>98.3</td>
<td>92.2</td>
<td>113.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>NNK (ng/cig.)</td>
<td>95.2</td>
<td>153.4</td>
<td>38.3</td>
<td>34.7</td>
<td>0.6</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>NNK 6p (ng/cig.)</td>
<td>23.3</td>
<td>53.9</td>
<td>43.7</td>
<td>45.2</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>LARC Group 2A carcinogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead (ng/cig.)</td>
<td>34.8</td>
<td>39.4</td>
<td>22.3</td>
<td>18.5</td>
<td>1.4</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>LARC Group 2B carcinogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaldehyde (μg/cig.)</td>
<td>1416.0</td>
<td>1654.0</td>
<td>1449.0</td>
<td>1492.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Isopropen (μg/cig.)</td>
<td>1043.0</td>
<td>1164.0</td>
<td>1040.0</td>
<td>1172.0</td>
<td>0.9</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Carbohydr (μg/cig.)</td>
<td>130.0</td>
<td>117.0</td>
<td>149.0</td>
<td>148.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Acrylonitrile (μg/cig.)</td>
<td>78.6</td>
<td>85.6</td>
<td>74.1</td>
<td>81.8</td>
<td>0.9</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Styrene (μg/cig.)</td>
<td>76.0</td>
<td>84.7</td>
<td>87.5</td>
<td>108.0*</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7*</td>
</tr>
</tbody>
</table>

Table 2.3.3 Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes. International Organization for Standardization (ISO) a machine-smoking parameters b


WHO region

<table>
<thead>
<tr>
<th>ALL students who never smoked, % (95% CI)</th>
<th>Exposed to SHS at home, % (95% CI)</th>
<th>Exposed to SHS in places other than home, % (95% CI)</th>
</tr>
</thead>
<tbody>
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<td>WHO region</td>
<td>All students who never smoked, % (95% CI)</td>
<td>Exposed to SHS at home, % (95% CI)</td>
</tr>
<tr>
<td>Africa (n = 103,906)</td>
<td>79.3 (75.8-82.7)</td>
<td>22.6 (19.5-25.61)</td>
</tr>
<tr>
<td>Americas (n = 236,687)</td>
<td>75.4 (72.2-78.6)</td>
<td>24.1 (21.1-27.1)</td>
</tr>
<tr>
<td>Eastern Mediterranean (n = 92,075)</td>
<td>84.4 (82.0-86.8)</td>
<td>35.6 (33.7-37.4)</td>
</tr>
<tr>
<td>Europe (n = 154,759)</td>
<td>69.0 (65.0-73.0)</td>
<td>40.6 (38.7-42.5)</td>
</tr>
<tr>
<td>South-East Asia (n = 91,459)</td>
<td>87.4 (85.8-88.9)</td>
<td>35.2 (32.8-37.6)</td>
</tr>
<tr>
<td>Western Pacific (n = 168,717)</td>
<td>49.8 (47.4-52.2)</td>
<td>37.3 (34.8-40.0)</td>
</tr>
<tr>
<td>Global</td>
<td>72.8 (71.7-73.9)</td>
<td>38.8 (37.7-40.0)</td>
</tr>
</tbody>
</table>

Table 2.3.2 Indicators of exposure to secondhand tobacco smoke

| WHO region | All students who never smoked, % (95% CI) | Exposed to SHS at home, % (95% CI) | Exposed to SHS in places other than home, % (95% CI) |
| WHO region | All students who never smoked, % (95% CI) | Exposed to SHS at home, % (95% CI) | Exposed to SHS in places other than home, % (95% CI) |
| Africa (n = 103,906) | 79.3 (75.8-82.7) | 22.6 (19.5-25.61) | 38.2 (34.2-42.4) |
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| Europe (n = 154,759) | 69.0 (65.0-73.0) | 40.6 (38.7-42.5) | 79.4 (75.8-82.7) |
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| Western Pacific (n = 168,717) | 49.8 (47.4-52.2) | 37.3 (34.8-40.0) | 52.6 (49.5-55.7) |
| Global | 72.8 (71.7-73.9) | 38.8 (37.7-40.0) | 47.8 (46.4-49.3) |

* Determined by answers to two questions: “During the past 7 days, on how many days have people smoked in your home, in your presence?” and “During the past 7 days, on how many days have people smoked in places other than your home?” Students who answered 1 or more days were considered exposed to SHS.

CI = Confidence Interval

** IARC Group 1 carcinogens: Known human carcinogens

** IARC Group 2A carcinogens: Probable human carcinogens

** IARC Group 2B carcinogens: Possible human carcinogens

** IARC Group 3 carcinogens: Not classifiable as to carcinogenicity to humans

** IARC Group 4 carcinogens: Probably not carcinogenic to humans

** N1-nitrosonornicotine; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; ND, not detectable

** Prevalence of smoking in men and women

** Smoking in the household

** Number of smokers

** Smoking by partner(s)

** Number of cigarettes smoked

** Smoking in the workplace

** Presence of secondhand tobacco smoke

** Number of smokers

** Concentration of secondhand tobacco smoke components

** Nicotine

** Respirable particles

** Other markers

** Biomarker concentrations

** Carboxyhaemoglobin

** Cotinine

** Biomarker concentrations

** Concentration of secondhand tobacco smoke components

** Number of smokers

** Smoking in the workplace

** Number of cigarettes smoked

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** Carboxyhaemoglobin

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** Biomarker concentrations

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Table 2.3.7 Indoor air concentration of nicotine (µg/m3) in a variety of workplaces

<table>
<thead>
<tr>
<th>Workplace</th>
<th>Sex</th>
<th>Sampled</th>
<th>Mean A/B</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offices</td>
<td>both</td>
<td>22</td>
<td>940</td>
<td>0.8-22.1</td>
</tr>
<tr>
<td>Restaurants</td>
<td>women</td>
<td>7</td>
<td>43</td>
<td>1.6-21.0</td>
</tr>
<tr>
<td>Restaurants</td>
<td>men</td>
<td>17</td>
<td>63</td>
<td>3.6-34.0</td>
</tr>
<tr>
<td>Bowling alleys</td>
<td>women</td>
<td>3</td>
<td>4</td>
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Table 2.3.8 Exposure to environmental tobacco smoke at work

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<th>Exposures</th>
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Table 2.3.9 Relative risk (RR) and 95% confidence interval (95% CI) of lung cancer among never smokers: a pooled analysis of two large studies.

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Table 2.3.10 Indoor air concentration of nicotine (µg/m3) in a variety of workplaces

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<th>Mean A/B</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offices</td>
<td>both</td>
<td>22</td>
<td>940</td>
<td>0.8-22.1</td>
</tr>
<tr>
<td>Restaurants</td>
<td>women</td>
<td>7</td>
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</tr>
<tr>
<td>Restaurants</td>
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<td>17</td>
<td>63</td>
<td>3.6-34.0</td>
</tr>
<tr>
<td>Bowling alleys</td>
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<td>4</td>
<td>8.0-10.7</td>
</tr>
<tr>
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<td>2</td>
<td>6</td>
<td>10.3-10.7</td>
</tr>
<tr>
<td>Billiard halls</td>
<td>women</td>
<td>2</td>
<td>13</td>
<td>8.9-19.4</td>
</tr>
<tr>
<td>Billiard halls</td>
<td>men</td>
<td>3</td>
<td>3</td>
<td>3.1-11.8</td>
</tr>
<tr>
<td>Bars</td>
<td>men</td>
<td>10</td>
<td>27</td>
<td>7.4-65.4</td>
</tr>
<tr>
<td>Bingo parlors</td>
<td>men</td>
<td>2</td>
<td>3</td>
<td>76.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66.5-81.2</td>
</tr>
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Table 2.3.8 Exposure to environmental tobacco smoke at work

<table>
<thead>
<tr>
<th>Exposures</th>
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</tr>
</thead>
<tbody>
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<td>0.2 little smoke</td>
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<tr>
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<tr>
<td>4+ heavy smoke</td>
<td>3.70 (2.9-4.7)</td>
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Table 2.3.9 Relative risk (RR) and 95% confidence interval (95% CI) of lung cancer among never smokers: a pooled analysis of two large studies.

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Table 2.3.10 Indoor air concentration of nicotine (µg/m3) in a variety of workplaces

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<tr>
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During most of the 20th century, use of oral and nasal snuff tobacco products has been significant in India and other Asian countries, as well as in some parts of Africa, although it has declined in Northern Europe and North America. However, during the last few decades an increase in use has been observed in the United States, and some Northern European countries, in particular among young people.

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Globally, a wide variety of different smokeless tobacco products are used. These may be used on their own, mixed with other products, such as tobacco, licorice, or cinnamon, and are referred to as “spit” or “swish” products (Figure 2.4). The prevalence of use of smokeless tobacco varies substantially not only across countries, but also within countries, by gender, age, ethnicity, and socioeconomic characteristics. In the United States in 2000, 4.4% of men and 0.3% of women were current users of smokeless tobacco products. Current use was more common among young men, non-Hispanic Whites, people of lower attained level of education, southern states and rural areas [1]. The major form of smokeless tobacco used in Sweden is moist snuff (“snus”). In 2004, 20% of men and 5% of women aged 16-75 years used moist snuff and the prevalence of use was higher in young adults, and among manual workers [2].

In India, a large variety of commercial or home-made smokeless tobacco products exist. The practice of chewing tobacco (betel quid) often showed with betel nut in other preparations including area mu is more prevalent than the use of snuff; applying smokeless tobacco products as a dentifrice is also common. According to a 1998–99 survey, 28.1% of adult men and 12.0% of women reported chewing tobacco products [3]. Smokeless tobacco products are also widely used in other countries in Southeast Asia. There are many other products used in other regions and countries, including naswar in Central Asia, paan in Western Asia, maras in Turkey, toombak in Sudan, chīmō in Venezuela and njīm in Alaska [4].

The available studies from countries in Northern Europe and the United States indicate an increased risk of oral cancer for use of smokeless tobacco in the United States, while results of studies in the Nordic countries do not support such an association [5,6]. In the case of esophageal and pancreatic cancer, the available evidence points toward the presence of a causal association, mainly based on the results of the studies from Nordic countries. Results on lung cancer risk are not conclusive, and data for other cancers are inadequate.

Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; cause cancers of the oral cavity, the pharynx, and the esophagus [4]. Several case-control studies from India, Pakistan and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco paste) products, with relative risks as high as 10 [6]. Additional evidence comes from ecological studies showing positive correlations between use of all smokeless tobacco products, rates of oral cancer (e.g. in Sudan, Central Asia and Saudi Arabia), as well as from case reports and case series from different regions across the world, in which cases of oral cancer reported high prevalence of use of smokeless tobacco products [6].

A few studies from India and North Africa support the hypothesis of an association between nasal snuff use and risk of cancer of the oral cavity, the esophagus and the lung [6]. In one study in the USA, men who switched from cigarette smoking to use of spit tobacco (“switchers”) had a 2.6-fold higher mortality from cancer of the oral cavity and pharynx than men who quit using tobacco entirely (“quitters”) [7]. Compared to men who never used any tobacco product, the risk of lung cancer among switchers was increased 5-6 fold.

There are over 30 carcinogens in smokeless tobacco, including volatile and tobacco specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals [4]. Smokeless tobacco product use entails the highest known non-occupational human exposure to the carcinogenic nitrosamines, NNK and NNN [Figure 2.4.2]. Exposure levels are 100 to 1000 times greater than in foods and beverages consumed containing these carcinogens. The uptake of NNK and NNN by smokeless tobacco users has been demonstrated in many studies by detection of their metabolites in urine. Twenty years of smokeless tobacco use would expose its user to an amount of NNK (75-130 mg, or about 1.3 mg/l kg body weight) similar to that which has caused tumours in rats (1.8 mg/l kg body weight), or in some cases to considerably higher exposure to NNK [8].

There is also consistent among the target tissues for cancer in smokeless tobacco users in rats treated with NNK or NNN, since a mixture of NNK and NNN swallowed in the rat oral cavity caused oral tumours, and NNK and its metabolite NNNAl caused pancreatic tumours in rats upon administration in the drinking water, and NHHOH given in the drinking water to rats produces esophageal and lung tumours [5]. Tobacco specific nitrosamines and their metabolites have also been quantified in the urine of smokeless tobacco users, and their levels were generally higher than in smokers [9].

There is a spectrum of risk arising from use of tobacco products that is due to the wide variation in the types used, their chemical composition and the way in which they are used, leading to opportunities for harm reduction initiatives within the field. This is compounded by the fact that tobacco use is marketed in sophisticated ways in high-resource countries and this practice is facilitating to low-resource country markets with some rapidity.

Harm (risk) reduction can be achieved by reduction of dose or change of product. This may involve substitution of one risk for another but may nevertheless lead to a lower overall risk of cancer. A policy concession that switching to smokeless tobacco may benefit cigarette smokers, while certainly true in many cases, has the downside that it may have the side effect of actually increasing the number of continuing smokers. While these arguments are support the notion that a global switch from smoking to smokeless tobacco would reduce global cancer risk over time [10], comparative risk estimates depend on many assumptions, including particular the expected effect of the introduction of new smokeless products in populations where the habit has not been prevalent. Data are available on a possible beneficial effect of switching from smoking to smokeless tobacco in a few studies and models in the United States and Sweden. Overall, there is not enough evidence to support promotion of such products as substitutes for cigarettes in populations with a high prevalence of smoking and no tradition of use of smokeless tobacco.
REFERENCES


The Programme of Action for Cancer Therapy (PACT) was created within the IAEA in 2004 to build upon this experience to enable low- and middle-income countries to introduce, expand and improve their cancer care capacity by integrating radiotherapy into a comprehensive cancer control programme that maximises its therapeutic effectiveness and impact. Such a programme also addresses other challenges such as infrastructure gaps and builds capacity and long-term support for continuous education and training of cancer care professionals, as well as for community-based action.

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To achieve its goals, PACT is being implemented in overlapping stages that raise awareness about cancer, assess cancer control needs, develop demonstration projects and attract donors to establish effective new funding mechanisms beyond those currently available from the IAEA and bilateral or multilateral donors. Through these collaborations, PACT and its partners will place cancer on the global health agenda and comprehensively address cancer control needs in the developing world over the next 10 to 20 years. The IAEA will continue to invest in PACT with personnel and resources as one of its key priorities.

CANCER INSTITUTE PROFILE: PACT/IAEA

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The hypothesis of the contagious nature of a given cancer was envisaged in the beginning of the 20th century, when researchers could prove the transmission of cancer in animals using cell-free filtrates of cancer cells. FeLV and FIV, and a few years later Ros, showed that inoculation of cell-free filtrates from extracts of ill to healthy chickens could lead to development of cancer. Smiley et al. in their studies in 1978 confirmed the contagious nature of certain types of cancers. These findings led to the discovery of several carcinogenic animal viruses, e.g. Rous sarcoma virus, Lusó frog renal carcinoma virus, mammary mouse tumour virus and many more [1]. However, despite the clear indications, cancer could be transmitted from ill to healthy animals, the idea of involvement of infectious agents in carcinogenesis was only a relatively new concept. This was mainly due to the lack of appropriate detection methods, such as electron microscopy and molecular techniques. Despite the isolation of EBV in Burkitt’s lymphoma cells in 1964, it took several years to completely accept the role of EBV in cancer [1]. Around 1970, H. Haas suggested that the link between HIV and cervical cancer. A few years later, Ossmann and de Villiers, within the group of Haas, isolated and characterised the first onco-associated viral type, HPV, which then allowed the identification of several other mucosal HPV types, including HPV16, fully supporting their original idea [2]. Nowadays, HPV is accepted as a necessary cause of cervical cancer.

Epidemiological and biological studies have now conclusively proved that a variety of infectious agents are among the main causes of cancer worldwide. At least six different viruses have been linked to the development of specific types of human cancers. Other infectious agents involved in human carcinogenesis include parasites and zoonotic diseases (Table 2.5.1).

Hepatitis B virus and hepatitis C virus

Hepatitis B virus (HBV) is a small partially double-stranded hepatitis DNA virus that belongs to the Hepadnaviridae. HBV infection is a major public health problem worldwide. Approximately two billion people are infected worldwide, and more than 400 million are chronic (lifelong) carriers of HBV [3]. However, the geographical distribution of chronic cancer rates varies considerably. The majority of chronically infected people live in Southeast Asia and sub-Saharan Africa. HBV infections occur in all age groups, however, most of the chronic infection (70%–80%) occurs during the perinatal period, 25%–30% in infancy or early childhood, and less than 10% in adults [3]. Other risk factors for HBV infection are: margins of infected people live in Southeast Asia and sub-Saharan Africa. HBV infections occur in all age groups, however, most of the chronic infection (70%–80%) occurs during the perinatal period, 25%–30% in infancy or early childhood, and less than 10% in adults [3]. Other risk factors for HBV infection are: 

- Maternal infection through vertical transmission from mother to child (vertical transmission), child to child (horizontal transmission), and contact with infected blood (transfusion, non-sterilized syringes, tattooing, scarification procedures) or blood products.
- Chronic (lifelong) carriers of HBV [3]. However, approximately 15–20% of cancers worldwide have been attributed to infection with HBV, HCV and other viral agents. These include: hepatitis B virus (HBV) or human hepatitis C virus (HCV), cervical cancer and other malignancies associated with human papillomavirus (HPV), lymphomas and others associated with Epstein-Barr virus (EBV). Lassa fever associated with Lassa fever virus (LHFV), Kaposi sarcoma associated with human herpes virus 8 (KHSV), gastric cancer with Helicobacter pylori (H. pylori) and cancer of the urinary tract with Schistosoma haematobium.

- Other infectious agents, e.g. HBV, HCV and HPV, appear to have an indirect role, inducing a chronic inflammatory response. In some cases, chronic HBV infection also has an indirect effect, mediating its effects on cancer risk by lowering host immunity to other oncogenic infections.

- In the last two decades several strategies against cancer-associated infectious agents have been developed. These include antiviral therapy against H. pylori and two prophylactic vaccines against HBV and HCV.
lines (LCIs). EBV can also infect other cell types, including epithelial, but with much less efficiency. EBV is thought to be transmitted orally, and primary infection is generally asymptomatic. However, when the infection occurs during adolescence, EBV can cause infectious mononucleosis, a benign self-limited disease. After remission, EBV remains in infected individuals for the lifetime, making it among the most persistent viruses that infect humans. In individuals with severe inherited or acquired deficiencies in T-lymphocyte immunity or infectious mononucleosis, EBV can infect the cells and lymphoma, and gastric carcinoma [13]. In individuals with severe inherited deficiencies in T-lymphocyte immunity, EBV-infected cells may proceed without immune control and cause Hodgkin disease, non-Hodgkin lymphoma, and gastric carcinoma [13]. EBV-induced transformation growth factor in a complex interaction between viral encoded proteins and the cellular regulatory machinery, and the EBV latent proteins, particularly the Latent Membrane Protein 1 (LMP1), play an important role in this process (Klein E, Kis LL and Klein G, 2007).

Human T-cell lymphotropic virus

Human T-cell lymphotropic virus type 1 (HTLV-1) is part of the deltaretrovirus family and is responsible for the development of adult T-cell leukemia (ATL). Based on the diversity in the nucleotide sequence, HTLV is classified into eight different genotypes (A to H) with different geographical distributions. Studies reported mainly from Asia indicate that HTLV genotypes may influence the HCC outcome. Patients infected with HTLV genotype C being more susceptible to develop HCC. Other genotypes have been identified (HTLV-2-4). HTLV-2 was isolated from a few cases of leukemia and neurological disease, but its pathology is not clear. Little is known about HTLV-3 and HTLV-4. HTLV-1 is endemic in southwestern Japan, Africa, the Caribbean Islands and South America, while it is frequent in Melanesia, Papua New Guinea, the Solomon Islands and in Australia among the aboriginal population.

Cancer

Hepatitis B virus infection (HBV) and chronic injury hypothesis. Persistent infection in few individuals produce chronic hepatitis which may lead to hepatocellular carcinogenesis in a multistep process. Epidemiological studies have clearly shown that H. pylori infection is associated with peptic ulcer disease, gastric cancer and mucosa-associated lymphoma tissue (MALT). In 1994, it was classified as a group 1 carcinogen by the International Agency for Research on Cancer. H. pylori is one of the most common infections in humans, with an estimated prevalence of 50% worldwide and 90% in developing countries. One striking feature of H. pylori biology is its high allelic diversity and genetic variability. To date, an incredibly high number of strains have been described. In addition, the bacteria can undergo genetic alteration during the infection, due to an elevated mutation rate and frequent recombination. Recent developments in this area has shown that this genetic variability, which affects both host immunity and virulence genes, may contribute to host adaptation and persistence of the infection.

Parasites

Two liver flukes, Opisthorchis viverrini and Clonorchis sinensis, have been associated with cholangiocarcinoma in parts of Asia. Infections by these flukes are acquired by eating raw or undercooked freshwater fish containing the infective stage of the fluke. The fluke matures and produces eggs in the small intrapathic ducts. The incidence for cancer causation by O. viverrini is parasite mainly prevalent in Thailand, is stronger than for C. sinensis. The incidence of

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Global burden of cancer attributed to infectious agents

The total of infection-attributable cancer in the year 2002 has been estimated at 1.9 million cases, or 17.8% of the global cancer burden [7]. The principal agents are Helicobacter pylori (5.5% of all cancer), HPV (5.2%), HBV and HCV (4.9%), EBV (1.0%) and HHV8 (0.9%). The proportion of infection-attributable cancer is higher in developing countries (26%) than in developed countries (8%), reflecting the higher prevalence of infection with the major causative agents (e.g. HBV, HP, HPV and HIV), and lack of screening for HPV-related precancerous cervical lesions.

The calculation of attributable fractions is largely based on two parameters, the population prevalence of infection, and the relative risk for developing cancer given infection. These parameters may remain under-estimated for certain infections. For example, HCV seroprevalence surveys tend to over-sample young individuals at low risk of HCV infection (e.g. blood donors and pregnant women), and a review of liver cancer cases, suggested that the attributable fraction of HCV might be higher, particularly in developing countries [20]. Furthermore, the current estimate of non-cardia gastric cancer attributable to Helicobacter pylori is 63%, which is based on a relative risk of 5.9 for Helicobacter pylori strains. However, much higher relative risks observed for certain strains of Helicobacter pylori suggest that the true attributable fraction may be somewhat higher [21].

Fig. 2.5.7 The burden of cancers causally linked to infections in women

Fig. 2.5.8 The burden of cancers causally linked to infections in men

H. pylori infection

Normal gastric mucosa

Gastric atrophy

Intestinal metaplasia

Secondary events

Adenocarcinoma

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**Fig. 2.5.9** Phylogenetic tree of HPyV. The different types of papillomavirus have been grouped in genera according to similarity in HPV sequence. The most-related types of HPV associated with cervical cancer are included in genus Alpha. *Papillon et al.* (2006), Ystologis 204(1):1727. *Papillon et al.* (2006), Ystologis 204(1):1727.
of host immuno-surveillance allowing viral early genes, E5, E6 and E7, result in evasion of tumor suppressors, p53, and retinoblastoma (pRB), respectively [17].

Mechanisms of carcinogenesis

Direct and indirect pathogenic mechanisms have both been implicated for infectious agents involved in human carcinogenesis. HPV, EBV, HTLV, HCV and HBV encode oncoproteins that play a direct role, being able to deregulate fundamental events, e.g. cellular proliferation, DNA repair, apoptosis, chromosomal stability, and the immune response. These virus-induced events are explored by the fact that the replication of their DNA is totally dependent on cellular mechanisms. These infectious agents have developed mechanisms to keep the infected cells alive and in a high proliferative state, even in the presence of cellular stresses and antigens that normally lead to exit of cell cycle and/or apoptosis. In doing so, these viruses facilitate the accumulation of chromosomal abnormalities, leading to long-term cellular transformation, and inhibition of apoptosis. Hence, LMP1 promotes cell immortalization. Therefore, LMP1 acts as a constitutively activated protein 1 (protein 1) activates transcription factor NF-kappaB through a TRAF (Tumour necrosis factor receptor-associated factor) recruitment and CDK (cyclin-dependent kinase) complexes, cycD2/CDK4 or 6. As shown for HPV, EBV and HCV, the expression of pathways and down-regulate MHC class I. The presence in the bacterium genome of a region containing a nitroso compound induces gastric pH, changing the gastric flora and increasing cellular proliferation, and the immune system would drastically reduce the risk of generation of precursor cancer cells. Thus, the carcinogenic potential of these viruses is facilitated by their ability to stimulate cellular proliferation and their efficiency in evading the host immune surveillance.

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A causal association has been established between alcohol drinking and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and, in women, breast (1). An association is suspected for lung cancer. Some studies have shown an increased risk of pancreatic cancer with heavy drinking, but the epidemiologic evidence for this is weak.

For squamous-cell carcinomas of the upper aerodigestive tract (oral cavity, pharynx, larynx, esophagus), a causal relationship was first demonstrated in the mid-1950s (2). In epidemiologic studies of this group of tumours, an effect of heavy alcohol intake and an elevated risk with amount of drinking has been consistently shown. A synergism between alcohol drinking and tobacco smoking was demonstrated in the 1970s, and has since become a paradigm of interaction of two environmental factors in human carcinogenesis. A carcinogenic effect of alcohol drinking independent from that of tobacco (a risk of head and neck cancers in non-smokers) was first reported in 1961 (2), and replicated in a recent large-scale pooled analysis (Figure 2.6.1) (3).

Heavy alcohol intake increases the risk of hepatocellular carcinoma, with the most likely mechanism through development of liver cirrhosis, although alternative mechanisms such as viral hepatitis and a close temporal relationship of alcohol drinking does not appear to increase the risk of non-alcoholic cancers. In the case of ovarian and kidney cancers, the evidence is epidemiologic of a possible protective effect, but further investigation is necessary to clarify the relationships. A reduced risk of non-Hodgkin lymphoma among alcohol drinkers has also been reported. This effect, if real, might differ by lymphoma type, which would contribute to explaining the inconsistencies in results of earlier studies of alcohol and lymphoma.

The major non-neoplastic diseases caused by alcohol drinking include hypertension, haemorrhagic stroke, liver cirrhosis and fibrosis, as well as acute and chronic pancreatitis (1). In addition, alcohol drinking is a major cause of several types of alcohol consumption during pregnancy is associated with various adverse effects including fetal alcohol syndrome, spontaneous abortion, low birth weight, prematurity and intravenous gestational abotion. On the other hand, there is strong evidence that moderate consumption of alcohol reduces the risk of ischemic heart disease, ischemic stroke and cholecystitis.

A global assessment of the burden of alcohol drinking on human health is complicated by several factors, including (i) the background rate of the major diseases, including ischemic heart disease and liver cancers, (ii) the age-distribution of the population, since the incidence of many alcohol-related injuries decreases with age while that of cancer and ischemic heart disease increases with age and (iii) the pattern of consumption, since the protective effect on ischemic heart disease is not present at high levels of intake. Further comprehensive assessment of the number of deaths either caused or prevented by alcohol drinking has been conducted within the WHO Global Burden of Disease project (4). According to this estimate, in 2000 in developed countries the drinking of alcohol was responsible for 185 000 deaths among men, while it prevented 27 000 deaths in men for the same year. For women in developed countries, 29 000 deaths were prevented compared with the 142 000 caused by alcohol. The picture is different in developing countries, because of a lower burden of cardiovascular disease and a greater role of injuries. Alcohol drinking is responsible for 1,324,000 extra deaths among men and 301,000 among women. The global burden of alcohol-associated mortality therefore represents 1,645,000 deaths, or 3.2% of all deaths.

The mechanisms by which alcohol drinking exerts its carcinogenic effects are not fully elucidated, although possible mechanisms include the production of reactive oxygen and nitrogen species and the alteration of folate metabolism.

There is growing evidence that the effect of alcohol is modulated by polymorphisms in genes encoding for enzymes involved in ethanol metabolism, such as alcohol dehydrogenases, aldehyde dehydrogenases and cytochrome P450 2E1, as well as folate metabolism and DNA repair.

For priorities for a research agenda on alcohol-related carcinogenicity would include: (i) the effect of drinking patterns, (ii) investigations on the gastrointestinal cancers in suspected target organs and (iii) elucidation of the role of genetic variants.
differences in acetaldehyde exposure due to the presence of some well-studied common genetic variants with a functional role. Cytochrome P-450 2E1 (CYP2E1) is induced by ethanol, oxidizes ethanol into acetaldehyde, and also activates tobacco procarcinogens including nitrosamines (6). Methyleneetetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which is important for DNA synthesis and methylation. Sequence variants in DNA repair genes such as those on the nucleotide excision pathway, and on the base excision pathway have been studied as susceptibility factors for various cancers. While the study of genetic variants in alcohol metabolizing genes and their association to cancer is a promising area of research (7), it is unclear at present whether the observed associations are true, and whether they will have clinical or public health relevance.

Alcohol drinking is one of the most important known causes of human cancer. With the exception of aflatoxin, for no single dietary factor is there such a strong and consistent evidence of carcinogenicity. In some populations, namely countries of Central and Eastern Europe, where alcoholic intake is thought to be high (Table 2.6.2), the burden of alcohol-associated cancer (and of other alcohol-associated diseases) is substantial. Alcohol consumption is rapidly increasing in large regions of the world, such as East Asia (8). In the case of breast and colorectal cancer, two major human neoplasms, a causal association with alcohol drinking has been established only recently, and the public health implications of these associations have not been fully elucidated. In many countries, people of lower socioeconomic status or education consume more alcohol, which contributes to social inequalities in the cancer burden (9).

Despite its importance in human carcinogenesis, research on alcoholic and cancer mechanisms is only beginning. Priorities for a research agenda on alcohol-related carcinogenicity would include: (i) better epidemiological studies on the effect of drinking patterns (in particular binge drinking, the prevalence of which is increasing in many countries) and of specific alcoholic beverages, (ii) investigations on the risk of cancer in suspected target organs, including pancreatic and kidney cancer, and (iii) elucidation of the role of genetic variants in modifying the risk of alcohol-associated cancer, which would also shed light on possible mechanisms of action.

### Table 2.6.2

<table>
<thead>
<tr>
<th>Country</th>
<th>Beer</th>
<th>Wine</th>
<th>Spirits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic</td>
<td>9.43</td>
<td>9.43</td>
<td>Republic of Moldova</td>
</tr>
<tr>
<td>Ireland</td>
<td>9.24</td>
<td>8.38</td>
<td>Reunion</td>
</tr>
<tr>
<td>Switzerland</td>
<td>7.49</td>
<td>7.16</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>Germany</td>
<td>7.36</td>
<td>6.99</td>
<td>Saint Lucia</td>
</tr>
<tr>
<td>Acquas</td>
<td>6.42</td>
<td>6.42</td>
<td>Macedonia</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>6.16</td>
<td>6.23</td>
<td>Thailand</td>
</tr>
<tr>
<td>Uganda</td>
<td>6.14</td>
<td>5.63</td>
<td>Bahrain</td>
</tr>
<tr>
<td>Denmark</td>
<td>6.02</td>
<td>5.07</td>
<td>Latvia</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>5.97</td>
<td>4.95</td>
<td>Haiti</td>
</tr>
<tr>
<td>Belgium</td>
<td>5.90</td>
<td>4.78</td>
<td>Belarus</td>
</tr>
</tbody>
</table>

Table 2.6.2 Areas with the highest alcohol consumption (APC) in litres of pure alcohol by alcoholic beverage type.  
Adapted from the WHO Global Status Report on Alcohol, 2004 [7].

**REFERENCES**

Further elements strengthen the association that estrogen increases tumour development. Evidence is accumulating in the literature on the implication of endogenous hormones (particularly sex steroids and growth factors) in the etiology and in the development of several human cancers, especially breast cancer and those of the female reproductive organs (such as ovary and endometrium).

Breast cancer

The incidence of breast cancer is very low in females below the age of 15, and increases very steeply (in the order of about a hundred-fold) by the age of 50. After menopause, the production of estrogens and progesterone from the ovaries ceases, and the increase in breast cancer incidence rates with age slows down. In pre-menopausal women the ovaries stop producing estrogens, which are instead produced by the aromatisation of androgens in the adipose tissues. Obese women have higher estrogen and lower sex hormone binding globulin [SHBG] levels compared to non-obese women, and therefore increased concentrations of bioavailable estrogens to target tissues. Early age at first pregnancy, high parity and prolonged breastfeeding have been associated with decreased risk of breast cancer (Figure 2.7.2) [1], mainly explained by the difference in mammary tissue induced by pregnancy-related hormones. Pregnancy has, however, a double effect on breast cancer risk: a short-term increase and a long-term reduction in risk. The most likely explanation for this double effect is related to the hormone-related differentiation of the cells of the glandular tissues, which reduces the number of susceptible cells (long-term effect), but also stimulates the growth of already existing pre-clinical cancers (short-term effect).

Results from re-analyses and from large-scale prospective epidemiological studies have confirmed a strong implication of endogenous sex steroids in the onset of breast cancer in post-menopausal women (Figure 2.7.3) [2]. Results from these studies showed that women with higher serum estrogen (estradiol, estrone and free estradiol), as well as androgen (testosterone, free testosterone, androsterone and dehydroepiandrosterone) concentrations in the upper quintile of the hormones examined were at about two-fold increase in breast cancer risk compared to women in the lowest quintile. SHBG levels were inversely associated with cancer risk.

It has also been suggested that the association of circulating sex hormone levels may be stronger with breast cancer positive for estrogen and progesterone receptors. A large prospective study also provided strong evidence of an association of serum endogenous androgens (testosterone, androsterone, and DHEAS) with breast cancer risk in pre-menopausal women, but no increase in risk was observed for estrogens [3] (Figure 2.7.4).

Breast Cell Proliferation

Breast cancer risk among pre-menopausal women is related to estrogen concentrations in a non-linear manner [3]. A decrease in breast cancer risk among pre-menopausal women was observed with increasing progestrone levels.

Prolactin is a hormone that is involved in the normal development of the normal breast and in lactation. In vitro, it promotes cell proliferation and survival, and supports tumour vascularity. In vivo, experiments in animals have shown that prolactin increases tumour growth and proliferation of metastases. A number of case-control studies nested within large cohorts have suggested a positive association between breast cancer incidence and prolactin levels, although results have been more consistent in post-menopausal women than in pre-menopausal women [4].

Insulin-like growth factor I (IGF-I) is a polypeptide hormone that is involved in several cellular responses related to cell growth, DNA, RNA and protein synthesis. It has mitogenic and anti-apoptotic properties, and co-regulates the proliferation of many cell types, including breast epithelium [5]. Several epidemiological studies have been published on the relationship of circulating IGF-I to breast cancer risk, with different results. Preliminary studies reported an overall 2-4 fold increase in risk with increasing circulating IGF-I levels only in women who had a diagnosis of breast cancer at a relatively young age before 50 years of age [6]. While more recent studies reported a moderate increase in risk of about 30% in women who had a diagnosis of breast cancer when older than 50 years [7].

Evidence is accumulating in the literature on the implication of endogenous hormones (particularly sex steroids and growth factors) in the etiology and in the development of several human cancers, especially breast cancer and those of the female reproductive organs (such as ovary and endometrium).
Endometrial cancer

Endometrial cancer is a tumor that is very responsive to hormone stimulation. Risk factors such as an early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity suggest a strong involvement of endogenous hormones in endometrial cancer etiology. The long-term estrogen use may well explain the relationship between endometrial cancer and sex steroids [9]. This hypothesis is supported by the finding that endometrial cancer risk is increased in women who have relatively high circulating estrogen concentrations that are not counterbalanced by high progesterone concentrations. This theory was mainly developed from the observation that women with polycystic ovary syndrome who maintain their maximum proliferation rates during the follicular phase of the menstrual cycle (a phase in which progesterone concentrations are very low), and from the fact that the use of estrogen-containing only exogenous hormones (without progesterone) increases the risk of endometrial cancer. While estrogen reduces the production of ovarian epithelium either directly or indirectly through increased ovarian concentrations of IGF-I, all factors that have been associated with increased risk of endometrial cancer.

Ovarian cancer

Most ovarian malignancies arise from the surface epithelium of the ovary. The epithelium is first trapped within the stroma to form inclusion cysts, which are then transformed into endometrial cancer. In vitro and in vivo experiments have shown that ovarian epithelial cell proliferation is stimulated by both androgens and estrogens. Polycystic ovary syndrome (a condition associated with increased ovarian androgen secretion) is associated with an increase in ovarian cancer risk, while oral contraceptive use (which suppressors pituitary luteinizing hormone secretion and androgen production) has a strong and long-lasting protective effect [12]. Only a few prospective epidemiological studies have been published so far on the association between endogenous circulating hormones and ovarian cancer risk, with inconsistent results. However, the sample size of these studies was relatively small.

Table 2.7.1: Relative risk of endometrial cancer in postmenopausal women by quartiles of serum steroid concentrations [11]

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Estrogen</th>
<th>Progesterone</th>
<th>Testosterone</th>
<th>DHEAS</th>
<th>SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(0.38-1.00)</td>
<td>(0.69-2.94)</td>
<td>(0.69-2.94)</td>
<td>(0.88-3.70)</td>
<td>(0.20-1.05)</td>
</tr>
<tr>
<td>2</td>
<td>(1.05-4.24)</td>
<td>(1.16-4.55)</td>
<td>(1.76-9.72)</td>
<td>(0.88-3.46)</td>
<td>(1.71-7.88)</td>
</tr>
<tr>
<td>3</td>
<td>(2.30-6.50)</td>
<td>(2.15-5.00)</td>
<td>(2.15-5.00)</td>
<td>(1.05-4.40)</td>
<td>(0.007)</td>
</tr>
<tr>
<td>4</td>
<td>(4.13-12.00)</td>
<td>(2.15-5.00)</td>
<td>(2.15-5.00)</td>
<td>(1.05-4.40)</td>
<td>(0.007)</td>
</tr>
</tbody>
</table>

The “unopposed estrogen” hypothesis can explain most of the risk factors already identified, such as early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. Strong support for the unopposed estrogen hypothesis comes from epidemiological studies, where case-control and prospective studies indicate an increase in risk with increasing circulating estro- 
diolar concentrations (Table 2.7.1) [10,11].

While androgens do not seem to have a direct proliferative effect on endometrial cells, they do seem to be involved in endometrial carcinoma (possibly through increasing estrogen levels) in women with polycystic ovary syndrome (PCOS) (a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes), which are at higher endometrial cancer risk compared to normal women and tend to develop pre-menopausal endometrial cancer [10]. Obese women are very often insulin resistant, so they constantly have very high levels of circulating insulin in their blood. Insulin induces endome- 
trial cell proliferation, increases IGF-I activity, stimulates androgen synthesis and down-regulates SHBG concentrations [9], all factors that have been associated with increased risk of endometrial cancer.
suggest a relationship between 5-alpha reductase activity and increased prostate cancer risk. Similarly, experiments in animals showed an increase in epithelial prostate cancer cell proliferation with exposure to androgens. All these data suggest that men exposed to elevated circulating levels of endogenous androgens may be at an increased risk of developing prostate cancer, but for the time being this hypothesis has received only very limited support from epidemiological studies. Results from the Prostate Cancer Prevention Trial showed an approximately 23% reduction in prostate cancer prevalence over the 7-year period of intervention in men taking finasteride (α-1-blockade inhibit). With the proportion of high-grade cancers detected in the finasteride group 23% higher than that in the placebo group [14]. Updated analysis of the trial has revealed that finasteride reduces the overall risk of prostate cancer by 30% and reduces the risk of clinically significant prostate cancer, including high-grade tumours. For tumours with Gleason scores ≥7, men in the finasteride arm had a relative risk reduction (RRR) of 27% (RR 0.73 95% CI 0.56, 0.96) [15]. For tumours with Gleason scores ≥7, men in the finasteride arm had an RRR of 27% (RR 0.73 95% CI 0.56, 0.96) [15].

A review of eight prospective studies showed no difference in androgen concentrations between cases and matched controls except for a small increase in androstenediol glucuronide [16]. Studies on circulating sex steroids and prolactin showed very little evidence for the implication of these hormones in prostate cancer etiology [16]. Studies on circulating estrogens and prolactin showed very little evidence for the implication of these hormones in prostate cancer etiology [16].

REFERENCES

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**Summary**

- Oral contraceptive (OC) use reduces the risk of ovarian and endometrial cancer, and this protection persists for at least 20 years after stopping use.
- Current OC use is associated with a modest increase in risk of breast and cervical cancer, which however disappears a few years after stopping use.
- Hormone replacement therapy (HRT) in menopause is associated with an excess in breast cancer risk that levels off 5-10 years after stopping use.
- Unopposed estrogen HRT increases endometrial cancer risk.
- HRT may favourably influence colorectal cancer incidence, but the evidence is not conclusive.

**This chapter considers the cancer risks (and benefits) related to oral contraception and hormone replacement therapy (HRT) use. The use of OCs is associated with a slight increase in breast cancer risk, and ovarian cancer risk is extremely rare in young women, and the risk of cervical cancer is very low.

**Breast cancer**

Most information on the relation between breast cancer and OC use is derived from a collaboration of re-analyses of individual data involving 53,197 women with breast cancer who tested negative for a functionally relevant SNP in the breast cancer susceptibility gene BRCA 1 and 2, and 100,000 control women who tested positive for another SNP in the same gene [3].

In 1984-1985, postmenopausal women from the USA, previous OC users were not at increased breast cancer risk, and there was a negative interaction between combined hormone replacement therapy (CHRT) use and past OC use. In fact, the excess risk for CHRT use was restricted to never OC users, but it was not observed in past OC users. A few other studies from the USA and Europe (e.g. [4]) have suggested that use of more recent, low-dose OC is not materially related to breast cancer risk.

**Cervical cancer**

The cervical dataset includes data from 146,000 women in 14 countries [5]. A few additional cohort [7-9] and case–control studies of OC and breast cancer [10-17] have been published after this collaborative review. In a recent review, the Royal College of Obstetricians and Gynaecologists oral contraception study including 46,000 women (918), as well as in the Oxford FFPA cohort study (99), no relevant association was found between breast cancer incidence and breast cancer risk. However, OCs are carcinogenic to humans based on epidemiological studies [6].

**Ovarian cancer**

An indication of the favourable impact of OCs on ovarian cancer came from an epidemiological study. In several developed countries, young women showed declines in ovarian cancer mortality over the last few decades. Cohort analyses of trends in mortality from ovarian cancer in the USA since 1920 (i.e. the generations who had used OCs) had reduced ovarian cancer rates, and the downward trends were greater in countries where OCs have been more widely used [2]. The protection was similar for newer, low-dose estrogen-progestin pills [41], as well as for various histotypes of ovarian cancer [42].

The overall estimate of protection for ever use is approximately 30%, and the favourable effect of OCs on ovarian cancer persists for at least 20 years after stopping use according to the CASH study, and probably continues for 30-40 years. The RR was 0.8 up to 20 years after stopping use in a pooled analysis of European studies [44]. 0.5 for 11-20 years, and 0.8 for 20 years or more. For cases who stopped OC use after 1990 (i.e. the generations who had used OCs) reduced ovarian cancer rates, and the downward trends were greater in countries where OCs have been more widely used [2]. The protection was similar for newer, low-dose estrogen-progestin pills, as well as for various histotypes of ovarian cancer [42].

**Fig. 2.8.1** Relative risk of ovarian cancer by duration and time since last use of oral contraceptives (OCs). Standardized for age, parity and hysterectomy.

**Fig. 2.8.2** Absolute risk of ovarian cancer by duration and time since last use of oral contraceptives (OCs). Standardized for age, parity and hysterectomy.
Endometrial cancer

OC use also reduces the risk of endometrial cancer by approximately 30% [2,3]. The reduced risk of endometrial cancer persists at least 20 to 30 years after cessation of use. In the CASH study, the OR was 0.5 for 10–14 years since stopping use, and 0.8 for 20 years or more after stopping OC use [2,3]. When duration and recentness of use were evaluated jointly in a case–control study from Washington State [47], longer use (>5 years) was associated with a reduced risk, irrespective of recentness of use. In a Swiss population-based national case–control study [48], the OR was 0.4 for 10–19 years after stopping use, and 0.8 for 20 years or more. In a population-based national case–control study from Sweden [49], the OR was 0.2 for 10 or more years of use, and the subsequent use of hormone replacement therapy did not modify the long-term protective effect of OC. The RR of endometrial cancer death was 0.2 in the 10-year follow-up of the Oxford FPA study [50], and that of incidence was 0.58 after 35 years [9]. Endometrial cancer cases were less frequent in OC users in a case–control study from China [50].

Colorectal cancer

A role of hormonal and reproductive factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer in tumors [51,52]. A reduction in risk for hormone replacement therapy (HRT) in menopause has also been reported [53,54]. Several studies have provided information on OC use and the risk of colorectal cancer. The IFCC Monograph 72 [2] reviewed four cohort studies, three of which showed RR for ever OC use below unity. Among 11 case–control studies, the RR was below unity in nine, and significant in two. In a meta-analysis of epidemiological studies on colorectal cancer published up to June 2000, and including qualitative information on OC use, the pooled RR of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies, and 0.82 from all studies combined [55]. However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer. The RR was 0.8 for ever OC use in a recent Swiss case–control study [56]. Only two studies [57,58] included information on recentness of use, and gave some indication that the apparent protection was stronger for women who had used OCs more recently. However, the RR below unity (RR = 0.79, 95% CI 0.58–0.90) for ever OC users in the 35 years follow-up of the RCGP cohort study [9].

In these analyses, scanty information was available on the type and formulation of OC, but no consistent trend across calendar year of use [which in several countries is a good proxy of type of preparation] was observed.

Lung cancer

A population-based case–control study of 811 women with lung cancer and 922 controls from Germany [58] showed a reduced lung cancer risk (RR = 0.86, 95% CI 0.51–0.92) among ever OC users, in the absence however of any trend in risk with duration of use, age at first use, or calendar year at first use. The RR was non-significantly above unity in the 30-year follow-up of the Oxford FPA cohort study [9] and 1.05 and the 35-year follow-up of the RCGP cohort study [9].

Thus, it is unlikely that any major association is present between OC use and lung cancer risk.

Conclusions: OC use

OC use reduces the risk of endometrial and ovarian cancer by approximately 40%, its protection increases with longer use and is long-lasting. The data for colorectal cancer are suggestive of a protective effect of OC, but not conclusive.

With reference to breast cancer, of particular relevance on a public health level is the absence of a persistent excess breast cancer risk in the medium or long term after cessation of OC use, independent of duration of use. In terms of risk assessment for OC use and indications for prescription, these data indicate that any potential increase in risk during OC use, and in the short term after stopping, is of little relevance for younger women whose baseline breast cancer incidence of the disease is extremely low [6].

The same line of reasoning applies to cervical cancer. In any case, the association between OC and cervical cancer would be of major relevance in low-resource countries, where cervical cancer rates are higher and cervical screening is not adequate [20,29].

HRT and cancer risk

Menopausal has a profound effect on the risk of breast and other female-hormone-related cancers, since the slope of incidence for most of these neoplasms levels off after menopause [61]. The most reliable estimate of the influence of HRT on breast cancer risk is given by a collaborative re-analysis of individual data from 17 epidemiological studies, which included 52,000 women with breast cancer and 108,000 without breast cancer [62], which estimated an increased risk of 2.85% per year of delayed menopause.

With reference to HRT, in the same data set an elevated risk of breast cancer was reported in current and recent users. The risk increased with longer duration of use by about 2.3% per year, but dropped after cessation of use.

Unopposed estrogen use has been strongly related to endometrial cancer risk in observational studies [2], but cyclic combined estrogen/progestin treatment apparently does not reduce such an excess risk. Indeed, combined HRT may increase the risk of colorectal cancer in long-term users and reduce it in overweight areas. However, combined HRT is associated with a higher risk of breast cancer as compared with unopposed estrogens [54,63].

Ovarian cancer risk also appears to be unfavorably influenced by HRT use [64]. Between 1979 and 1998, the Breast Cancer Detection Demonstration Project (BCDDP) cohort study and 329 cases of ovarian cancer were observed [65]. The RR for estrogen-only HRT was 1.6 (95% confidence interval [CI]: 1.2–2.6) for ever users, and rose to 1.8 for 10–19 years of use, and to 2.3 (95% CI: 1.7–3.7) for 20 years of use. In the Million Women Study [18], the RR for current HRT users was 1.23 (95% CI 1.00–1.48). The RR increased with duration, and was similar for various types of preparations. There was no excess risk among past users [RR = 0.97].

In contrast, HRT has been related to decreased colorectal cancer risk, the overall RR being about 0.8 among ever users [2,53,64].

The most valid evidence on cancer risk in users of combined (estrogen and progestagens) HRT derives, however, from clinical trials, including the Women’s Health Initiative [67], a randomized controlled primary prevention trial including 83,056 women aged 50–70 treated with combined CHRT group and 85,012 untreated women. For breast cancer, no difference in risk was apparent during the first 4 years after starting treatment, but an excess risk became evident thereafter, as well as a reduced risk of colorectal cancer. Overall, at 7 years follow-up, 166 breast cancer cases were registered in the CHRT group vs. 124 in the placebo group, corresponding to a RR of 1.24 (95% CI 1.03–1.46).

Data from two other smaller randomized studies on HRT are available, one (Heart and Estrogens/Progestin Replacement Study, HEARS) with combined estrogen/progestin therapy [68], and one (Women’s Estrogen for Stroke Trial, WEST) with estrogen only [69].

Table 2.8.1 Relative risk of ovarian cancer in ever users of oral contraceptives compared with first- or never users, by age at first use and duration of use of oral contraceptives

| Ever-usersa | Duration of use of oral contraceptives | Percent decline in the risk for every 5 years use (95% CI), comparing ever-users
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>&lt;5 years</td>
<td>5–9 years</td>
<td>10 years</td>
</tr>
<tr>
<td>First use before age 20 years</td>
<td>Relative risk (95% CI)</td>
<td>0.71 (0.60–0.84)</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>1009/4381</td>
<td>509/2159</td>
</tr>
<tr>
<td>Mean duration of use</td>
<td>5.4 years</td>
<td>1.9 years</td>
</tr>
<tr>
<td>First use at age 20–24 years</td>
<td>Relative risk (95% CI)</td>
<td>0.69 (0.56–0.87)</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>205/1934</td>
<td>116/5603</td>
</tr>
<tr>
<td>Mean duration of use</td>
<td>5.3 years</td>
<td>1.8 years</td>
</tr>
<tr>
<td>First use at age 25–29 years</td>
<td>Relative risk (95% CI)</td>
<td>0.72 (0.64–0.79)</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>1310/6678</td>
<td>825/3881</td>
</tr>
<tr>
<td>Mean duration of use</td>
<td>4.8 years</td>
<td>1.6 years</td>
</tr>
<tr>
<td>First use at age 30 years or older</td>
<td>Relative risk (95% CI)</td>
<td>0.75 (0.67–0.84)</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>1762/9337</td>
<td>1313/5833</td>
</tr>
<tr>
<td>Mean duration of use</td>
<td>4.2 years</td>
<td>1.6 years</td>
</tr>
</tbody>
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alcohol and the reduced risk seen in the estrogen-only arm of the WHI (RR= 0.77, however no excess breast cancer risk in the combined analysis of the three randomised carcinogenesis [73] probably do not play an important role in lung absence consistent association between HRT and lung 24 cases were observed in the combined HRT treatment (pooled RR=0.64, 95% CI 0.45–0.92, [70]). With reference to colorectal cancer, in the WHI overall, and the placebo groups became apparent 4 effect of stopping use. With reference to colorectal cancer, in the WHI overall, and the placebo groups became apparent 4 effect of stopping use. With reference to colorectal cancer, in the WHI overall, and the placebo groups became apparent 4 effect of stopping use. With reference to colorectal cancer, in the WHI overall, and the placebo groups became apparent 4 effect of stopping use. With reference to colorectal cancer, in the WHI overall, and the placebo groups became apparent 4 effect of stopping use.
CANCER INSTITUTE PROFILE: Instituto Nacional de Enfermedades Neoplásicas (INEN)

The Instituto Nacional de Enfermedades Neoplásicas “Eduardo Cáceres Graziani”, better known by the acronym INEN, is the most important cancer hospital in Peru and perhaps can be placed among the best in South America. The INEN is the main cancer treatment center in Peru, with a catchment area of 20 million people.

The INEN has a patient load of 120,000 per year, with 50% of the cases being cancer. The institute has treated more than 500,000 patients since its inception in 1952. The INEN is a teaching hospital that trains oncologists and medical students. It is also involved in research and clinical trials, collaborating with important groups in the United States and Europe.

website: www.inen.sld.pe
Diet, Obesity and Physical Activity

Summary

- There were great expectations that epide-

miological studies would discover the dietary habits associated with increased or decreased risk of cancer.

- Results from large prospective cohort studies and randomised trials provided evidence that apart from some specific cancers (e.g. stomach cancer), diet accounted for at least a minority of cases. In particular, intakes of fat, of fruit and vegetables and of meat were either not associated or only slightly associated with colorectal, breast, and prostate cancer occurrence.

- New promising research avenues investi-

gated combinations of dietary patterns and of lifestyle (e.g. the Mediterranean pattern), and make greater use of biomarkers of exposure to specific nutrients.

Epidemiological studies have found strong associations between diet and cardiovascular disease that have been largely reproduced in laboratory experiments. These findings have led to the development of efficient primary prevention of ischaemic cardiovascular disease and the discovery of pharmaceuticals that can be used for both primary prevention and treatment (e.g. statin therapy). Ischaemic cardiovascular disease, diet, and cancer remain at present a major and complicated area of study.

In the 1960s, ecological observations pointed to a relation between incidence of stomach cancer and dietary habits. Figure 2.9.1 is an example of such a correlation often found between a diet component and a cancer. Additionally, studies in migrants showed that subjects moving from areas with a low incidence of several cancers, including colorectal and breast cancer, tended to acquire the cancer incidence levels of the host population.

The incidence of and mortality from stomach cancer have declined dramatically over the past 50 years in most industrialised countries. This decline is deemed to be partly due to changes in food preparation (e.g. refrigeration instead of salting or smoking) and nutritional habits (e.g. greater availability of fresh fruits and vegetables). A decline in Helicobacter pylori colonisation of the stomach due to antibiotic treatment for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden.

All these observations led to the hypothesis that nutrition was the predominant non-genetic factor responsible for cancer. In their seminal work on cancer mortality in the USA, Doll and Peto in 1981 estimated that 35% of cancer deaths could be attributable to dietary and nutritional practices, while 30% could be attributable to tobacco smoking. However, the 35% estimate was within a wide “range of acceptable estimates” ranging between 10% and 70%. This estimate of 35% has been widely quoted and used without comment, usually without quoting the wide range of acceptable estimates. Most of the evidence available at the time of Doll and Peto’s report was based on case-control studies, and selection and recall biases have been found to be particularly influ-

ential in nutrition-related case-control studies. More recently, Doll and Peto reviewed new evidence of which 25% of cancer deaths could be due to “diet”, with a range of acceptable esti-

mates of 15 to 35% [5,7]. As their 1981 esti-

mates Doll and Peto provided little detail on how these estimates were computed.

Because ecological and case-control studies are well-known to be prone to biases and difficult to control for confounding factors, more robust studies were needed in order to establish more firmly the possible links between dietary patterns and cancer. Prospective cohort studies were mounted in the 1980s mainly in the USA, and later in other parts of the world. Several randomised trials were also organised in the USA, e.g. on fibre intake and colorectal cancer. Contrary to all expectations, these welldesigned large-scale cohort studies and ran-

domised trials have provided evidence against a major direct role of nutritional factors in cancer occurrence.

Diet, lifestyle and colorectal, breast and prostate cancer

Table 2.9.1 provides a brief overview of the main results of prospective cohort and ran-

domised trials on the diet-cancer association, and on overweight/obesity and lack of activity as risk factors on three major cancers: colorectal, breast, and prostate. Randomised trials provide stronger scientific evidence, but such trials testing the impact of modification of dietary habits on cancer risk are complex and expen-

sive. Also, for ethical and practical reasons, many questions cannot be addressed with trials. Systematic review with meta-analysis of prospective cohort studies is the second best source of evidence. In the absence of meta-

analysis, the prospective cohort studies them-

selves are the best source of evidence, and several reviews [without meta-analysis] have summarised key findings from cohort studies. Case-control studies are not to be taken any account when studies with more robust designs exist. References in the table are intended to provide the reader to useful publications for more detailed literature searches.

Preserved meat and red meat probably increase the risk of colorectal cancer, but rela-

tive risks found so far are of a 30% increase for very high versus very low intakes of red meat. Higher consumption of milk and calcium is associated with a reduced risk of colorectal cancer, with the reverse asso-

ociation probably limited to cancers of the distal colon and the rectum.

For breast cancer, systematic reviews with meta-analysis have found no protective effect of fat intake and breast cancer, but a randomised trial organised within the Women’s Health Initiative trial suggested a small reduction (9%) of borderline significance in breast cancer occurrence with decreased fat intakes [5,9,10].

No association between dietary patterns and prostate cancer has been discovered. The small increase in prostate cancer risk sometimes found with intake of dairy products is probably linked to high calcium intakes rather than to fat intake. Alcoholic beverages are part of the diet, and have been repeatedly found to be risk factors for colorectal cancer, but not for prostate cancer (see Alcohol Drinking, Chapter 2.6).

The associations between dietary factors and colorectal cancer are of particular interest since this organ may be influenced by foodstuffs in transit through the large bowel. By biological substances absorbed by the colorectal epi-

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Lifestyle factors


cancer. The association was downsized from "convincing" in the first WCRF report in 1997 to "probable" in the second WCRF report of 2007.

**Overweight and obesity**

The body mass index (BMI) is the weight in kg divided by the square of the height (in meters) of an individual. According to international standards, male and female adults with a BMI between 25 and 29.9 kg/m² are considered overweight, while those with a BMI equal to or greater than 30 kg/m² are obese. Overweight and obesity represent risk factors of considerable importance for cardiovascular diseases, diabetes mellitus and arthritis. An IARC Working Group [13] found that overweight and obesity were consistently associated with:

- in both men and women: adenocarcinoma of the esophagus, kidney cancer;
- men: colon cancer;
- women: breast and endometrial cancer in post-menopausal women.

The IARC systematic review concluded that there was insufficient evidence for an association of overweight or obesity with prostate cancer (Table 2.9.1). More recent cohort studies [14] and a meta-analysis [15] confirmed findings from the IARC review, and added evidence for a risk of obesity in gallbladder cancer in women.

In most industrialised countries, overweight and obesity are increasing, which will contribute to substantially higher numbers of several cancers in the future. In the coming decades, if there is no reversal in the currently observed trends, obesity and overweight will significantly contribute to further increases in cancer incidence.

**Physical activity**

The evidence for a cancer-preventive effect of physical activity was evaluated by an IARC Working Group [13] which concluded that "there is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast, and preventive effects increase with increasing physical activity in terms of duration and intensity. This protective effect was independent of the effect of body weight. Conversely, physical inactivity is a risk factor for cancer (Table 2.9.1).

To the best of our knowledge, no study has yet tried to estimate the optimal level of physical activity for cancer prevention. However, for colon cancer, the IARC Working Group on physical activity noted that "at least 30 minutes per day of more than moderate level of physical activity might be needed to see the greatest effect in risk reduction" [13]. For breast cancer, the "risk reduction begins at levels of 30–60 minutes per day of moderate-intensity to vigorous activity in addition to the usual levels of occupational and household activity of most women" [13].

**New approaches in the lifestyle-diet-cancer association**

Disease occurrence among people following a strict vegetarian diet (i.e. implying no meat, very low-fat diet, and sometimes no animal products at all) has been extensively studied. The most striking observation is that the incidence of breast and prostate cancer is similar among vegetarians than in the background population, while the incidence of colorectal cancer is about half that of the background population [16]. Of interest also, was the finding that the magnitude of decrease in cancer risk (e.g. the colorectal cancer risk) was substantially more associated with a lean body mass index, regular physical exercise than with vegetarianism. These observations prompted the working hypothesis that what really matters is not a particular nutrient or class of nutrients, but rather the combination of dietary pattern and lifestyle habits that influence the likelihood of disease, and of cancer in particular.

The scientific relevance of this working hypothesis has been demonstrated by recent cohort studies that showed decreased risk in overall mortality, and in cancer and cardiovascular, and non-cancer, non-cardiovascular mortality in subjects who had a diet close to the "Mediterranean dietary pattern", rich in carbohydrates, vegetal oil, fish, fruits and vegetables, and poor in meat and animal fat [17,18]. Each single dietary item typically part of the Mediterranean diet is considered as equally associated with healthy lifestyle, which also contributes to health benefits associated with this dietary pattern. Also in line with the working hypothesis, another prospective study showed that the combination of physical activity, absence of smoking and of obesity, low alcohol intake and higher serum vitamin C levels was associated with lower death rates [20].

Another promising research area is the use of biomarkers of exposure, which are likely to provide more reliable reflections of exposures to a variety of food items and behaviours than questionnaire. For instance, the plasma phospholipid elaidic acid and breast cancer occurrence [21].

Table 2.9.2 lists summary of reviews from cohort studies and randomized trials on food intake, lifestyle habits and colorectal, breast and prostate cancer incidence, potentially immune with meta-analysis of prospective cohort studies. IARC: International Agency for Research on Cancer; meta-analysis of prospective cohort studies, but not meta-analysis CRC: colorectal cancer.
REFERENCES


Ionising Radiation

Summary

- Exposure to ionizing radiation from natural as well as from industrial, medical and other sources can increase the risk of a variety of neoplasms, including leukaemia, breast cancer and thyroid cancer.

- Over 20 years have passed since the nuclear accident at Chernobyl, and it is now estimated that 85 000 cases of thyroid cancer and 28 000 cases of other cancers in Europe as a result of this accident.

- Natural and man-made sources generate radiant energy in the form of electromagnetic waves. Their interaction with biological systems is principally understood at the cellular level. Electromagnetic waves are characterised by wavelength, frequency or energy. Effects on biological systems are determined by the intensity of the radiation, the energy in each photon and the amount of energy absorbed by the exposed tissue.

- Radiation from external sources can cause radiation damage, repair and carcinogenesis. A number of the subatomic particles (neutrons, electrons, 

- Fig. 2.10.1 The spectrum of electromagnetic fields and their use in daily life.

- The electromagnetic spectrum extends from waves at very low frequency (low energy), referred to as ‘electrical and magnetic fields’, to those at very high frequencies, which are often called ‘microwaves’. The high-energy electromagnetic radiation is X- and gamma-radiation, which have sufficient photon energy to produce ionisation i.e. create positive and negative electrically-charged atoms or parts of molecules and thereby break chemical bonds. Other forms of ionising radiation are the subatomic particles (neutrons, electrons, beta-particles and alpha-particles) that make up cosmic rays and are also emitted by radioactive atoms. Non-ionizing radiation is a general term for that part of the electromagnetic spectrum which has photon energies too weak to break chemical bonds, and includes ultraviolet radiation, visible light, infrared radiation, radio- frequency and microwave fields, extremely low frequency (ELF) fields, as well as static electric and magnetic fields.

- Ionising radiation is one of the most intensely studied carcinogenic agents. There are two effects of ionizing radiation, together with the corresponding estimated numbers of years of life lost per radiation-induced case. The current recommendations of the International Commission for Radiological Protection are to limit exposures to the general public to 1 mSv per year, and to occupational exposures and other sources can increase the risk of a variety of neoplasms, including leukaemia, breast cancer and thyroid cancer.

- In a study of nuclear industry workers from 15 countries, 1-2% of cancer-relate
d deaths other than leukaemia may be attributable to low-dose radiation exposure while on the job.

- Internalised radionuclides that emit alpha-particles and beta-particles are carcinogenic to humans. For most people, exposure to ionizing radiation from natural sources, such as fallout from atmospheric nuclear weapons testing, is not considered to be hazardous. However, exposure to high levels of ionizing radiation from diagnostic medical X-rays and the use of radiopharmaceuticals, with lower doses from fallout from atmospheric nuclear weapons testing, is considered to be hazardous.

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exposed as children and adolescents in the most heavily contaminated areas following the accident. There has been anecdotal evidence of rises in other cancers, but such increases could not be differentiated from improvement in registration, diagnosis and reporting [12].

A large increase in the incidence of childhood thyroid cancer was reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially I-131. Cardis et al. [13] studied 275 case patients with thyroid cancer through 1998 and 1300 matched control subjects, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject based on their whereabouts and dietary habits at the time of the accident and in the following days, weeks and years; their likely stable iodine status at the time of the accident was also evaluated. A strong dose–response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk (P<.001). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer risk was three times higher in iodine-deficient populations compared with iodine-supplemented populations [14].

An increased risk of thyroid cancer has been reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially I-131. Cardis et al. [13] studied 276 case patients versus no consumption).

The risk of radiation-related thyroid cancer is associated with exposure to 131I in childhood. A linear dose–response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk (P<.001). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer varied from 3.3 (95% CI = 3.1–9.5) to 8.4 (95% CI = 4.1–17.3), depending on the risk model. A linear dose–response relationship was observed up to 1.5–2 Gy.

The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas (relative risk [RR] = 3.2, 95% CI = 1.9–5.5) than elsewhere. Administration of potassium iodide as a dietary supplement substantially reduced the risk of radiation-related thyroid cancer by a factor of 3 (RR = 0.34, 95% CI = 0.1–0.9) for consumption of potassium iodide versus no consumption). Exposure to 131I in childhood is associated with an increased risk of thyroid cancer. Both iodine deficiency and iodine supplementation appear to modify this risk. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodine in the case of exposure to radioactive iodine in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures.

Table 2.10.3 Various forms and sources of radiation that are carcinogenic to humans (IARC Group 1) or probably carcinogenic to humans (IARC Group 2A)

<table>
<thead>
<tr>
<th>Agent or substance</th>
<th>Cancer site/cancer</th>
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<tbody>
<tr>
<td>X-rays and gamma-radiation</td>
<td>Various → all sites</td>
</tr>
<tr>
<td>Solar radiation</td>
<td>Skin</td>
</tr>
<tr>
<td>Radon-222 and its decay products</td>
<td>Lung, bone, lung, bone, skin</td>
</tr>
<tr>
<td>Lanthane-232 and its decay products</td>
<td>Liver, including haemangiosarcoma, leukaemia</td>
</tr>
<tr>
<td>Radium-226, -228, -228 and their decay products</td>
<td>Bone</td>
</tr>
<tr>
<td>Plutonium-239 and its decay products (tarsessum)</td>
<td>Lung, liver, bone</td>
</tr>
<tr>
<td>Phosphorus-32</td>
<td>Leukaemia</td>
</tr>
<tr>
<td>Neutrons</td>
<td>Various</td>
</tr>
<tr>
<td>Alpha (α) particle-emitting radionuclides</td>
<td>Various</td>
</tr>
<tr>
<td>Beta (β) particle-emitting radionuclides</td>
<td>Various</td>
</tr>
<tr>
<td>IARC Group 1: Carcinogenic to humans</td>
<td></td>
</tr>
<tr>
<td>IARC Group 2A: Probably carcinogenic to humans</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES

Sunlight and Ultraviolet Radiation

Summary

- Sunlight is by far the most significant source of ultraviolet irradiation and causes several types of skin cancer, including cutaneous melanoma, squamous and basal cell cancer, and of cutaneous leukemia.
- Genetically determined sensitivity to sunlight, associated with high propensity to sunburn, past tanning ability, red hair and freckles.
- Artificial sources of ultraviolet radiation have become common in many countries, mainly as sunlamps for indoor tanning purposes. Indoor tanning is associated with increased risk of cutaneous melanoma and of squamous cell cancer when exposure started before 30 years old.
- Sun protection should be based on using sunscreens or protective clothing.

Exposure to sunlight has been shown to be the main cause of skin cancer, including cutaneous melanoma (CM), basal skin cancer (BCC) and squamous skin cancer (SCC), and since 1992 solar radiation has been classified as a Group I carcinogenic agent by the IARC [1]. Approximately 5% of the total solar radiation received at the surface of the earth is ultraviolet range, and the sun is the main source of exposure to UVR for most individuals. Sufficient evidence exists that the ultraviolet radiation (UVR) is the main environmental cause of SCC and BCC. This radiation is also deemed to be the main environmental cause of CM in humans. There are currently no recommendations for “safe doses” for human skin, i.e., there is no threshold UVR dose below which there would not be an increased risk of skin cancer. Sunlight and UVR are also suspected to play a role in cutaneous melanoma, but further evidence of a possible causative association is needed.

Sunlight consists of visible light (400–700 nm), infrared radiation (>700 nm), and UVR. UVR belongs to the non-ionizing part of the electromagnetic spectrum and ranges from 100 nm to 400 nm; 100 nm has been chosen arbitrarily as the boundary between non-ionizing and ionizing radiation. UVR radiation is conventionally categorised into 3 regions: UVA (>315–400 nm), UVR (>280–315 nm) and UVC (>100–280 nm). The quality (spectrum) and quantity (intensity) of sunlight are modified during its passage through the atmosphere. The ozone contained in the stratosphere (10–50 km above the earth’s surface) stops almost all UVR radiation (>290 nm) [UVC] as well as 70% to 90% of the UVR.

On the Mediterranean coast at noon in the summer, the UVR radiation from sunlight consists of about 95% UVA and about 5% UVB. UVB has long been recognized as the carcinogenic component of UVR. Since the end of the 1970s, both UVA and UVB have been shown as having carcinogenic effects, but much more UVA is needed to achieve carcinogenic effects (e.g. DNA damage) similar to those observed with UVB. Also, UVA penetrates deeper into the skin than UVB, and causes biological damage that is qualitatively different from that induced by UVB, and which might also be implicated in skin carcinogenesis.

An individual’s level of exposure to UV varies with latitude, altitude, time of year, time of day, clouding of the sky and other atmospheric components such as air pollution. At the Earth’s surface, compared to UVA, UVR irradiation is more related to latitude (highest around the equator and lowest at the poles), season (highest in hot seasons, lowest in colder seasons), time of day (highest around 10 AM-2 PM solar hours), altitude (higher at altitude than at sea level), and earth surface (e.g. UVR is reflected by snow or by water).

Ozone depletion

Ozone depletion has been caused by substances released into the atmosphere that destroy the ozone (ozone-depleting substances (ODS)). For instance, the chlorofluorocarbons (CFCs) that were used as spray propellants until 1990, when an international ban known as the revised Montreal Protocol came into application between non-carcinogenic substances [2]. The stratospheric ozone levels have decreased annually since the 1970s, especially in the southern hemisphere. Because the atmosphere in the tropics is thinner, the ozone depletion is maximal at the most Northern and most Southern areas, and lowest at the equator. Thus the Northern countries, Australia, New Zealand, Canada, and Russia, all generally populated with light-skinned people, are at higher risk of increased SCC and cutaneous melanoma because of ozone depletion [3].

In the past few years, the ozone layer seems to have stabilised, and current prospects of recovery of the ozone layer are also linked to the evolution of global climate change [4,5].

Acute effects of exposure to sunlight and other sources of UVR

The most common acute skin reaction induced by exposure to sunlight and other sources of UVR is an inflammatory process at skin level expressed as an erythema i.e. skin reddening in light-skinned individuals). With increasing UVR dose, skin erythema develops as sunburn that is often painful and may sometimes be complicated with blisters. The minimal erythemal dose (MED) was the first way to biologically quantify exposure to UVR in humans, and is defined as the minimal amount of energy from sunlight (or other UVR sources) required for producing a qualitatively erythematous response, usually after 24h.

Acquisition of a suntan is the other acute effect. But contrary to many beliefs, an acquired tan offers no protection against skin cancer. An acquired tan is mainly triggered by UVB-induced DNA damage itself, and is thus more an indicator of carcinogenic skin damage than a protection against this damage. It is the constitutive pigment that represents as real protection against the damaging effects of UVR.

UVR is far more efficient than UVA in inducing the synthesis of melanin, and for producing a deep, persistent tan UVB is also one thousand times more potent than UVA for inducing sunburn.

Individual susceptibility to skin carcinogenic damage due to sunlight and UVR

Susceptibility to cargenic effects of sunlight and UVR is highly genetically determined. The most susceptible individuals are those with very pale skin who always burn and never tan when in the sun. These are usually light-skinned females (or solar lentigines) on the face, arms or shoulders are other host characteristics indicative of high sun sensitivity. The latter characteristics are sometimes termed the “Caucasian phenotype,” which has been discovered to be associated with mutations in the MC1R gene. This gene regulates the formation of eumelanin (black or brown) and phaeomelanin (red or yellow) of hair, skin and nails, and may confer resistance to chronic actinic damage. People who have red hair and freckles are at greater risk of actinic keratoses than those who do not [6]. These mutations also lead to the synthesis of phenylalanine (instead of eumelanin) that is red or yellow and is suspected to also play a role in skin cancer occurrence [6].

Individuals with light skin but low propensity to sunburn and who tan easily are much less susceptible to carcinogenic effects of sunlight and UVR. Individuals with naturally pigmented skin (i.e. constitutive pigmentation) have a very low susceptibility to carcinogenic effects of sunlight or UVR. As a result, skin cancer is rare in dark-skinned populations. The rare cutaneous melanomas occurring in individuals with naturally pigmented skin will often develop on the soles of feet or under toenails, as a result of skin insult due to barefoot walking.

Individual susceptibility may be greatly increased by inherited or acquired disorders or by treatments. For instance, subjects with rare inherited defects in DNA repair (e.g. xeroderma pigmentosum) develop hundreds of times more skin cancers. African American subjects are at high risk of developing multiple SCC. Pсорiasis patients treated with PUVA (oral psoralens combined with sessions of UVA irradiation) have a much higher risk of developing SCC as well as BCC. Patients under immune suppression therapy for organ transplant have a high risk of developing skin cancer.

Age and susceptibility to sunlight and UVR

A large body of data shows that in light-skinned populations, susceptibility to carcinogenic effects of sunlight and UVR relevant to cutaneous melanoma (and probably also to BCC) are greater during childhood and adolescence. Studies in migrants indicate that the younger the age at exposure, the greater the risk of cutaneous melanoma in later life [7]. Also, sun exposure during adult life is associated with cutaneous melanoma occurrence only if sun exposure took place during childhood [8]. This age-related susceptibility is most probably related to the immaturity of the skin, i.e. being more vulnerable to UVR-induced damage in younger populations.

Gender and anatomical differences in susceptibility to sunlight and UVR

Sharp gender contrast exists for the body distribution of cutaneous melanomas: in males, most cutaneous melanomas occur on the trunk and shoulders, then on the upper arms and on the face, while in women, most cutaneous melanomas occur on the legs and arms. This may be related to hormonal factors.
melanoma occur on the lower limbs, and then on the upper limbs [11]. The number of acquired nevi is the strongest individual predictor of cutaneous melanoma, and the body distribution of new in young children parallels the body dis-

bination of CM in adults [12]. These findings further underline the importance of childhood exposure to sunlight for the development of CM during adult life. They also illustrate that different body parts have different susceptibility to sun-

ight and UVR that this also varies with gender.

BCC usually occurs on the head and the neck, but recent data show increasing BCC incidence on body sites that are only intermittently sun-

exposed, e.g. the trunk [13]. SCC occurs nearly always on chronically sun-exposed areas, such as the head and the neck.

Sunlight, artificial sources of UVR and human behaviours

Exposure to sunlight or to other sources of UVR encompasses a large variety of behaviours. In the 1980s, epidemiological studies evidenced that SCC was more associated with the chronic sun exposure pattern, i.e. lifetime accumulation of exposure to sunlight (e.g. outdoor workers, farmers), while cutaneous melanoma was associated with the so-called intermittent sun exposure pattern, i.e. subject to spent-off of their time indoors and having brutal acute sun exposures during holidays in sunny areas, with often the pursuit of tanned skin as a “Healthy look” [14,15]. BCC was associated with both exposure patterns.

More recently, it has been suggested that all these behaviours can be grouped into two broad categories distinguishing between non-intentional and intentional sun exposure [16,17]. Non-intentional sun exposure (NSE) represents exposures during daily activities, without will-

ingly acquiring a tan or intentionally spending a long time in the sun. During NISE, skin areas (e.g. outdoor workers, patients under photostimulating treatment) the ability of a fabric to block UVR is called the ultraviolet protection factor (UPF), recommended for individuals highly suscepti-

ble to the damaging effects of UVR (e.g. red-

hared people, patients under photostimulating treatment). The ability of a fabric to block UVR is called the ultraviolet protection factor (UPF), and is sometimes supplemented with the sunbed session are well above what is expe-

rienced during daily life or during sunbath-

ing. Annual UVA doses received by frequent indoor tanners may be 1.2 to 4.7 times that received from the sun, and in addition to those received from the sun. Such powerful sources of UVR radiation probably do not exist on the Earth’s surface, and repeated exposures to high doses of UVA results in new phenomenon in humans. Health hazards associated with repeated exposures to powerful indoor tanning devices remain largely unknown, as this fashion developed quite recently, and the full health effect of such exposure may not be seen for another one or two decades.

A systematic review carried out by an IARC Working Group in 2006 has shown that the risk of cutaneous melanoma is increased by 70% when sunbed use starts about 30 years of age (Figure 2.11.2) [19-20]. This finding is in line with known susceptibility to carcinogenic effects of UVR at younger ages. Recent surveys have revealed that substantial numbers of tanners use indoor tanners without much awareness of the risk of skin damage caused by sunbed use should concern con-

sumers, especially young people and adolescents [19-21].

Sun protection

The main goal of sun protection is to decrease the incidence of SCC, BCC and cutane-

ous melanoma through methods that have in common the reduction of exposure to sunlight and to other sources of UVR. Avoidance of sunshine or exposure to UVR sources, and seeking of shade are the most straightforward sun protection methods. When in the sun, barrier-

ers to UVR usually consist of wearing a hat and clothing, and use of sunscreens. The psychological benefits of sunbed use may simply reflect the genetically determined propensity to sunburn [22,23]. Also, UVR can induce biological damage (such as immune suppression or oxidative damage) at doses lower than those needed to induce an erythema [19].

Observational and randomized studies have provided evidence that during NISE, reduc-

tion of amounts of UVR reaching skin surface through clothing, sunscreen use or reduction of time spent in the sun can decrease the occur-

rence of SCC, and also of sunburns and skin precursor lesions of SCC [e.g. skin keratoses] [24-27].

During SE, however, observational and ran-

domized studies have demonstrated that sunscreen use may have the consequence of increasing the time spent in the sun, mainly because tan acquisition is longer when a sun-

screen is used, and also because it takes more

immunomodulatory components, and upregulated expression of local spontaneous immune responses.

The sun protection factor (SPF) of sunscreens pro-

vides an internationally standardised estimate of the ability of a thin layer of sunscreen to delay the occurrence of a sun-induced skin erythemal reaction. The higher the SPF, the longer the time needed to develop an erythema. Because sunburn occurrence is associated with greater risk of skin cancer, the SPF has been thought to be an indicator of the ability of sunscreens to protect against sun-induced skin carcinogenic phenomena. However, the causal link between sunburn and melanoma is questioned, as this has not been firmly established yet [28]. Sunburns may simply reflect the genetically determined propensity to sunburn and severe sunburns can be an indicator of the ability of sunscreens to delay sunburn occurrence [19].

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time to get a sunburn [24, 28, 29]. So, sunscreen use during UVR exposure actually increases the risk of cutaneous melanoma [and probably also of BCSC] [17]. Sunscreen use during UVR does not decrease incidence and predispose sunseekers to adopt more hazardous sun exposure behaviors, such as sunbathing around noon, when UVR irradiation is maximal [10, 24, 28, 30]. In contrast, during UVR situations, clothing protects against melanoma occurrence and nevi development in children [31]. Hence, sunscreens should be rather used during NSB and in these situations, application onto the skin should be liberal, as the usual tendency is to apply too small a quantity of sunscreen, which results in an actual SPF 3 to 5 times lower than indicated on the bottle.

In this respect, generous application of SPF 15 sunscreen is better than parsimonious application of a sunscreen of higher SPF. If one cannot refrain from intentional sun exposure (essen- tionally for tan acquisition), it is better to avoid using a sunscreen in order to avoid staying in the sun longer than if a sunscreen was not used. It is also better not to sunbathe during the hottest hours of the day, when UVB irra-

Modifiers: 2.3%

15N: 0.1%

35S: 2.9%

55N: 7.3%

Increase in UVB (%)

LATITUDE:

EQUATOR

65N: 6.8%

55S: 9.9%

65S: 11.0%

25N: 1.2%

15N: 0.1%

55S: 9.9%

MC1R variants across populations.


821-833.


821-833.


2.12 \textbf{Electromagnetic Radiation}

\textbf{Summary}

- Extremely low frequency electromagnetic fields generated by electrical power transmission have been associated with an increased risk of childhood leukaemia, but the findings are not conclusive. Even if this association is real, the number of excess cases is likely to be very small.

- Radiofrequency radiation emitted by mobile telephones has been investigated in a number of studies. There is some evidence that long-term and heavy use of mobile telephones is associated with an increased risk of childhood leukaemia and other neoplasms asso-

- With reference to radio frequency, available data do not show any excess risk of brain cancer and other neoplasms associated with the use of mobile phones. With reference to ELF fields, available data allow us to exclude any excess risk of childhood leukaemia.

- To date there is no convincing biological or biophysical support for a possible association between exposure to ELF fields and the risk of leukaemia or any other cancer.

Although a source of exposure to man for many decades, electromagnetic fields (EMF) have seen an unprecedented increase in the number and diversity of sources in recent years ([1], principally extremely low frequency and radiofrequency fields. Sources include all equipment using electricity, television, radio, computers, mobile telephones, microwave ovens, anti-theft gates in large shops, radios and equipment used in industry, medicine and commerce. Static fields and extremely low frequency fields occur naturally, and also arise as a consequence of the generation and transmission of electrical power and through the operation at a range of industrial devices and domestic appliances, the latter often at a greater field intensity. Exposure to extremely low frequency fields is mainly from human-made sources for the generation, transmission and use of electricity. Occupational exposure occurs, for example, in the electric and electronics industry, in welding and in the use and repair of electrical motors. Environmental exposure to extremely low frequency fields occurs in residential settings due to proximity to electricity transmission lines and use of electric appliances. Levels of exposure from many environmental sources are typically low ([2].

Exposure to radiofrequency radiation can occur in a number of ways. The primary natural source of radiofrequency fields is the sun. Manmade sources, however, are the main source of exposure. Radiofrequency fields are generated as a consequence of commercial radio and television broadcasting and from telecommunications facilities. Radiofrequency fields in the home are generated by micro-wave ovens and burglar alarms. However, mobile telephones are now the greatest source of radiofrequency exposure for the general public. A major obstacle in conducting epidemiological studies of EMF is the difficulty in accurately measuring the dose and exposure pattern. This is particularly true in the case of mobile telephones, where the dose emitted by phones has been changing between models and over time, and the use pattern of left or right side also varies within individuals. Measuring exposure to total EMF is also fraught with difficulty, including study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study.

Results of natural analyses of the relation between mobile phone use and risk of specific tumour types in some of the participating countries have indicated that in most studies, the CIR related to ever having been a regular mobile phone user was below 1, in some instances statistically significantly. This possibly reflects participation bias or other methodological limitations.

For glioma, although results by time since start of use and amount of phone use vary, the number of long-term users is small in individual countries and results are therefore comparable. Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of glioma related to use of mobile phones for a period of 10 years or more on the side of the head where the tumour developed ([5]. This finding could either be causal or artifactual, related to differential recall between cases and controls. For meningioma and acoustic neuroma, most National studies provided little evidence of an increased risk. The numbers of long-term heavy users in individual studies were even smaller than for glioma, however; and prevent any definitive conclusion. A number of methodological limitations are essential in the interpretation from the study. For parotid gland tumours, no increased risk was observed overall for any measure of exposure investigated. In a combined analysis of data from Sweden and Denmark ([7], a non-significantly increased risk of benign tumours was observed for parotid use of 10 years or more, while a decreased risk was seen for controls use, possibly reflecting differential recall between cases and controls. In the Israeli study, where study subjects tended to report substantially heavier use of mobile phones, results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumours. Additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm these findings. In respect of the work environ-

- Separate studies have been carried out for acoustic neuroma, glioma, meningioma and tumours of the parotid gland. The studies used a common core protocol and were carried out in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Details of the study protocol and procedures have been pub-

- The INTERPHONE study is an ambitious project aiming at assessing the risk of cancer from mobile telephones. A number of methodological issues have been addressed, including study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study. For glioma, although results by time since start of use and amount of phone use vary, the number of long-term users is small in individual countries and results are therefore comparable. Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of glioma related to use of mobile phones for a period of 10 years or more on the side of the head where the tumour developed ([5]. This finding could either be causal or artifactual, related to differential recall between cases and controls. In the Israeli study, where study subjects tended to report substantially heavier use of mobile phones, results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumours. Additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm these findings. In respect of the work environ-

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- Fig. 2.12.1 The spectrum of electromagnetic fields and their use in daily life.

Table 2.12.1 Frequency bands and their uses.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Class</th>
<th>Type of device or service</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 – 300 kHz</td>
<td>LF (low)</td>
<td>LF broadcast and long-range radio</td>
</tr>
<tr>
<td>300 – 3,000 kHz</td>
<td>MF (medium)</td>
<td>AM radio, radio navigation, ship-to-shore</td>
</tr>
<tr>
<td>3 – 30 MHz</td>
<td>HF (high)</td>
<td>CB radio, amateurs, HF radio communications and broadcast</td>
</tr>
<tr>
<td>30 – 300 MHz</td>
<td>VHF (very high)</td>
<td>FM radio, VHF TV, emergency services</td>
</tr>
<tr>
<td>300 – 3,000 MHz</td>
<td>UHF (ultra high)</td>
<td>UHF TV, paging, mobile telephones, amateur radio</td>
</tr>
<tr>
<td>3 – 30 GHz</td>
<td>SHF (super high)</td>
<td>Microwave communication, point to point microwave communications</td>
</tr>
<tr>
<td>30 – 300 GHz</td>
<td>EHF (extremely high)</td>
<td>Radar, radioastronomy, short-link microwave communications</td>
</tr>
</tbody>
</table>

Fig. 2.12.2 Child and cellphone.
in the broadcasting, transport and communication industries, and in antenna repair, military personnel (e.g. radar operators) and police officers (utilizing traffic control radars). These are also industrial processes that use radiofrequency fields, including dielectric heaters for wood lamination and sealing of plastics, industrial induction heaters and microwave ovens, medical diathermy equipment to treat pain and inflammation of body tissues, and electrosurgical devices for cutting and welding tissues.

Cancer causation

Several expert groups have recently reviewed the scientific evidence concerning the carcinogenicity of extremely low frequency fields [8-10]. A number of epidemiological studies on childhood leukaemia indicate a possible relationship between risk and exposure to extremely low frequency fields. Studies of adult cancers following occupational or environmental exposures to extremely low frequency fields are much less clear. There is little experimental evidence that these fields can cause mutations in cells. Mechanistic studies and animal experiments do not show any consistent positive results, although sporadic findings concerning biological effects (including increased cancer in animals) have been reported. IARC has classified extremely low frequency fields as possibly causing cancer in humans (Group 2B), based on childhood leukaemia findings [11].

The evidence for the carcinogenicity of radio-frequency fields is even less clear. A few epidemiological studies in occupational settings have indicated a possible increase in risk of leukaemia or brain tumours, while other studies indicated decreases. These studies suffer from a number of limitations. The experimental evidence is also limited, but suggests that radio-frequency fields cannot cause DNA mutations. The lack of reproducibility of findings limits the conclusions that can be drawn.

REFERENCES

Chapter 2.13: Occupational Exposures

Summary

> Twenty-nine occupational agents, as well as 15 exposure circumstances are carcinogenic to humans.

> Exposure is still widespread for several important carcinogens such as asbestos, polycyclic aromatic hydrocarbons, heavy metals and silica.

> The burden of occupational cancer among exposed subjects may be substantial.

> Prevention of occupational cancer is feasible and has taken place in industrialized countries during recent decades.

> Limited data on occupational cancer risk are available from low-income countries.

It has been known for over 200 years that exposures encountered at the workplace are a cause of cancer. Occupational cancers were initially detected by clinicians. From the early findings of Port of Bristol cancer among chimney sweeps in 1779 [1] to Goeth and Johnson’s identification of angiosarcoma of the liver among vinyl chloride workers two centuries later [2], numerous cancers among persons with unusual occupations were sufficient evidence to judge that the occupational exposures caused the cancer. The era of initial identification of occupational cancer by a clinician has extended to a complete evaluation of the importance of occupational exposures started after World War II. Knowledge of the occupational and other public settings.

Knowledge of the occupational and other public exposures that have been investigated with respect to the presence of a carcinogenic risk.

Structure and characteristics of individual agents or (more frequently) because new carcinogenic agents are substituted by other agents or (more frequently) because new industrial processes or materials are introduced. Finally, any list of occupational exposures can only refer to the relatively small number of chemical exposures that have been investigated with respect to the presence of a carcinogenic risk.

The same factors complicate the estimates of the burden of cancer attributable to occupational exposures. As a result, only a small fraction of all cancer deaths have been proposed in the past [4], but estimates based on systematic evaluations of relative risks and data on exposure prevalence have resulted in lower estimates, in the order of 2–3% [5, 6]. A single figure on the proportion of cancers due to occupations might be misleading as occupational exposures are a cause of cancer. The period of formal epidemiological assessment of the occurrence of cancer in relation to workplace exposures started after World War II. The burden of cancer in the workplace in the earlier decades of this century was substantial, and in extreme cases, all of the most heavily exposed to develop cancer as occurred in some groups of manufacturers of 2-naphthylamine and benzidine, while coal-tar and fumes and asbestos have been so widespread that tens of thousands of skin and lung cancers have developed. While the remaining hazards are now starting to disappear through elimination of these substances and to exposures of them, some of the consequences of the earlier exposures are still vast. Estimation of the burden of occupational cancer in high-resource countries are in the order of 2–5% [3].

At present, there are 29 chemicals, groups of chemicals and mixtures for which exposures are mostly occupational, that are established human carcinogens (Table 2.13.1). While some agents, such as asbestos, benzene, and heavy metals, are currently widely used in many countries, other agents have a historical interest (e.g. mustard gas and 2-naphthylamine). An additional 28 occupational agents are classified as probably carcinogenic to humans (Group 2A) there are listed in Table 2.13.2, and include exposures that are currently prevalent in many countries, such as diesel engine exhaust and trichloroethylene. A large number of important occupational agents are classified as possible human carcinogens (Group 2B) are arsenic, bis(chloromethyl)ether, carbon black, chloroform, chlorophenyl derivatives, DDT, dichlorodiphenyltrichloroethane, glass, polyvinylchloride and styrene. The complete list can be found on the IARC web site (http://monographs.iarc.fr).

The distinction between occupational and environmental carcinogens is not always straightforward. Several of the agents listed in Tables 2.13.1 and 2.13.2 are also present in the general environment, although exposure levels tend to be higher at the workplace. This is the case for the examples of 2,3,7,8-TCDD, diesel engine exhaust, radionuclides and asbestos. On the other hand there are agents that have been evaluated in IARC groups 1 or 2A, for which exposure is not primarily occupational, but which are often encountered in the occupational environment. They include drugs such as cyclophosphamide and cyclosporin. Industrial exposure can occur in pharmacies and during their administration by nursing staff, food contaminants such as aflatoxins, to which food processors can be exposed, biological agents, such as Hepatitis B virus, Hepatitis C virus and Human Immunodeficiency virus, to which medical personnel can be exposed, environmental agents, in particular solar radiation (exposure in agriculture, fishing and other outdoor occupations), and viral agents, in particular secondhand tobacco smoke in bars and other public settings.

Polycyclic aromatic hydrocarbons (PAHs) represent specific problem in the identification of occupational carcinogens. This group of chemicals includes several potent experimental carcinogens, such as benzo[a]pyrene, benzo[a]anthracene and dibenz[a]anthracene. However, humans are always exposed to mixtures of PAHs (several of which are listed in Table 2.13.1 and 2.13.2 e.g. coals, soots, creosote), and an assessment of the carcinogenicity of individual PAHs in humans is difficult.

Current understanding of the relationship between occupational exposures and cancer is far from complete, in fact, for many experimental carcinogens no definitive evidence is available from exposed workers. In some cases, there is considerable evidence of increased risks associated with particular industries and occupations, although no specific agents can be identified as etiological factors. Table 2.13.3 reports on occupational cancers and industries that entail or are suspected to entail a carcinogenic risk on the basis of the IARC Monographs programme. Fifteen occupations and industries are listed in IARC Group 1 and four in Group 2A.

Constructing and interpreting lists of chemical or physical carcinogenic agents and associating them with specific occupations and industries is complicated by a number of factors. Information on industrial processes and exposures is frequently poor, not allowing a complete evaluation of the importance of specific carcinogenic exposures in different occupations or industries. In addition, exposures to well-known carcinogenic exposures, such as vinyl chloride and benzene, occur at different intensities in different occupational situations. Furthermore, changes in exposure occur over time in a given occupational situation, either because identified carcinogenic agents are substituted by other agents (or more frequently), because new industrial processes or materials are introduced. Finally, any list of occupational exposures can only refer to the relatively small number of chemical exposures that have been investigated with respect to the presence of a carcinogenic risk.

Table 2.13.1 Agents, groups of agents and mixtures classified as established human carcinogens [9], for which exposure is mainly occupational. (Group 1 and four in Group 2A).

Table 2.13.1 Agents, groups of agents and mixtures classified as established human carcinogens [9], for which exposure is mainly occupational. (Group 1 and four in Group 2A).

It is not applicable (agent classified in Group 1 on the basis of mechanistic evidence).
While the study of occupational cancer has concentrated on specific jobs, industries and agents, it is likely that indirect effects of occupation have become more important. For example, the increasing employment of women in jobs outside the home may entail an increased risk of hormone-related cancers. Recently, shiftwork that involves circadian disruption has been classified as a probable human carcinogen by the IARC (2007).

Occupational cancer is likely to be a more important problem in medium- and low-resource countries than in high-resource countries because of the importance of the informal sector, the lack of stringent implementation of existing regulations, the low level of attention paid by management to industrial hygiene, and the presence of child labour (8). However, detailed information on prevalence of exposure and cancer risk is currently lacking.
Environmental Pollution

Summary

- Environmental pollution contributes to the world's cancer burden in a limited way.
- Many known, probable and possible carcinogens can be found in the environment, and all people carry traces of these pollutants in their bodies.
- Some environmental pollutants are widely dispersed, and others are concentrated in small geographic areas.
- There are wide disparities in exposure, and pollution levels can be high in newly-industrialised countries with less stringent regulations.
- Much environmental pollution can be prevented.

In a broad sense, environmental factors are implicated in the causation of the majority of human cancers [1]. "Environmental factors" is generally understood to encompass everything that is not specifically genetic in origin. This includes many significant causes of cancer that are considered discretionary, although marketing and societal influences are also important: tobacco smoking, alcohol consumption and dietary habits. Evidence for the role of environmental factors comes from a variety of sources: geographical variations in the distribution of the world cancer burden, from time trends showing increases or decreases in different forms of cancer, from studies of people migrating from one country or decreases in different environments. The role of environmental factors comes from studies of people migrating from one country or increases in different environments.

Environmental factors include many significant causes of cancer that are considered discretionary: tobacco smoking, alcohol consumption, and dietary habits. In addition, some environmental pollutants are concentrated in small geographic areas near specific industrial sources. These results in wide disparities in the level of exposure to environmental pollutants, and some population groups may face higher risks that do not have a noticeable impact on national cancer incidence statistics. Nonetheless, there are several examples to indicate that the carcinogens that pollute our environment do contribute to the world cancer burden (Table 2.14.1).

In common with occupational exposure, exposure to asbestos due to residential circumstances results in an increased risk of mesothelioma, a rare tumour derived from the cells lining the peritoneum, pericardium or pleura [3]. Likewise, non-occupational exposure to asbestos may cause lung cancer, particularly among smokers [4]. A very high incidence of mesothelioma as a consequence of neighbourhood exposure is evident among inhabitants of villages in Turkey where houses and natural surroundings contain the mineral sericite.

Outdoor air pollution

Ambient air pollution has been implicated as a cause of various health problems, including cancer, and in particular as a cause of lung cancer. Air pollution entails a complex mixture of different gaseous and particulate components whose concentrations vary greatly with place and time. Human exposure to air pollution is therefore difficult to quantify. It may be possible, however, to attribute some carcinogenic risk to specific atmospheric pollutants, including benzene, benzo[a]pyrene, benzo[e], 1,3-butadiene, some metallic compounds, particulate matter (especially finer particles) and polychlorinated biphenyls.

Emissions of traditional industrial air pollutants such as sulphur dioxide and particulate matter have decreased in developed countries, whereas their use has increased in some impoverished regions [7]. Localised air pollution may be a hazard in relation to residence near to specific sources of pollution, such as coal-fired power plants, petroleum refineries, metal manufacturing plants, iron foundries, incinerators and smelters. In general, an increased risk of lung cancer in the proximity of pollution sources has been demonstrated. In three Scottish towns, for example, increased lung cancer mortality was observed in the vicinity of foundries from the mid-1960s to the mid-1970s and later subsided in parallel with emission estimates in relation to quantitative or semi-quantitative exposure to pollutants. In general, these studies have provided evidence for an increased risk of lung cancer among residents in areas with higher levels of air pollution.

Table 2.14.1 Some carcinogens that are found in the environment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer sites/Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IARC Group 1</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td>Liver, lung, skin</td>
</tr>
<tr>
<td>Arsenic and arsenic compounds*</td>
<td>Lung, pleura, peritoneum</td>
</tr>
<tr>
<td>Benzene</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>Chrom[VI] compounds</td>
<td>Lung, nasal cavity</td>
</tr>
<tr>
<td>Engravic</td>
<td>Lung, pleura</td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>Lung</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Radon and its decay products</td>
<td>Lung</td>
</tr>
<tr>
<td>Solar radiation</td>
<td>Skin</td>
</tr>
<tr>
<td>Silica, crystalline</td>
<td>Lung</td>
</tr>
<tr>
<td>2,3,7,8-TCDD</td>
<td>Several organs</td>
</tr>
</tbody>
</table>

IARC Group 2A

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer sites/Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diesel engine exhaust</td>
<td>Lung, bladder</td>
</tr>
<tr>
<td>Ultraviolet radiation A</td>
<td>Skin</td>
</tr>
<tr>
<td>Ultraviolet radiation B</td>
<td>Skin</td>
</tr>
<tr>
<td>Ultraviolet radiation C</td>
<td>Skin</td>
</tr>
<tr>
<td>Polyhalogenated biphenyls</td>
<td>Liver, bile ducts, leukemias, lymphomas</td>
</tr>
<tr>
<td>Tetrachlorodibenzo-p-dioxin</td>
<td>Esophagus, lymphoma</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Kidney, lues, lymphomas</td>
</tr>
</tbody>
</table>

In general, air pollution has been implicated as a cause of various health problems, including cancer, and in particular as a cause of lung cancer. Air pollution entails a complex mixture of different gaseous and particulate components whose concentrations vary greatly with place and time. Human exposure to air pollution is therefore difficult to quantify. It may be possible, however, to attribute some carcinogenic risk to specific atmospheric pollutants, including benzene, benzo[a]pyrene, benzo[e], 1,3-butadiene, some metallic compounds, particulate matter (especially finer particles) and polychlorinated biphenyls. Table 2.14.1 lists substances that are found in the environment.
reductions [9]. Similar results were obtained in studies focusing on industrial emissions of arsenic from coal burning and the construction of metal smelting. The evidence for an increased risk of cancers other than lung cancer from outdoor air pollution is inconclusive at present.

Air pollution by chlorofluorocarbons (CFCs) is increasingly recognized as indirectly responsible for global increases in UVB radiation (see Chapter 2.14). These chemicals, including halons, carbon tetra- chloromethane and methyl chloroform, are emitted from home air conditioners, foam cushions and many other products. CFCs are carriers by winds into the stratosphere, where the action of strong solar radiation releases chlorine and other gases. Outdoor air pollution by sulfur, nitrogen and particulate matter has also been associated with increases in skin cancers around the globe. These chemicals, including halons, carbon tetra-chloromethane and methyl chloroform, are emitted from home air conditioners, foam cushions and many other products. CFCs are carriers by winds into the stratosphere, where the action of strong solar radiation releases chlorine and other gases. Outdoor air pollution by sulfur, nitrogen and particulate matter has also been associated with increases in skin cancers around the globe.

Passive smoking, Chapter 2.3).

There is strong evidence of an increased risk associated with consumption of chlorinated drinking water (see Chapter 2.14), although doubts remain as to whether such associations are causal because of the way in which the studies measured exposure [51]. Given the large number of people exposed to chlorination by-products, however, even a small increase in risk is considered sufficiently large to be significant. Chlorination by-products and other trihalomethanes are among those already identified as carcinogenic [13]. Chloroform and other haloalkanes are among those most commonly found. Studies of bladder cancer have suggested an increased risk associated with consumption of chlorinated drinking water (see Chapter 2.14), although doubts remain as to whether such associations are causal because of the way in which the studies measured exposure [51]. Given the large number of people exposed to chlorination by-products, however, even a small increase in risk is considered sufficiently large to be significant. Chlorination by-products and other trihalomethanes are among those already identified as carcinogenic [13]. Chloroform and other haloalkanes are among those most commonly found. Studies of bladder cancer have suggested an increased risk associated with consumption of chlorinated drinking water, but whether such associations are causal because of the way in which the studies measured exposure [51]. Given the large number of people exposed to chlorination by-products, however, even a small increase in risk is considered sufficiently large to be significant. Chlorination by-products and other trihalomethanes are among those already identified as carcinogenic [13]. Chloroform and other haloalkanes are among those most commonly found.

Many of the carcinogens in our environment were first recognized as such through studies in experimental animals or through studies of highly-exposed workers (see identifying human carcinogens, Chapter 2.1). Accordingly, the total cancer burden from environmental exposure in the general population can only be estimated by mathematical models. Several analyses have suggested only a small percentage of cases of cancer to environmental pollution. [2,17]

These reviews generally considered only endogenous human carcinogens, most of which were identified through occupational studies several decades ago and are less present in today’s environment thanks to government regulation. Environmental pollution levels may be higher in newly-industrialized countries with less stringent regulations or enforcement, and there is not as much information about cancer risks in less studied groups such as women, children, and the elderly.

Also important is the potential cancer burden from exposure to hundreds of probable and possible human carcinogens that have been identified and from thousands of new chemicals that have not been tested for cancer potential. Little is known about risks from combinations of exposures at levels found in the environment or from exposures during critical time windows of development or in susceptible populations. Cancers may have multiple causes, so that believed to contribute to cancers that are attributed to occupational or lifestyle factors. The known interactions between radiation and smoking or between asbestos and smoking support the idea that individuals may have multiple causes.

Finally, it is important to remember that environmental pollution is not only a risk in pollution. Much environmental pollution can be prevented, and reducing environmental pollution can contribute to reductions in diseases other than cancer and to increases in aesthetics and the overall quality of life.
Cancer genetics comprises two main subfields: genetic susceptibility and somatic cell genetics. Genetic susceptibility refers to an inherited (constitutive or germline) genetic variation in cancer susceptibility genes, and the effects of these inherited variations on an individual’s lifetime cancer risk. In contrast, somatic cell genetics focuses on mutations that arise in an individual’s cells during their lifetime and the role that these mutations play during tumor initiation and progression.

What kinds of genes can be cancer susceptibility genes? Known and bioinformatic screens of cancer genes are largely organized into three groups: oncogenes, tumor suppressor genes, and risk modifier genes.

Genetic susceptibility genes are a continuous variable

Somatic cell genetics provides a systematic route to localising high-risk breast cancer susceptibility genes and genomewide SNP association studies are beginning to find strong evidence of new linkages in the very large female breast cancer cohort. Cancer cell lines are one major approach to cancer genomics. For breast cancer, molecular studies have revealed that the FRR attributable to a non-malaria susceptibility genotype TP53 and the breast/ovarian cancer susceptibility gene BRCA1.

The FRR of breast cancer susceptibility genes is about 2.5, and studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.5. Although we do not currently know how much risk is attributable to variants in this frequency range, modest risk variant association studies are beginning to find replicable evidence for risk association for some SNPs [22,33], and the optimistic view is that most common main effect genotype associations with risk of breast cancer, colon cancer, prostate cancer and some of the less common cancer susceptibility genes should be found in the next few years.

The contour lines of gPAF and FRR plotted in Figures 2.15.1 and 2.15.2 provide another view of both potential importance and likelihood of the five risk a factor segments. Individual deleterious sequence variants can be represented in a genetic population attributable fraction contour map.

Genetic population attributable fraction contour map Figure 2.15.2 (sectors 2 and 3) would have been found long ago by linkage analysis, but it appears that none exist. While linkage analyses followed by positional cloning led to the discovery of susceptibility genes, such as APC, MSH2, and BRCA2, that harbour many rare, high-risk variants, studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.5, and studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.5. Although we do not currently know how much risk is attributable to variants in this frequency range, modest risk variant association studies are beginning to find replicable evidence for risk association for some SNPs [22,33], and the optimistic view is that most common main effect genotype associations with risk of breast cancer, colon cancer, prostate cancer and some of the less common cancer susceptibility genes should be found in the next few years.
sented as a point on the graph. Alternatively, an ensemble of high-risk genes, each with OR=10 and a population carrier frequency of 0.1%, could account for all of the unexplained familial relative risk and yet not account for the unexplained gPAF. Point to mention that linkage studies exclude the possibility of enough unidentified high-risk genes to account for the missing FRR. On the other hand, the missing genetic component of breast cancer risk cannot be explained entirely by modest-risk susceptibility genes, and the biochemical pathways in which they function. For the known high-risk susceptibility genes, our growing understanding has led to genetic tests and to medical and surgical interventions that would lead to similar medical utility remains a question for the future.

Whether improved understanding of intermediate-risk and modest-risk susceptibility genes will lead to similar medical utility remains a question for the future.

REFERENCES

Medical and Iatrogenic Causes

Summary

- Chronic inflammation has been associated with excess risk of lung cancer, mesothelioma, oesophageal, colorectal, bladder and several other cancers.
- Chronic pancreatitis has been related to a gross excess risk of pancreatic cancer.
- Subjects with cirrhosis have an overall tenfold excess risk of primary liver cancer.
- Diabetes is associated with excess risk of endometrial, colorectal, liver and possibly pancreatic cancer.
- Excess cancer risk has been reported in subjects treated with chemotherapy, radiotherapy, HRT, phenacetin and selective serotonin reuptake inhibitors.

Inflammation

The association between chronic inflammation and several malignancies has been recognised for many years. As early as 1863, the German pathologist Rudolf Virchow noted leukocytes in necrotic tissues and made a connection between inflammation and cancer. Most of the early data were derived from descriptions of chronic cutaneous lesions, such as ulcers, burn scars or draining sinus tracts [12]. Since then, the association between chronic inflammation and pancreatic cancer has been confirmed in many conditions (bladder cancer after schistosomiasis, ovarian cancer after pelvic inflammation, cirrhosis and pancreatic cancer). Subjects with cirrhosis have an excess risk of liver cancer (see chapter 5.4). A pancreatic cancer cell has now been detected in patients with chronic pancreatitis [9]. Cirrhosis is a chronic degenerative lesion of the liver that is caused by infections (hepatitis B and C) and also by toxic substances, mainly alcohol. Subjects with cirrhosis have a gross excess (over 10-fold) of subsequent primary liver cancer risk [13].

Chronic pancreatitis and pancreatic cancer

Chronic pancreatitis has several causes, but the most common in western countries is heavy alcohol consumption. The frequency of chronic pancreatitis is low in light and moderate drinkers [i.e. less than about 20 units of alcohol per week]. Most patients with chronic alcoholic pancreatitis have consumed six or more drinks per day for a period of 20 years. Several studies have now linked chronic pancreatitis with an increased risk of pancreatic cancer [4]. The evidence comes from different types of studies, with case-control studies being the most frequent. Most of these studies have shown that compared to control subjects without chronic pancreatitis, patients with chronic pancreatitis have an increased risk of pancreatic cancer.

Cohort studies provide the most reliable evidence to substantiate a link between chronic pancreatitis and pancreatic cancer. Several such studies have been performed, and all show an elevated risk of pancreatic cancer even after excluding patients where there has been a short interval between the onset of pancreatitis and cancer [5-7]. Recent linkage studies based on electronically stored data have also confirmed a link between pancreatitis and pancreatic cancer. Besides alcohol there are other causes of chronic pancreatitis where the risk is also increased. Hereditary pancreatitis is a rare inherited disease with symptoms and findings that mimic other types of chronic pancreatitis. It is inherited as an autosomal disease with an onset in childhood or early adulthood. The cumulative lifetime risk of pancreatic cancer in these patients is about 40% [5,6]. Smoking appears to advance the age of onset of cancer, suggesting a gene-environment interaction [7].

Topical pancreatitis has many of the characteristics of other forms of pancreatitis, except that the disease is found primarily in south- ern India and in parts of sub-Saharan Africa. Diabetes and abdominal pain are prominent features; pancreatic cancer is an ominous late development.

Although the link between chronic pancreatitis and pancreatic cancer is established, the molecular pathway for this association has not been fully investigated. In chronic pancreatitis, as in other benign diseases with an increased cancer risk, increased cell turnover and defective DNA repair could lead to pancreatic cancer. Loss of p16 expression, a common precursor of cancer, has been noted in patients with chronic pancreatitis [8]. Kras mutations, found in nearly all pancreatic carcinomas, have also been detected in patients with chronic pancreatitis [9].

Other medical causes

Cirrhosis is a chronic degenerative lesion of the liver that is caused by infections (hepatitis B and C) and also by toxic substances, mainly alcohol. Subjects with cirrhosis have an excess risk (over 10-fold) of subsequent primary liver cancer risk [13]. Since then, cirrhosis is considered a pathogenic step in liver carcinogenesis [10].

History of cirrhosis has also been related to increased risk of oral, pharyngeal and esophageal cancers [11], but incomplete allowance for alcohol drinking remains an open issue for causal inference.

Diabetes [and particularly type II diabetes] is related to hyperinsulinaemia, and to changes in the insulin growth factor (IGF) system, which has been implicated in tumour promotion. Diabetes has been consistently related with excess risk of endometrial cancer, even after allowance for measures of body weight [12], and to colorectal, liver and perhaps pancreatic cancer risk [13].

There is no consistent evidence, in contrast, that stress (defined using several heterogeneous indicators) is related to excess cancer risk or cancer mortality [14].

In any case, the benefits of drugs and other therapies are usually much greater than the potential cancer risk.
CANCER EFFORTS IN THE WHO WESTERN PACIFIC REGION

Cancer is now the second-leading cause of death, after cardiovascular disease, in the Western Pacific Region. It claimed some 2.5 million lives in the Region in 2005, with the number expected to increase by more than 60% to over 4 million deaths in 2030. Cancer also is the leading cause of death in all developed countries in the Region—Australia, Brunei Darussalam, Hong Kong (China), Japan, Macao (China), New Zealand, the Republic of Korea and Singapore. At present, the cancer registry information available for 17 countries in the Region shows that the leading cancers in terms of mortality are lung, liver and stomach cancers. Since 2006, WHO has provided support to Brunei Darussalam, Fiji, Malaysia, Mongolia and Viet Nam for further development of cancer registries and for the development of national cancer control programmes. Support for middle- and low-income countries in the Region has focused on the prevention of lung, liver and cervical cancers, particularly through the development of national cancer control programmes.

Hepatitis B immunizations have been advocated as the principal measure in liver cancer prevention. In 1991, 29 of the 37 countries and areas in the Region had a hepatitis B virus (HBV) carrier rate greater than 8%. The Regional Office for the Western Pacific has strongly promoted the introduction of HBV vaccine into the national immunization programs of all the Member States. In 2005 a regional goal was set to reduce chronic hepatitis B infection rates to less than 2% among children 5 years of age by 2012. Since then, the Regional Office has been working with countries with high proportions of home births on strategies to deliver timely HBV birth doses. At present, 26 countries and areas in the Region, including China, are estimated to have achieved less than 2% hepatitis B chronic infection rates among children 5 years old, down from an average of 8–14% in the pre-vaccination era. Figure 1 shows the decline in chronic hepatitis B infection rates, especially in children and adolescents, in China.

Figure 2 shows that rates of cervical cancer are highest among the less-developed countries of the Western Pacific Region. Cytology (Pap smear) is carried out in developed countries in the Region and visual inspection (with acetic acid) is promoted as a cost-effective method for developing countries. The Regional Office for the Western Pacific supported Member States in the introduction of two human papillomavirus (HPV) vaccines. Australia was the first country in the world to introduce HPV vaccine, targeting all women age 12–26 years.

website: www.wpro.who.int
Mechanisms of Carcinogenesis
**Summary**

Cancer is a complex disease that is very variable in its presentation, development, and outcome from one patient to the other. The same heterogeneity and variability exist at the cellular and molecular level. Cancer is a multistep process during which cells undergo profound, metabolic, and behavioural changes, leading them to proliferate in an excessive and uncontrolled way to escape surveillance by the immune system and to invade surrounding tissues. These changes arise through the coordination and modification of molecular programmes that control cell proliferation and differentiation, relationships with neighbouring cells, and capacity to escape the immune system.

Modifications that lead to cancer include genetic changes that modify the DNA sequence. Another way to change the programme of cells is to modify the conformation of chromatin, the structure that wraps up DNA and regulates its access by DNA reading, copying and repair machineries. Such changes are called epigenetic.

Among the 23 pairs of chromosomes that constitute the human genome, a few hundred are commonly targeted by genetic or epigenetic changes. These genes are parts of networks of genes that regulate cell division, differentiation and life span.

The emergence of technologies for genome-wide analysis of genetic and epigenetic changes is advancing our capacity to define contexts that are specific for each particular cancer, paving the way to personalised medicine based on molecular diagnosis.

Advances in cancer molecular biology are opening new ways to inhibit the growth of cancer, leading to new, more selective and less toxic forms of cancer chemotherapy.

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agents. For example, a number of chemicals classified as carcinogens can attack DNA bases and cause mutations in the coding sequence. UV light can form typical changes by bridging together adjacent pyrimidines. This results in double mutations, where two Cs are replaced by two Ts. These mutations are "adaptive" in that they can help skin cancers. Ionizing radiations induce single or double DNA strand breaks. The main cause of DNA damage in cancer cells is radiation. This may result in its disruption, conferring on the cell a new property that may make them better adapted to life within the deregulated microenvironment of a growing cancer cell. This may thus in its result, conferring an advantage on a new property that may make them better adapted to life within the deregulated system of a growing cancer cell. The key to the cancer box lies in the way these three processes are interconnected. The main connection is ensured by a very special chromosomal locus, located at the far end of the short arm of chromosome 9. It contains a gene called CDKN2a. This locus is quite unique in the fact that it is made of two overlapping genes that use the same DNA segments as templates for RNA and protein synthesis. In other words, this locus can direct the synthesis of two different proteins that do not have a single common amino-acid. One is called p16 and is a negative regulator of cell cycle (thus exerting anti-proliferative effects). p16 belongs to a family of regulators called CDK inhibitors, that is, factors that inhibit enzymes (cyclin-dependent kinases) that drive cells to enter the cell cycle. By blocking these enzymes, CDK inhibitors prevent cell division and induce a mechanism called cell cycle arrest. The other is called p14ARF (for apoptosis). P14ARF is involved in the activation of p53. Thus, through its two products, the cancer box controls both the progression of the disease and the outcome. It is not a simple matter to choose which of the two products is more important. However, it is clear that the CDKN2a gene is altered by several mechanisms in almost every cancer.
Genetic changes

Genetic changes are the cornerstone of cancer. The sequencing of the entire human genome has made it possible to identify genetic alterations in cancers in unprecedented detail. About 300 different genes have been shown to be mutated at some frequency in human cancers. Within this catalogue, a shortlist of 20-30 genes appear to be frequently mutated in almost any type of cancer (including those of the “cancer box” Table 3.1). These genes may be seen as “master genes” that control very basic functions essential for cell division control.

Detecting mutations in cancer cells has many potential implications for both research and individual patients. First, mutations can be informative of the evolutionary process of cancer and provide clinically interesting prognostic or predictive information. Second, the first mutations that contribute to cancer occur, by definition, prior to the development of a lesion. Detecting these mutations may thus help in early cancer diagnosis. Finally, in several cases mutations may be good indicators of therapeutic responses, and may help to select therapies that have greater chances of success. This is the case, for example, for mutations in the EGF receptor (EGFR) that are found in 20–40% of lung cancers in never smokers. These mutations constitutively activate the receptor, generating a constant cell proliferation signal. The signal can be blocked by small inhibitory drugs such as gefitinib (Iressa) or erlotinib (Tarceva). These drugs have interesting therapeutic effects in patients with EGFR mutations, but are poorly effective in most other patients.

Cells of many cancers accumulate mutations at a rate significantly higher than in normal cells, a property referred to as “Mutator Phenotype”. This property of transformed cells is believed to be critical for the development of cancer, as well as for the development of resistance to cancer treatments [8]. The Mutator Phenotype is the consequence of mutations in genes that normally control DNA repair and integrity. Cells with such mutations become unable to correctly repair mutations, leading to an accumulation of DNA damage, and thus accumulate mutations at a much higher rate than normal cells. Molecular mechanisms underlying the Mutator Phenotype may include defects in DNA repair, gene transcription, cell cycle control and cell death.

TP53 tumour suppressor: an example of common genetic change

The most studied of all cancer genes is TP53, which encodes the p53 protein, a tumour suppressor that is mutated in about half of all human cancer cases. A database of all these mutations is maintained at the International Agency for Research on Cancer [9]. It includes about 24 000 TP53 mutations detected in almost every type of human cancer. We now have a very good understanding of the molecular effects of these mutations. Most of them fall within a part of the protein that binds to DNA, allowing p53 to regulate several dozen of other genes. The mutations are often single base substitutions, leading to the replacement of one amino-acid in the protein by another one. This small change is enough to perturb protein folding and to prevent it to bind to DNA, thus inducing a loss of function.

Close examination of the distribution of these mutations shows that they occur in a non-random fashion and there are significant differences in mutation patterns among cancers that are strongly associated with exposure to environmental mutagens. These differences are due to the fact that different mutagens can damage DNA in particular ways, thus leading to different types of mutations. Thus, mutations in TP53 can be seen as “molecular signatures” of mutagenic events that contribute to cancer. This makes the TP53 mutation profile a potent biomarker in molecular epidemiology, as a potential reporter of specific mutagenic exposures. This is supported by the evidence showing that mutation patterns in common cancers differ significantly depending on geographic variations in incidence, indicative of differences in exposure to specific environmental carcinogens [10]. For example, in liver cancers, the type and frequency of mutations is very different between patients in Europe and the USA and those in many countries of Africa or Southwest Asia. The difference is due to the impact of a particular mutagen, aflatoxin, which is produced by a fungus that contaminates many food components in tropical areas. This mutagen is virtually absent from the western diet, but induces a characteristic pattern of TP53 mutation in patients with liver cancer in regions of sub-Saharan Africa and South-East Asia.

In many cancers, presence of a mutation in TP53 is correlated with a rather poor prognosis and rapid response to treatment. So far, this fact has had only limited impact in the clinics because the survival advantage of those who could be identified from the markers routinely scored by the pathologist the size of the tumour, its grade, the extension of the disease into lymph nodes, etc. However, it has recently been recognised that TP53 mutations may help to distinguish between tumours that, to the pathologist, look the same. For example, in breast cancers, presence of a TP53 mutation allows the identification of tumours that are at a high risk of progression among tumours classified by the pathologist as of “good prognosis”. It is therefore possible to single out those patients and offer them more aggressive treatment. It would not be justified to give such a treatment to all patients because the risk of secondary effects would outweigh the benefits, since most of them actually do not need such treatment.

TP53 mutations can also be detected outside tumour tissues, in particular in bodily fluids such as blood. The presence of mutant TP53 in blood is due to the fact that cancer masses release small amounts of dead cells that originate from the tumour and therefore contain the same mutation. Detection of such mutations in the plasma may be exploited for early cancer detection. Indeed, TP53 mutations in plasma DNA have been reported in patients with cancers of the colon, pancreas, lung and liver. For example, the aflatoxin-induced TP53 mutation mentioned above is detectable in the plasma of patients who have asymptomatic subjects from Africa who are chronic carriers of Hepatitis B virus.
In broader sense, epigenetics can be considered as an interface between genotype and phenotype. In other words, epigenetics encompasses mechanisms that modify the final outcome of the genetic code without altering the underlying DNA sequence. The importance of epigenetic principle is highlighted by the fact that all cells in any given organism share an identical genome with other cell types, but they exhibit strikingly different morphological and functional properties. Therefore, it is obvious that epigenetic events define the identity and proliferation potential of different cells in the body, the features that are typically deregulated in cancer. Accordingly, epigenetics may be defined as the study of all changes that are subject manifested over many rounds of cell divisions, but that do not alter the nucleotide sequence (genetic code). Epigenetic inheritance includes DNA methylation, histone modifications, and RNA-mediated silencing, all of which are essential mechanisms that allow the stable propagation of gene activity states from one generation of cells to the next. Consistent with the importance of epigenetic mechanisms, deregulation of epigenetic states is intimately linked to human diseases, most notably cancer [6,12].

DNA methylation

The best-studied epigenetic mechanism is DNA methylation. The methylation of DNA refers to the covalent addition of a methyl group to the 5-carbon (C5) position of cytosine bases that are located 5’ to a guanine base. This is a very small chemical modification of the DNA molecule that while it does not alter the DNA code, may have major regulatory consequences. Aberrant DNA methylation is highly connected to a wide variety of human cancers. Two forms of aberrant DNA methylation are found in human cancer: the overall loss of 5-methylcytosine (global hypomethylation) and gene promoter-associated (CpG island-specific) hypermethylation [31,34]. While the precise consequences of genome-wide hypermethylation are still debated (activation of cellular proto-oncogenes, induction of chromosome instability), hypermethylation of gene promoters is in turn associated with gene inactivation. When hypermethylated, gene promoters become unable to bind the factors that are responsible for gene expression. The gene thus becomes inactivated. A large number of studies indicated that the silencing of tumour suppressor genes and other cancer-related genes may occur through hypermethylation of their promoters.

Unsupervised hypermethylation of gene promoters represents an attractive target for early diagnosis, risk assessment and cancer prevention. For example, the genes that are the target of DNA hypermethylation early in tumour development, in a high percentage of cases, and specific to cancer type, are of particular interest. A number of studies showed that the p16/CDKN2A tumour suppressor gene is among the most frequently silenced cancer-associated genes in human cancer, and that this silencing is associated with promoter hypermethylation. Unsupervised addition of methyl markers (de novo methyltransferase) at the p16/CDKN2A promoter is one of the most frequent epigenetic alterations detected in a wide range of human cancers. In addition, silencing of p16/CDKN2A by promoter hypermethylation is highly tissue-specific and appears to be the earliest event in some cancer types, making this gene an attractive target for preventive strategies. While cancer epigenetics have focused primarily on DNA methylation, increasingly tissue-specific modifications of chromatin proteins (histones) and the expression profiles of microRNAs (a family of small RNA molecules important for stable repression of specific genes) as potential biomarkers remain largely unexploited.

The CIMP phenotype

The studies on DNA methylation involving multiple genes revealed that some cancer types exhibit a particular profile of hypermethylation of cancer-associated genes, a phenomenon known as the CpG island methylator (CIMP) phenotype [10]. This is an epigenetic condition that has been studied primarily in colorectal cancer, other studies provided evidence that the CIMP phenotype may also be present in different cancer types including hepatocellular carcinoma, gastric cancer, pancreatic cancer, glioblastoma, oral cancer, leukemias and solid tumours [15]. However, it should be noted that the CIMP-positive tumours represent only a subset of all cancers with hypermethylation. Analogous to the contribution of the Mutator phenotype to genetic changes, the presence of the CIMP phenotype may provide a more adequate assessment of methylated genes in some (but not all) cancer types. This may be exploited for prognostic purposes but also in the design of “epigenetic therapy”.

Despite a wealth of studies providing evidence for an association between abnormal DNA methylation patterns in a variety of human cancers, the causes and underlying mechanism of this phenomenon remain unclear. Specific agents (e.g. environmental) or combinations of factors in the environment, diet or lifestyle may contribute, and/or relieve resistance against unsched-uled methylated and/or histone modifications, leading to altered gene expression and oncogenic processes. Large population-based cohorts and case-control studies may offer excellent opportunities to test the contribution of repeated and chronic exposure to epimutagens in the environment and nutrition to abnormal levels and patterns of DNA methylation in specific cancers.

Perspectives for combating cancer

Until recently, genetic and epigenetic studies on cancer have so far been exploited primarily for improving the knowledge of the mechanisms of cancer development. However, the recent emergence of powerful technologies for genome-wide analysis of genetic and epigenetic changes is dramatically advancing our capacity to identify multiple changes in gene expression as well as genetic or epigenetic changes in cancer cells.
Common oncogenes and tumour suppressor genes involved in human cancer

<table>
<thead>
<tr>
<th>TUMOUR SUPPRESSOR GENES</th>
<th>Functions and Cancer Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Involved in breast and ovarian cancers</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Involved in breast, salivary gland and ovarian cancers</td>
</tr>
<tr>
<td>CDKN2A or MTS1</td>
<td>Involved in neuroblastoma (a nerve cell cancer) and glioblastoma</td>
</tr>
<tr>
<td>TP53</td>
<td>Involved in lung, ovarian, colon and pancreatic cancers</td>
</tr>
<tr>
<td>RB1</td>
<td>Involved in retinoblastoma and bone, bladder, small cell lung and breast cancer</td>
</tr>
<tr>
<td>CDKN1A or PRAD1</td>
<td>Involved in colorectal cancer</td>
</tr>
<tr>
<td>CTNB1</td>
<td>Codes for beta-catenin, involved in liver cancers</td>
</tr>
<tr>
<td>DPC4</td>
<td>Involved in gastric cancer</td>
</tr>
<tr>
<td>APC</td>
<td>Involved in colon and stomach cancers</td>
</tr>
<tr>
<td>NF1</td>
<td>Involved in meningioma and ependymoma (brain cancers) and schwannoma (affecting the wrapping around peripheral nerves)</td>
</tr>
<tr>
<td>PTEN</td>
<td>Involved in breast, colon and breast cancer</td>
</tr>
<tr>
<td>TFE3</td>
<td>Involved in renal cell cancer</td>
</tr>
<tr>
<td>VHL</td>
<td>Involved in renal cell cancer</td>
</tr>
</tbody>
</table>

ONCOGENES

| PDGF                    | Codes for platelet-derived growth factor. Involved in glioma (a brain cancer) |
| EGF                     | Codes for the receptor for epidermal growth factor. Involved in glioblastomas (a brain cancer) and breast cancer |
| HER-2 or ERBB2          | Codes for a growth factor receptor. Involved in breast, salivary gland and ovarian cancers |
| RAS                     | Codes for a growth factor receptor. Involved in thyroid cancer |
| KRAS                    | Involved in lung, ovarian, colon and pancreatic cancers |
| NRAS                    | Involved in leukemias |
| MYC1                    | Involved in leukemias and breast, stomach and lung cancers |
| NMYC                    | Involved in neuroblastomas (a nerve cell cancer) and glioblastomas |
| LMRC                    | Involved in lung cancer |
| BCL2                    | Codes for a protein that normally blocks cell suicide. Involved in follicular B & lymphomas |
| CDK40 or PRAD1          | Codes for cyclin D1, a regulatory component of the cell cycle clock. Involved in breast, head and neck cancers |
| CTNB1                   | Codes for beta-catenin, involved in liver cancers |
| MDM2                    | Codes for an antagonist of the p53 tumor suppressor protein. Involved in sarcomas (connective tissue cancers) and other cancers |

Suggested further reading and links


3.2 Breaks (SSBs) and Double Strand Breaks (DSBs)

Agents or phenomena capable of inducing DNA damage are known as DNA damaging agents. There are a number of endogenous (cellular) and exogenous (environmental) genotoxic agents.

**Sources of DNA Damage**

**Exogenous Sources**

- Environmental agents, such as cigarette smoke and UV light, are the most frequent types of breaks caused by ionizing radiation.
- Other exogenous sources include ionizing radiation, mutagens, and reactive oxygen species.

**Endogenous Sources**

- DNA replication itself contributes about ten breaks per cell per day. In addition, it has been hypothesized that the presence of methylated CpG sequences is the major cause of mutation in mammalian genomes.
- DNA repair processes are complex and dynamic processes that require the orchestration of many enzymes, adaptors, and chromatin-modifying activities.
- Defects in key players and pathways involved in DNA repair and DNA damage can lead to cancer and other human diseases.

**DNA Damage Response and DNA Repair**

DNA repair mechanisms represent an arsenal of tools devised by cells to repair DNA damage and hence defend themselves against constant challenge to genomic integrity.

**Summary**

Even under normal cellular conditions, genomic DNA is under constant threat from DNA damage and DNA breaks that are constantly produced by endogenous and exogenous (environmental) genotoxic agents.

**DNA repair mechanisms**

- Replication fork bypass: Monofunctional gaps are filled by resynthesis of several bases in the damaged DNA chain, such as by gap-filling endonuclease (human AP1) [13]. Gap-filling may proceed by replacement of a single base or by reinsertion of several bases in the damaged strand (depending on the pathway employed).
- More complex and unusual forms of damage to DNA, such as double-strand breaks, clusters of base damage and non-coding lesions cause a 24- to 32-nucleotide oligonucleotide (IV), and the gap is filled in by PCNA-dependent polymerase (PCNA) epsilon and delta, and a DNA ligase, presumed to be LIG1 [14]. Nucleotide excision repair in regions that are transcribed (and hence code for protein) requires the action of THI2 [15]. DNA base excision repair (Figure 3.2.3) involves the removal of a single base by base excision of the sugar-phosphate backbone by a damage-specific DNA glycosylase [e.g., MSH1 or usual DNA glycosylase] and incision by an apurinic/apyrimidinic DNA repair enzymes. For instance, the aflatoxins B1 and B2 that are found in foodstuffs contaminated with aflatoxins, and the aflatoxin B1 metabolite B2 are classified by the IARC Group 1 as human carcinogens.
- Cells irradiated with ionizing radiation can also produce a covalent linkage between two adjacent purine or pyrimidine residues. Methylation increases the rate of depurination and deamination.
- DNA repair processes represent an arsenal of tools devised by cells to repair DNA damage and hence defend themselves against constant challenge to genomic integrity.

**Fig. 3.2.1**

- The first step in both base excision repair and nucleotide excision repair is the recognition of a modification in DNA by enzymes that detect either specific forms of damage or a distortion in the DNA helix. Recognition of damage is followed by an excision step, in which DNA containing the modified nucleotide is removed.
- Gap-filling DNA synthesis and ligation of the ends complete the repair process.
- Nucleotide excision repair may occur in the non-transcribed (non-protein-coding) regions of DNA, and DNA repair enzymes that act on DNA damaged by UV light is probably the most common exogenous mutagen to which human cells are exposed, and the importance of the nucleotide excision repair pathway in protecting against UV-induced carcinogenesis is clearly demonstrated in the inherited disorder xeroderma pigmentosum. Individuals who have this disease lack one of the enzymes involved in nucleotide excision repair and have a thousand-fold increased risk of developing skin cancer following exposure to sunlight than do other individuals. Several genes involved in nucleotide excision repair, from XRPA to XPA, are deficient in XP syndrome [1].

**Fig. 3.2.2**

- One of the great achievements of the last two decades has been the isolation and characterization of the genes, and their protein products, involved in nucleotide excision repair and nucleotide excision repair. It has become apparent that certain proteins so identified are not exclusively involved in DNA repair but play an integral part in other cellular processes such as DNA replication and recombination.

**Sources of DNA Damage**

- Exogenous sources. There are a number of agents or phenomena that produce DNA lesions (Figure 3.2.1). They result in DNA base modifications, formation of covalent bridges between complementary strands, single strand breaks (SSBs) and double strand breaks (DSBs); and can also be induced by endogenous DNA lesion repair mechanisms.
- DNA repair and DNA damage are linked to the detection of damage on the DNA helix. Recognition of damage is followed by the excision step in which DNA containing the modified nucleotide is removed.
- Nucleotide excision repair in regions that are transcribed (and hence code for protein) requires the action of THI2 [15].

**DNA Repair**

- Genetic DNA within each human cell is constantly exposed to an array of damaging agents and environmental (including UV) DNA damage. Genotoxic agents include both environmental agents, such as tobacco smoke, and the aflatoxins B1 and B2 that are found in foodstuffs contaminated with aflatoxins, and the aflatoxin B1 metabolite B2 are classified by the IARC Group 1 as human carcinogens.
- DNA repair mechanisms represent an arsenal of tools devised by cells to repair DNA damage and hence defend themselves against constant challenge to genomic integrity.
- Cells irradiated with ionizing radiation can also produce a covalent linkage between two adjacent purine or pyrimidine residues. Methylation increases the rate of depurination and deamination.
- DNA repair processes represent an arsenal of tools devised by cells to repair DNA damage and hence defend themselves against constant challenge to genomic integrity.
- Cells irradiated with ionizing radiation can also produce a covalent linkage between two adjacent purine or pyrimidine residues. Methylation increases the rate of depurination and deamination.
In order for DSBs to be repaired efficiently, DNA damage first must be detected and the information transmitted to the effectors and DNA repair proteins through a signalling pathway. Of all these steps, however, the detection of DNA breaks is one of the least understood.

The major genes that can act as detectors and transducers in DNA damage response are the ATM (Ataxia Telangiectasia Mutated) superfamily of kinases and p53, activation of which seems to be important for DNA damage detection and repair against stress. Defects in these important players and pathways can lead to cancer and other human diseases. One of the first cellular responses to DNA damage signal events and the most easily detectable in DNA damage responsive treatment with an H2AX variant, H2AX at serine 139 by the phosphatidylinositol-3-kinase-like family of kinases (PI3K) at DSB sites. The presence of H2AX is important for both types of DSBs: repair HR (Homologous Recombination) and NHEJ (Non Homologous End Joining) and is required for the retention/accumulation of repair proteins at the break site. ATM, ATR and Rad3 related protein, and probably DNA-PKcs, all members of the PIKK family, are responsible for the phosphorylation of H2AX, and thus can represent the detectors of DNA damage. The activation of these detectors could be explained in two ways. First, DNA breaks produce a modification in the chromatin structure or spatial organisation, and this modification appears to be sufficient for the autophosphorylation of ATM and its activation. In the case of NHEJ repair, the heterodimer Ku70/Ku80 seems to be the first detector, because it instantly binds to the damaged ends and recruits DNA-PK. TRRAP is a member of the PIKK family, indicating that it, like other members of this family, may have a role in DNA damage response. However, TRRAP lacks the kinase catalytic activity, preventing it from phosphorylating downstream targets, but it still has an effect in later stages of DNA damage response through the P53 pathway. P53 acts as a critical control of cellular proliferation through the checkpoint activation.

Following DNA damage, several proteins involving Chk1, Chk2, ATM, ATR and DNA-PK can phosphorylate p53 leading to its stimulation and to an enhance binding to DNA. Mutations in these involved DNA damage detection and signalling are frequently found in human cancer.

- Repair of DSBs. Two major types of DSB repair, homologous HR and NHEJ, have evolved to deal with the DNA damage constantly generated (14).
- HR recombines the missing DNA using a homologous copy, usually the sister chromatin, whereas lower eukaryotes use NHEJ more prone. It processes DNA ends and religates them without any modifications, thus often creates errors.
- There also exists a third type of DSB repair that is used less often: Single strand annealing (SSA), which shares components with both NHEJ and HR and utilises a limited cohesion zone of several base pairs to religate DNA ends, in the same way as NHEJ.

The mammalian predominantly use HR whereas lower eukaryotes use mostly NHEJ more often. It is believed that that NHEJ plays a more important role than HR in mitotically replicating cells, HR may play a more prominent role...
Homologous recombination (HR). Generally, repair of DSBs by HR is considered most active in the late stages of the cell cycle (late S and G2), because homologous sequences in the form of sister chromatids or homologous chromosomes or DNA repair are required. The homologous sequence of the damaged sequence is used as template and non-template strand is lost or changed, making this type of repair error prone. However, even though it rarely generates errors, HR may result in crossovers and loss of heterozygosity (COH), and HR events can be classified according to whether or not they result in crossing over between the homologous sequences. HR is performed by the RAD52 eukaryotic group of proteins, which includes the products of RAD50, RAD51, and RAD59, the RAD51 paralogs RAD51b, c, d and APE1. In addition, HR also involves BRCA proteins (BRCA1, BRCA2), XRCC proteins (XRCC2 and XRCC3), and the MRN complex.

The first event believed to occur during HR is the recognition of the DNA break by single stand overhangs. In the next event the homologous sequences are involved to involve the MRN complex (Figure 3.2.4). However, this complex has no exonuclease activity, but it’s 5′-3′ exonuclease activity essential for the recognition of the damaged sequence, the MRN complex. This may help in unwinding the DNA at the DSB to facilitate access of other repair factors. BRCA1 and BRCA2 are believed to be important early points of HR and perhaps coordinate repair with other cellular processes.

The activities of all these different proteins lead to the formation of the so-called “Holiday junction” (Figure 3.2.4). In this context each single strand of the damaged strand is coupled with a homologous region of the model DNA strands. High fidelity is provided by the crossing over of different strands. HR can then go in either of two directions. Non-crossing over, resulting from disassociation of HR intermediates, and it is believed that Rad54 may help in unwinding the DNA at the DSB to facilitate access of other repair factors. BRCA1 and BRCA2 are believed to be important early points of HR and perhaps coordinate repair with other cellular processes.

During meiosis and when sister chromatids are available during late S and G2 stages of the cell cycle, whereas NHEJ is more important during G1 and early S stages. To simplify, it is generally accepted that the predominance of one mechanism over the other is dependent on the cell cycle stage and the type of DSB [14].

DNA repair by NHEJ is more error prone but less demanding than homologous recombination. This type of repair does not need to match the damaged sequence to its intact copy on the homologous chromosome (which is typically at a distant site in the nucleus) or bring the two DNA ends closer to each other. The next step is the recruitment of ligase IV through the DNA-PK. The effects of Ku and DNA-PK on the activity of XRCC4/ligase IV are complex, but it is known that all of these proteins, either alone or in a concert, promote end-to-end association of linear DNA-WRN, Artemis and APE1, all nucleases with putative roles in end-joining. Their catalytic activity could be important to process or “clean” the damaged bases on the break site before the ligation takes place.

The first step of NHEJ consists of first repositioning the damaged bases that have been eliminated and then religating the DNA ends. Additional factors involved in NHEJ repair include PNKP and BRCA1. BRCA1 binds to the MRN complex, and this interaction seems to be important for end joining in vivo. However, the exact in vivo function of BRCA1 during NHEJ is still not clear.

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The first event believed to occur during HR is the recognition of the DNA break in a single stand overhangs. In the next event the homologous sequences are involved to involve the MRN complex (Figure 3.2.4). However, this complex has no exonuclease activity, but it’s 5′-3′ exonuclease activity essential for the recognition of the damaged sequence. The MRN complex. This may help in unwinding the DNA at the DSB to facilitate access of other repair factors. BRCA1 and BRCA2 are believed to be important early points of HR and perhaps coordinate repair with other cellular processes. The activities of all these different proteins lead to the formation of the so-called “Holiday junction” (Figure 3.2.4). In this context each single strand of the damaged strand is coupled with a homologous region of the model DNA strands. High fidelity is provided by the crossing over of different strands. HR can then go in either of two directions. Non-crossing over, resulting from disassociation of HR intermediates, and it is believed that Rad54 may help in unwinding the DNA at the DSB to facilitate access of other repair factors. BRCA1 and BRCA2 are believed to be important early points of HR and perhaps coordinate repair with other cellular processes.
Repair of DSBs in the context of chromatin. Repair of DSBs is the processes that utilizes DNA as substrate and subsequently needs to access the naked DNA. However, in a cell, naked DNA is vulnerable to nucleosome digestion and other insults, and without some type of organisation, it would occupy more volume than necessary. Consequently, eukaryotic cells compact the DNA. The methyl group from the guanine base to the C6, the histone protein histone, fulfills essential functions not only by conserving and protecting DNA, but also in preserving genetic information and controlling gene expression. However, given its compacted structure, chromatin facilitates several important cellular processes including DNA detection and repair of DNA breaks [15]. Repair of DSBs, either through HR or NHEJ, is a complex and dynamic process that requires careful orchestration of many enzymes and adapter proteins. In addition, a major hurdle is compacted chromatin, which must first be relaxed to allow access of the DNA repair machinery to damaged DNA. To achieve this, cellular mechanisms that alter the structure of chromatin must first function so that the broken DNA is made accessible to repair factors. Recent studies provided evidence on how the repair machinery gains access to broken DNA in highly condensed chromatin and how the repair process is coordinated with other chromatin-based processes, such as transcription [16]. These studies showed that chromatin modifying/remodelling activities have been associated with DNA repair. Biochemical and molecular studies have revealed different histone modifications associated with DNA repair and identified molecular players responsible for these modifications [Figure 3.2.5]. Chromatin modifying/remodelling activities may thus be a part of an arsenal of histones and ATP-dependent nucleosome remodelling that extends beyond the genetic information. The presence of chromatin modifying/remodelling activities may thus be a part of an arsenal of histones and ATP-dependent nucleosome remodelling that extends beyond the genetic information. These studies reveal histone proteins as key carriers of epigenetic information, constituting a fundamental and critical regulatory system that extends beyond the genetic information [17]. Therefore, these findings are the foundation for further investigation into the role of chromatin-based mechanisms in critical cellular processes and human cancer. Other repair pathways Human cells, in common with other eukaryotic and prokaryotic cells, can also perform one very specific form of damage reversal, the conversion of the methylated adenine, O6-methylguanine, in DNA back to the normal base. O6-methylguanine is a miscoding lesion: both RNA and DNA polymerases ‘read’ it incorrectly when they transcribe or replicate a DNA template containing it. As this modified base can pair with both the base cytosine (its correct partner) and the base thymine (an incorrect partner), its presence in DNA can give rise to transition mutations by mispairing of relevant bases. A specific protein, O6-alkylguanine-DNA alkyltransferase, catalyses transfer of the alkyl group from O6-methylguanine to cysteine amino acid residue (located at the active site of the protein) [17]. This enzyme process restores the DNA to its original state but results in the inactivation of the repair protein. Consequently, repair can be saturated when cells are exposed to high doses of alkylating agents, and synthesis of the transferase protein is required before repair can continue. Mismatched bases in DNA arising from errors in DNA replication, for instance guanine paired with thymine rather than cytosine, are repaired by several pathways involving either specific glycosylases, which remove the mismatched bases, or long-patch mismatch repair involving homologues of the bacterial genes MutS and MutL. Insertion or deletion loops at microsatellite (Figure 3.2.6) sequences can be recognised by hMLH1 (a heterodimer of hMSH2 and hMSH6) or hMSH2 (heterodimer of hMSH2 and hMSH3). Subsequent recruitment of hPMS2 (a heterodimer of hMLH1 and hPMS2) to the altered DNA targets the area for repair, which requires excision, resynthesis and ligation. Single nucleotide mismatch repair requires hMLh1 function for recognition. One important requirement of such repair processes is that they are able to distinguish the correct base from the incorrect one in the mispair. Since both bases are normal constituents of DNA, this cannot be achieved by an enzyme that scans the DNA for a lesion or structure that is not a normal constituent of the DNA. Defects in at least four of the genes whose products are involved in mismatch repair, namely hMSH2, hMLH1, hPMS1 and hPMS2, have been associated with hereditary nonpolyposis colorectal cancer. This is one of the most common genetic diseases, affecting as many as 1 in 200 individuals, and may account for 4–13% of all colorectal cancers. Affected individuals also develop tumours of the endometrium, ovary and other organs. The DNA of hereditary nonpolyposis colorectal cancer tumours is characterised by instabilities in simple mono-, di- and trinucleotide repeats which are common in the human genome. This instability is also seen in certain sporadic colorectal tumour cells and arises directly from alteration in the proteins involved in mismatch repair [18]. Generally speaking, genomic instability is considered as an indicator of, and fundamental to the nature of, malignant cell growth.
REFERENCES


Currently there are 1051 beds and more than 1500 staff members in the Center, including 150 senior professionals. As a renowned tertiary care centre, it accepts 24,000 inpatients and 300,000 outpatients each year from all over China and Southeast Asia.

Professor Tian Zeng, the present director of the Cancer Center, is a member of the Chinese Academy of Sciences. Website: www.sysucc.com/en/index_en.htm
3.3
The Cell Cycle
Summary

>>The control of cell division is critical to
normal tissue structure and function. It
is regulated by a complex interplay of
many genes that control the cell cycle,
with DNA replication (S phase) and
mitosis as major checkpoints
>>The cell cycle is tightly regulated to minimise transmission of genetic damage to
subsequent cell generations
>>Progression through the cell cycle is
primarily controlled by cyclins, associated kinases and their inhibitors.
Retinoblastoma (RB) and p53 are major
suppressor genes involved in the G1/S
checkpoint control
>>Cancer may be perceived as the consequence of loss of cell cycle control and
progressive genetic instability

Cell proliferation occurs through a series of
stages that are collectively termed the cell cycle.
The “cell cycle” refers to the set of ordered
molecular and cellular processes during which
genetic material is replicated and segregates
between two newly generated daughter cells
via the process of mitosis. The cell cycle can be
divided into two phases of major morphological
and biochemical change: M phase (“mitosis”),
during which division is evident morphologically,
and S phase (“synthesis”), during which DNA
is replicated. These two phases are separated
by so-called G (“gap”) phases. G1 precedes S
phase and G2 precedes M phase.
During progression through this division cycle,
the cell has to resolve a number of critical challenges. These include ensuring that sufficient
ribonucleotides are available to complete DNA
synthesis, proof-reading, editing and correcting
the newly-synthesised DNA; that genetic mate210 - Section 3 - Mechanisms of Carcinogenesis

rial is not replicated more than once; that the
spatial organisation of the mitotic spindle apparatus is operational; that the packing and the
condensation of chromosomes is optimal; and
that there is equal distribution of cellular materials between the daughter cells. Moreover,
immediately before or after the cell cycle,
various factors interact to determine whether the
cell divides again or whether the cell becomes
committed to a programme of differentiation or
of cell death. Therefore, the term “cell cycle” is
often used in a broad sense to refer to, as well
as the basic, self-replicating cellular process, a
number of connected processes which determine pre- and post-mitotic commitments. These
may include the commitment to stop dividing
in order to enter a quiescent state, to undergo
senescence or differentiation, or to leave the
quiescent state to re-enter mitosis.

identification of scores of mutants with defects
in cell cycle progression; in mammalian cells,
these mutations would have been lethal and it
would therefore have been impossible to characterise them. These mutants were called “cdc”,
for cell division cycle mutants, and many of them
have been accorded wider recognition through
the application of their names to the mammalian
homologues corresponding to the yeast genes.

Molecular architecture of the cell
cycle
The molecular ordering of the cell cycle is a
complex biological process dependent upon
the sequential activation and inactivation of
molecular effectors at specific points of the
cycle. Most current knowledge of these processes stems from experiments carried out in the
oocyte of the frog, Xenopus laevis, or in yeast,
either Saccharomyces cerevisiae (budding
yeast) or Schizosaccharomyces pombe (fission
yeast). The Xenopus oocyte is, by many criteria,
one of the easiest cells to manipulate in the laboratory. Its large size (over a millimetre in diameter) means that cell cycle progression can be
monitored visually in single cells. Microinjections
can be performed for the purpose of interfering with specific functions of the biochemical machinery of the cell cycle. The Xenopus
oocyte has proven to be an invaluable tool in
the study of the biochemistry of the cell cycle,
allowing, among other findings, the elucidation
of the composition and regulation of maturation
promoting factor (MPF), a complex enzyme
comprising a kinase (p34cdc2) and a regulatory subunit (cyclin B), which drives progression
from G2 to M phase[1]. In contrast, the exceptional genetic plasticity of yeast has allowed the

Fig. 3.3.1 Proliferating cells in the basal parts of the colonic
crypts, visualised by immunohistochemistry (stained brown)

One of the earliest genes to be identified
in this way was cdc2. Isolated in S. pombe,
cdc2 was determined to be able to correct a
G2 cell cycle arrest defect. The product of this
gene, a serine-threonine kinase of molecular
weight 32–34 000 daltons, was subsequently
shown to be the yeast homologue of the kinase
contained in the Xenopus MPF. This enzyme
became the paradigm of a class of enzymes
now called cyclin-dependent kinases (CDKs).
In their active form, CDKs form heterodimers
with cyclins, a class of molecules synthesised in
a time-dependent manner during the cell cycle.
The progression of the cell cycle depends upon
the sequential activation and inactivation of
cyclin/CDK complexes [1], a process which
requires the synthesis of cyclins, the formation
of a complex between a specific cyclin and a
CDK and post-translational modification of the
CDK to convert the enzyme to an active form
(Figure 3.3.3).
Progression through the cell cycle as mediated by cyclins is, in turn, determined by
factors categorised as having either regulatory (upstream) or effector (downstream) roles.
Upstream of cyclin/CDKs are regulatory
factors called cyclin-dependent kinase inhibitors (CDKIs), which regulate the assembly
and the activity of cyclin/CDK complexes.
Downstream of cyclin/CDKs are effector molecules, essentially transcription factors, which

Gene (chromosome)

Fig. 3.3.2 A human osteosarcoma cell nucleus during
mitosis. Cell division proceeds clockwise from upper right
through interphase, prophase (centre), prometaphase,
metaphase, anaphase and telophase. During the cycle, the
chromosomes are replicated, segregated and distributed
equally between the two daughter cells

control the synthesis of proteins that mediate
the molecular and cellular changes occurring
during each phase.
CDKIs are small proteins that form complexes
with both CDKs and cyclins [2]. Their role is
primarily to inhibit the activities of cyclin/CDK
complexes and to negatively regulate cell
cycle progression. They constitute the receiving end of many of the molecular cascades
signalling growth promotion or suppression
of growth. Thus CDKIs may be considered as
the interface between the cell cycle machinery
and the network of molecular pathways which
signal proliferation, death or stress responses.
However, by virtue of their complexing properties, some CDKIs also play a positive role in cell
cycle progression by facilitating the assembly of
cyclin/CDK complexes. For example, p21, the
product of the CDKN1A gene (also known as
WAF1/CIP1), promotes the assembly of cyclin
D/cdk2 complexes in G1 at a stoichiometric
1:1 ratio, but inhibits the activities of these complexes when expressed at higher levels. There
are three main families of CDKIs, each with
distinct structural and functional properties: the
WAF1/CIP1 family (p21), the KIP family (p27,
p57) and the INK4 family (p16, p15, p18)
(Figure 3.3.3).
Downstream effectors of cyclin/CDKs include
proteins mediating three main functional cat-

Product

Type of alteration

egories: (1) those involved in the control of
the enzymes responsible for DNA replication,
proof-reading and repair, (2) those involved
in chromosome and chromatin remodelling
and in the control of genomic integrity, and
(3) those involved in the mechanics of cell division (including the formation of the centrosome
and the mitotic spindle, and in the resorption
of the nuclear membrane). These processes
require the coordinated synthesis of hundreds
of cellular proteins. Transcription factors of the
E2F family play a critical role in the control of
gene transcription during cell cycle progression (Figure 3.3.4). In G1, factors of the E2F
family are bound to their DNA targets but are
maintained in a transcriptionally inactive state
by the binding of proteins of the retinoblastoma (pRb) protein family. At the G1/S transition, the sequential phosphorylation of pRb
by several cyclin/CDKs dissociates pRb from
the complexes, allowing E2Fs to interact with
transcription co-activators and to initiate mRNA
synthesis [3].
Through this mechanism, E2Fs exert a dual
function both as transcriptional repressors in
G1, when bound to pRb, and as transcriptional activators in G1/S and in S phase, after
dissociation of pRb from the complex. Recent
observations suggest that transcriptional
repression by E2Fs is essential to prevent the
premature activation of cell cycle effectors,

Role in cell cycle

Involvement in cancer

p53 (17p13)

p53

Mutations, deletions

Control of p21, 14-3-3σ, etc.

Altered in over 50% of all
cancers

CDKN2A (9p22)

p16 and p19arf

Mutations, deletions,
hypermethylation

Inhibition of CDK4 and 6

Altered in 30-60% of all cancers

RB1 (13q14)

pRb

Deletions

Inhibition of E2Fs

Lost in retinoblastomas, altered
in 5-10% of other cancers.

CCND1

Cyclin D1

Amplification

Progression into G1

10-40% of many carcino­­mas

CDC25A, CDC25B

cdc25

Overexpression

Progression in G1, G2

10-50% of many carcinomas

KIP1

p27

Down-regulation

Progression in G1/S

Breast, colon and prostate
cancers

Table 3.3.1 Cell cycle regulatory genes commonly altered in human cancers

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which would scramble the temporal sequence of molecular events and preclude cell cycle progression.

Cell cycle checkpoints

The notion of “cell cycle checkpoints” is also derived from early studies in Xenopus oocytes and in yeast mutants. In S. cerevisiae, commitment to the mitotic cycle requires the crossing of a “restriction point” called the start transition. Failure to cross the transition results in cells being blocked in the G1 phase of the cycle. Another control point has been clearly identified in G2 phase, at the transition between G2 and M phases. Cells unable to cross this checkpoint are arrested in a post-mitotic, tetraploid state. Physiologically, this checkpoint is active in germ cells during the second division of meiotic cells that have undergone the first, asymmetric division of the meiotic cell cycle in G2 until completing the second division, which is triggered by fertilization. This concept of “cell cycle checkpoints” was later extended to all mammalian cells[4,5]. It is now common to envisage the mammalian cell cycle as a succession of checkpoints that must be negotiated in order for division to be achieved. There is no clear agreement on how many such checkpoints exist in the mammalian cell cycle, or on their exact position.

Control of cdk1 at G2/M transition

The regulation of the complex between cdk1 (also called p34cdc2) and cyclin B exemplifies a typical mechanism that controls the activation of cyclin/CDK complexes at a cell cycle checkpoint. This activation process requires co-operation between three levels of regulation: association between the two partners of the complex, post-translational modifications of the kinase and of the cyclin, and escape from the negative regulation exerted by the CDKIs.

In early G2, cdk1 is in an inactive form. Its activation requires first association with cyclin B, followed by post-translational modification of the kinase itself. This modification includes phosphorylation of a conserved threonine residue (Thr161) by a kinase complex called CAK (CDK-activating kinase), as well as dephosphorylation of two residues localized within the active site of the enzyme, a threonine (Thr14) and a tyrosine (Tyr15). The removal of these phosphate groups is carried out by the dual-specificity phosphatase 2A, an inhibitor of cyclin B/cdk1 complexes. The phosphatase is directly controlled by a number of regulators, including p16 (p16INK4a, INK4a), a protein phosphatase 2A, an inhibitor of the cyclin B/cdk1 complex, which complexes with cdc25, sequesters it in the cytoplasm and thus prevents it from dephosphorylating its nulceus targets. Of course, the action of cdc25 phosphatases is counteracted by kinases that restore the phosphorylation of Thr14 and Tyr15, named weel and wekl[5].

Following the activation process outlined above, the cyclin B/cdk1 complex is potentially able to catalyse transfer of phosphates to substrate proteins. However, in order to achieve this, it has to escape the control exerted by CDKIs, such as p21. The function of this CDKI is itself controlled by several activators, including MCA1, the product of a breast cancer susceptibility gene. The p21 protein is removed from the complex by a still poorly understood phosphorylation process, which also drives rapid degradation of the protein by the proteasome. This leaves the cyclin B/cdk1 complex free to function, after a final step of autophosphorylation, in which cdk1 phosphorylates cyclin B. The complex is now fully active and ready to phosphorylate many different substrates, such as nuclear lamins, during entry into mitosis.

Regulation of the cell cycle and control of genetic stability

During the cell cycle, a number of potential problems may arise during DNA damage. These problems may arise at three distinct stages: (1) during DNA replication, especially if the cell is under conditions of stress that favour the formation of DNA damage (oxidation, exposure to carcinogens, etc.); (2) following the termination of DNA replication, when the cell effectively “switches off” DNA synthesis cytoplasmic machinery; and (3) during M phase, when the cell must negotiate the delicate task of segregating chromatids equally. A tight coupling between the processes and cell cycle regulation is therefore crucial to allow the cell to pause during the cell cycle-in order to afford the time necessary for the successful completion of all the operations of DNA and chromosome maintenance. Failure to do this may result in both genetic and genomic instabilities, which are hallmarks of cancer. Genetic instability is characterized by an increased rate of gene mutation, deletion or recombination (essentially due to defects in DNA repair). Genomic instability results in chromosome translocations, loss or duplication of large chromosome fragments and aberrant chromosome numbers (aneuploidy).

Tons of molecules have been identified as components of the signalling cascades which couple detection of DNA damage and regulation of cell cycle. One of these is the product of the tumour suppressor gene p53, a p53 (e.g. p53 and another p53 gene, a still poorly understood phosphorylation process, which also drives rapid degradation of the protein by the proteasome. This leaves the cyclin B/cdk1 complex free to function, after a final step of autophosphorylation, in which cdk1 phosphorylates cyclin B. The complex is now fully active and ready to phosphorylate many different substrates, such as nuclear lamins, during entry into mitosis.

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an increased frequency of cancer. This observation illustrates one of the most important characteristics of cell cycle regulatory mechanisms: there is a large degree of redundancy and overlap in the function of any particular effector. Therefore, cancer-causing deregulation of the cell cycle requires a combination of alterations in genes encoding proteins that, either alone or in concert, are critical for the control of cell division.

Apart from inactivation of negative regulators, a few cell cycle genes may be activated as oncogenes, in that their alterations result in enhanced activity leading to accelerated cell proliferation. The best example of such a cell cycle oncogene is CCND1, the gene encoding cyclin D1, a G1-specific cyclin [11]. This gene is located on chromosome 11p13, within a large region that is amplified in up to 20% of several carcinomas (e.g. breast, head and neck, oesophageal and lung cancer).

There is also limited evidence for transcriptional activation of cyclin A (an S-phase cyclin) and for activating mutations of CDK4 (one of the partners of cyclin D1) in some cancers. Indeed, the high complexity of cell cycle effectors provides an extremely diverse range of possibilities for cancer-associated alterations. In this respect, cancer can be seen as, fundamentally, a disease of the cell cycle.

Telomeres and telomerase

Telomeres are specialised structures at the ends of eukaryotic chromosomes (Fig. 3.3.5). These structures contain many copies of a (TTAGGG)n repeat that are highly conserved in most eukaryotic species. Telomeres have arisen as an evolutionary response to the problem posed by the development of linear chromosomes. Chromosome ends may be damaged by “hiding” them from DNA damage recognition mechanisms: therefore cells needed a counting mechanism. Normal cells thus have a limited proliferative capacity and this acts as a major barrier against carcinogenesis.

Telomeres are instrumental in the regulation of cell proliferation. Telomere length is inversely related to cell senescence, and critically short telomeres cease to function as an effector and cause the cell to trigger cell suicide (apoptosis) or undergo senescence (permanent arrest of cell proliferation) [Fig. 3.3.6]. Therefore telomerase shortening during cell division appears to act as a cell division counting mechanism. Normal cells thus have a limited proliferative capacity, and this acts as a major barrier against carcinogenesis.

While it is now recognised that telomeres have many more functions than simply protecting chromosome ends, the initial concept of a replication barrier is still valid. Consistent with this notion, recent studies showed that most human cancers activate telomerase at some point during the process of tumour development and progression, a phenomenon typically absent in normal cells. That cells that have accumulated some carcinogenic changes are unable to form clonally significant cancers unless this proliferation barrier imposed by telomere clock is breached.

This is supported by the evidence that more than 85% of all cancer achieves this by expressing an enzyme, telomerase, that synthesises new telomeric DNA to replace the sequences lost during cell division [13].

The catalytic subunit of human telomerase, hTERT, was cloned in 1996 [14]. It has since been shown that genetic manipulations of hTERT which result in inhibition of telomerase activity in tumour cells limit their proliferative and often result in cell death. This raises the possibility that telomerase inhibitors may be a very useful form of therapy for many or most types of cancer. However, in tumours with long telomeres, it may take many cell divisions before telomerase inhibitors exert an antitumour effect. When such drugs are developed they will therefore need to be carefully integrated with other anticancer treatments.

It is interesting to note that not all tumours need to activate telomerase. Studies showed that approximately 10% of human tumours rely on a telomerase-independent mechanism to maintain their telomeres. This phenomenon, known as the alternative lengthening of telomeres (ALT) mechanism, relies on recombination between telomeres [15]. Telomerase assays have not yet entered routine clinical practice, but there is considerable interest in their possible use for cancer diagnosis and prognosis. For example, telomerase assays of urine sediments may be useful for diagnosis of urinary tract cancer, and telomerase activity levels may be a predictor of outcome in neuroblastoma [16]. In summary, there have been many important discoveries in the field of telomere research, suggesting that telomeres may be an attractive target for the development of therapeutic intervention in different types of human cancer [Fig. 3.3.7]. However, more clinical studies are needed to test telomerase-targeted approaches that could lead to effective cancer interventions with minimal side effects. Studies aiming to close many gaps in our understanding of telomere-maintenance mechanism will be instrumental in these endeavours.

REFERENCES

Cell Death

Summary

The term apoptosis refers to a type of cell death that occurs both physiologically and in response to external stimuli, including X-rays and anticancer drugs.

Apoptotic cell death is characterised by distinctive morphological changes different from those occurring during necrosis, which follows ischaemic injury or toxic damage.

Apoptosis is regulated by several distinct signalling pathways. Dysregulation of apoptosis may result in disordered cell growth and thereby contribute to carcinogenesis.

Selection of induction of apoptosis in tumour cells is among current strategies for the development of novel cancer therapies.

In the adult organism, the number of cells is kept relatively constant through cell death and division, and deregulation of this balance (homeostasis) may trigger pathological conditions such as neoplastic diseases and cancer. Apoptosis and necrosis are two forms of cell death, which will be discussed in this section.

While apoptosis accounts for most physiological cell deaths, necrosis is usually induced in response to external stimuli. Specific patterns of necrosis may be subject to apoptosis.

The process of apoptosis can be described by reference to distinct phases, termed "regulation", "effector" and "engulfing" [1]. The regulatory phase includes all the signalling pathways that culminate in commitment to apoptosis. This phase regulates only cell death, but many of the apoptotic signals are released in response to cell damage, proliferation, differentiation, stress and homeostasis. Critical to apoptosis signalling are the "initiator" caspases (including caspase-8, caspase-9 and caspase-10) whose activity is required to activate the activator "effector" caspases (including caspase-3 and caspase-7), which in turn, bring about the morphological changes associated with apoptosis.

Identification of genes mediating apoptosis in human cells has been critically dependent on the use of the nematode Caenorhabditis elegans, members of this gene family are homologous to human BCL2 (which suppresses apoptosis), APAF-1 (which mediates caspase activation) and the caspases themselves (proteases which mediate apoptosis). The central activity of apoptosis to cell biology is indicated by excess tumorigenesis in BCL2 transgenic and p53-deficient mice. Oncogene-mediated tumorigenesis can also be suppressed by apoptosis. These include angiogenesis, myc and E2F. Mutations in E2F that prevent its interaction with a specific transcriptional protein (pRb) accelerate S phase entry and apoptosis. A function of p53 is to suppress apoptosis: p53-deficient mice are more susceptible to p53-induced apoptosis. Agents such as radiation or cytotoxic drugs cause cell cycle arrest and/or cell death (4). The DNA damage caused by radiation or drugs is detected by various means (Figure 3.4.2). DNA-dependent protein kinase and the ataxia telangiectasia mutated gene (ATM) (as well as the related ATR protein) bind to damaged DNA and initiate phosphorylation cascades to transmit damage signals. DNA-dependent protein kinase is believed to play a key role in the response to double-stranded DNA breaks. ATM plays an important part in the response to DNA damage caused by ionizing radiation, controlling the initial phosphorylation of proteins such as p53, Mdm2, BRCAl, CHY and Pab1. Other sensors of DNA damage include mammalian homologues of the PCNA-like yeast proteins Rad1, Rad9 and Hus1. The yeast homologue of replication factor C, Rad7, specific molecules detect nucleotide mismatches or inappropriate methylation. Following exposure of mammalian cells to DNA-damaging agents, p53 is activated and among many targets, can be cleaved. The caspase-9 cleaved fragment is known as active caspase 9. Thus, the tumour suppressor gene p53 mediates two responses to the DNA damage by radiation or cytotoxic drugs: cell cycle arrest at the G1 phase of the cell cycle and apoptosis. The serine/threonine kinase CHK2 is also able to positively interact with p53 and BRCAl. CHK2 and the functionally related CHK1 kinase appear to play a role in the inhibition of entry into mitosis via inhibition of the phosphatase Cdc25.

The regulatory phase

Two major apoptotic signalling pathways have been identified in mammalian cells (the caspase-dependent pathway [3.4.2] and the mitochondrial pathway [3.4.3]). The “extrinsic” pathway depends upon the recognition of cellular signals by cell surface receptors following the binding of relevant ligands. The “intrinsic” pathway involves intrinsic changes within the cell, which result from growth factor deprivation, cytotoxicity or DNA damage induced by radiation or cytotoxic drugs.

Cell surface receptors

Apoptosis may be induced by signalling molecules, usually polypeptides such as growth factors or related molecules, which lead to “death” receptors on the cell surface. Such cell death was initially investigated in relation to the immune response, but has much wider ramifications. The best-characterised receptor families belong to the tumour necrosis factor (TNF) receptor gene superfamily [5] (Figure 3.4.5).

In addition to a ligand-binding domain, death receptors contain homologous cytoplasmic sequences termed the “death domain”. Members of the family include Fas/APO-I/CD95 and TNF-1 receptors (which binds TNFα). Activation of the Fas (or CD95) receptor by its specific ligand (FasL or CD95L) results in a conforma - tional change such that the “death domain” interacts with the adaptor molecule FADD which then binds procaspase-8. In some cell types, drug-induced apoptosis is associated with Fas activation. Uptake of radiation directly activates the Fas receptor in the absence of ligand. TRAIL (TNF-related apoptosis-inducing ligand, Apo-2L) has 28% amino acid identity to Fas. TRAIL induces cell death only in tumorigenic or transformed cells and not in normal cells [5].

The regulation of apoptosis by BCL2 family genes

While the members of the “death receptor” family and their ligands have structural elements in common, agents and stimuli initiating the mito - chondrial pathway to apoptosis are diverse. Common to these stimuli, however, is a change in mitochondrial function, often mediated by members of the BCL2 family [6]. In humans, at least 16 homologues of BCL2 have been identified. Several family members [including BCL2, BCLb (Bcl-W), BAX] suppress apoptosis, while others induce apoptosis and may be subdivided on the basis of their ability to dimmerize with BCL2 protein (Bad, Bcl-x, or not [Bax, Bak]). Phosphorylation of Bcl-X by a specific (AKT)/PKB and other kinases prevents dimerization with BCL2 and promotes cell survival. At least two distinct mechanisms of action are rec -
Apoptosis induced by cytotoxic drugs is accom-
pand by critical changes in mitochondria [2,7] Such apoptotic stimuli induce translocation of Bax from cytosol to mitochondria, which induces release of cytochrome c (Figure 3.4.3). Loss of transmembrane potential following cytochrome c release and is dependent on caspase activation (see below), whereas cytochrome c release is not. Bcl-2 and Bcl-xL reside chiefly in the outer mitochondrial membrane. Bcl-2, Bcl-xL, and Bax can form ion channels when they are added to synthetic membranes, and this may be related to their impact on mitochondrial biology [2,8].

In the cytosol after release from mitochondria, cytochrome c activates the caspases through formation of a complex (the “apoptosome”) with Apaf-1, procaspase-9, and ATP. It appears that Bcl-2/Bcl-xL may suppress apoptosis by either preventing release of cytochrome c or interfering with caspase activation by cytochrome c and Apaf-1. Sustained production of nitric oxide (NO) may cause the release of mitochondrial cytochrome c into the cytoplasm and thus contribute to the activation of caspases; however, nitric oxide is involved in several aspects of apoptosis and may act both as a promoter and inhibitor depending on conditions [9].

The effector and engulfing phases

In mammals at least 13 proteins that mediate the breakdown of cell structure during apoptosis have been identified and are designated caspases-1 through -13 [10]. All possess an active site cysteine and cleave substrates after aspartic acid residues. They exist as inactive zymogens, but are activated by different processes which most often involve cleavage of their pro-forms (designated procaspases-8, etc.) at particular sites, thereby generating subunits which form active proteases consisting of two large and two small subunits. Proteolytic cascades may occur with some caspases operating as upstream initiators (which have large N-terminal prodomains) and are activated by protease-protein interaction [11]. Despite the multiplicity of substrates, protease activity mediated by caspases is specific and appears to be almost unique for each of the morphological change associated with apoptosis. Caspases cleave key components of the cytoskeleton, including actin as well as nuclear lamins and other structural proteins. Classes of enzymes cleaved by caspases carry proteins involved in DNA metabolism and repair exemplified by poly(ADP-ribose) polymerase and DNA-dependent protein kinase [12,13]. Other classes of substrates include various kinases, proteins in signal transduction pathways and proteins involved in cell cycle control, exemplified by p21. Cleavage of some substrates is cell-type specific. Caspase activity accounts for intranuclear cleavage of DNA, one of the first characterised biochemical indicators of apoptosis. ICAD/DFF-45 is a binding partner and inhibitor of the CAD (caspase-activated DNAase) endonuclease, and cleavage of ICAD by caspase-3 relieves

Involvement of mitochondria

Apoptosis is the process of programmed cell death (apoptosis). The process is a critical cellular process that may be triggered in response to DNA damage and show the characteristic membrane blebbing seen in cells. Unlike necrosis, which typically involves groups of cells. Programmed cell death (apoptosis) is a critical cellular process that may be triggered in response to DNA damage and show the characteristic membrane blebbing seen in cells. Unlike necrosis, which typically involves groups of cells.
In theory, knowledge of critical signalling or expression of CAD (Figures 3.4.6 and 3.4.7).

**Therapeutic implications**

In theory, knowledge of critical signalling or expression of CAD (Figures 3.4.6 and 3.4.7).

**Drugs targeting signal transduction pathways**

In complex multicellular organisms, cell proliferation, differentiation and survival are regulated by a number of extracellular hormones, growth factors and cytokines. These molecules are ligands for cellular receptors and communicate with the nucleus of the cell through a network of intracellular signalling pathways. In cancer cells, key components of these signal transduction pathways may be subverted by proto-oncogenes through over-expression or mutation, leading to unregulated cell signalling and cellular proliferation. Because a number of these components may be preferentially over-expressed or mutated in human cancers, the cell signalling cascade provides a variety of targets for anticancer therapy.

Different approaches have been used to attack these targets and include classical cytotoxic agents as well as small molecule drug inhibitors. In addition, antisense oligonucleotides, vaccines, antibodies, ribozymes and gene therapy approaches have been utilized.

**The diagram in Figure 3.4.7 illustrates cell signalling pathways that are targeted by anticancer agents currently undergoing clinical testing. The drug imatinib is already in clinical use. It is hoped that in future, a combination of agents targeting parallel pathways, as well as combinations with classical cytotoxic agents will improve the outcome of cancer patients.**

**Table of Drugs targeting Signal Transduction Pathways**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Erlotinib, gefitinib</td>
</tr>
<tr>
<td>VEGF</td>
<td>Bevacizumab, ramucirumab</td>
</tr>
<tr>
<td>HER2</td>
<td>Trastuzumab, pertuzumab</td>
</tr>
<tr>
<td>p53</td>
<td>Nutlin, p38 inhibitors</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Bcl-2 antisense oligonucleotides</td>
</tr>
</tbody>
</table>

**Notes**

- In preclinical animal models, suppression of Bcl-2 by an antisense oligonucleotide has been shown to retard tumour growth and the approach is currently subject to clinical trial. Likewise, antisense oligonucleotides directed at survivin are being evaluated. The possibility of using recombinant TRAIL to induce apoptosis in malignant cells is under investigation. TRAIL is implicated as the basis of all-trans-retinoic treatment of promyelocytic leukaemia (17). Also noteworthy is the development of caspase inhibitors for the treatment of certain degenerative (non-cancerous) diseases characterized by excess apoptosis.

**Drugs shown to induce apoptosis specifically include chemotherapeutic agents, exemplified by 4-hydroxyphenylretinamide. Butyrate, a short-chain fatty acid produced by bacterial fermentation of dietary fibre, inhibits cell growth in vitro and promotes differentiation; it also induces apoptosis. Both roles may contribute to its prevention of colorectal cancer. Moreover, cyclo-oxygenase enzyme (COX-2) inhibitors may modulate intestinal apoptosis via changes in Bcl-2 expression. Aspirin and similar drugs which inhibit COX-2 may promote apoptosis and prevent tumour formation.**

**Inhibitory drugs**

- Inhibitors of ligands, such as recombinant human antibody to VEGF (rHu mAbVEGF)
- Receptors, anti-receptor antibodies and tyrosine kinase receptor inhibitors
- RAS farnesyltransferase inhibitors
- RAF inhibitors
- MEK inhibitors
- Rapamycin analogues
- Protein kinase C (PKC) inhibitors
- Inhibitors of protein degradation
- Inhibitors of protein trafficking
REFERENCES


CANCER INSTITUTE PROFILE
National Cancer Institute of Brazil (INCA)

The National Cancer Institute of Brazil (INCA) is the branch of the Ministry of Health responsible for formulating and ensuring the development of cancer control actions across the Brazilian territory. Throughout its 70 years of existence, the INCA has been a landmark in terms of cancer control in Brazil by implementing actions in strategic areas such as prevention, early detection, human resources development, research, surveillance, information and healthcare through SUS, the Brazilian National Unified Health System.

In 2005, INCA launched a new National Cancer Control Policy that considers cancer a public health problem, in compliance with international recommendations. The management of the disease should address early diagnosis and prevention, rather than focusing on the treatment of the advanced stages. The Institute has been developing a Cancer Control Network, where governmental and non-governmental organisations work in association with a purpose to reduce cancer incidence and mortality, and to ensure the best possible quality of life to patients undergoing treatment.

website: http://www.inca.gov.br/english
The ability of tumour cells to spread from their original location to invade and colonise distant organs is the final, destructive phase that distinguishes malignant from benign cancers. Metastatic disease is also the major cause of death from cancer. For example, sarcomas tend to metastasise to bone because they have osteolytic properties, whereas melanoma metastasises primarily to the brain and eye because of their affinity for these organs. This complex process implies that candidate metastatic cells acquire many properties that allow them to cross barriers and invade into healthy areas and cross vessel barriers to enter the lymphatic or blood circulation.

The metastatic process consists of a series of steps during which cancer cells leave the primary tumour site, enter lymph or blood circulation (a process called intravasation), survive and circulate, and extravasate to colonise distant organs. This complex process implies that candidate metastatic cells acquire many properties that allow them to cross barriers and invade into healthy areas and cross vessel barriers to enter the lymphatic or blood circulation. The metastatic process involves the expression of adhesion molecules, such as selectins and integrins, that line blood vessels. Interactions with these structures, such as reticular fibres in the subcapsular sinus of draining nodes or endothelial cells that line blood vessels, change the metastatic cells’ adhesion properties, which in turn allow them to invade other organs, to travel in the body, and to form colonies.

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The term "metastasis" refers to the process by which a tumour can form metastases. It consists of a series of steps by which growing tumours disturb the architecture of the tissue where they arise, take the space and place of normal cells, utilise healthy areas and cross vessel barriers to enter the lymphatic or blood circulation. Local-regional invasion is not in itself a factor of poor prognosis, but not as poor as distant metastases. A locally invasive (NI) tumour would normally contribute to the growing local tumour mass. Other cells may assume different shapes and roles and undergo morphological transitions to become independent from their organ of origin, to invade other organs, to travel in the body, and to form colonies. This view is challenged by recent discoveries on cancer stem cells, which are capable of self-renewed and also of generating daughter cells that evolve into different cell shapes and phenotypes depending upon interactions with their environment. Thus, in a given cancer, several lines of cancer cell development may exist. Most cells may develop in a certain direction, which preserve traits of the general architecture of the tissue where they arose. These cells contribute to the growing local tumour mass. Other cells may assume different shapes and roles and undergo morphological transitions to become independent from their organ of origin, to invade other organs, to travel in the body, and to form colonies. This view is challenged by recent discoveries on cancer stem cells, which are capable of self-renewed and also of generating daughter cells that evolve into different cell shapes and phenotypes depending upon interactions with their environment.

Organ preference of metastases

The distribution of metastases is not only a matter of route of dissemination. The most common places for the metastases to develop are the liver, the brain, the bones, the lung and the adrenal glands. There is a propensity for certain tumours to seed in particular organs. This was first recognised by Stephen Paget in 1889, based on his observation from autopsies of 700 women who died from metastatic breast cancer. He formulated the “seed and soil” hypothesis, proposing that specific cancer cells have an affinity for certain organs (the soil) [5]. Many cancers have a physiological need for calcium, selectively metastasise to bone because they can use it as an abundant source of calcium. In general, cancer cells tend to metastasise to organs where blood and energy supplies are abundant and tumours are rapidly removed by erosion from the immune system by a physical barrier (such as the brain).

Invasive and Metastasis

Table of classification of cancer of the colon and rectum

<table>
<thead>
<tr>
<th>T = primary tumour</th>
<th>N = regional lymph nodes</th>
<th>M = distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TK</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>No evidence of primary tumour</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>Cc</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Cancer in situ</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tumour invades submucosa</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tumour invades muscularis propria</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tumour invades through muscularis propria into submucosa or into non-peritonealised pericolic or perirectal tissues</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tumour directly invades other organs or structures and/or perforates visceral peritoneum</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
</tbody>
</table>

Table 3.5.1 TNM classification of cancer of the colon and rectum

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>Site of metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Adrenal (often bilateral)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Liver</td>
</tr>
<tr>
<td>Breast ductal carcinoma</td>
<td>Breast</td>
</tr>
<tr>
<td>Breast lobular carcinoma</td>
<td>Diffuse peritoneal seeding</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Bone, ovary</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Brain</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Brain</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Brain</td>
</tr>
</tbody>
</table>

Table 3.5.2 Site of metastases of cancer's colon cancer

The metastatic process consists of a series of steps during which cancer cells leave the original tumour site, enter lymph or blood circulation (a process called intravasation), survive and circulate, and extravasate to colonise distant organs. This complex process implies that candidate metastatic cells acquire many properties that allow them to cross barriers and invade into healthy areas and cross vessel barriers to enter the lymphatic or blood circulation. Metastasis initiation genes are those that provide a selective advantage in secondary sites but not in the primary tumour, thus participating in metastasis and roles and undergo morphological transitions to become independent from their organ of origin, to invade other organs, to travel in the body, and to form colonies. This view is challenged by recent discoveries on cancer stem cells, which are capable of self-renewed and also of generating daughter cells that evolve into different cell shapes and phenotypes depending upon interactions with their environment. Thus, in a given cancer, several lines of cancer cell development may exist. Most cells may develop in a certain direction, which preserve traits of the general architecture of the tissue where they arose. These cells contribute to the growing local tumour mass. Other cells may assume different shapes and roles and undergo morphological transitions to become independent from their organ of origin, to invade other organs, to travel in the body, and to form colonies. This view is challenged by recent discoveries on cancer stem cells, which are capable of self-renewed and also of generating daughter cells that evolve into different cell shapes and phenotypes depending upon interactions with their environment.
Chapter 3.5: Invasion and Metastasis

Adhesion. Epithelial cells are normally polarized and attached to each other via different types of cell-cell junctions, such as tight junctions, adherens junctions and desmosomes, as well as through intracellular adhesion molecules such as E-Cadherin. This is critical for the cells’ ability to sequester cells from cell-to-cell contacts that lead to their proper place in the epithelium. Thus, cancer cells usually demonstrate changes in the expression of cell adhesion components (3, 13). E-Cadherin, in particular, is a frequent target for genetic and epigenetic modulation and will regulate its function, which may be considered as a tumour suppressor gene. In fact, it is constitutively overexpressed in some human cancers (such as gastric cancer) and its re-introduction in leukemic normal stromal cells, indicating that its loss is tumorigenic. Secondly, it interacts with beta-Catenin, an important oncogene, and provides a signaling connection between structural cell adhesion and cell proliferation. Loss of E-Cadherin trees beta-Catenin from its anchor at the cell membrane and makes it available for translocation into the nucleus, where it can activate transcription factors involved in stimulating cell proliferation.

Epithelial cells entertain contacts with the basement membranes and with the ECM through many other classes of cell-surface receptors that can be subdivided into two distinct, but linked, subfamilies: the integrins (a family of adhesion receptors) and the selectins (a family of adhesion ligands). The integrin receptors are heterodimeric proteins consisting of two distinct transmembrane chains. One chain mediates interactions between the ECM and the cell surface, whereas the other mediates interactions between the ECM and the intracellular cytoskeleton.

Adhesive interaction. Adhesion is critical for cell survival and is required for the maintenance of cell function. It is also critical for the development of metastatic disease, as it is a key step in the dissemination of metastatic cells. The interaction between the cell and the ECM is mediated by integrins, which are a family of transmembrane proteins that play a critical role in mediating cell adhesion. Integrins are composed of two subunits, alpha and beta, which are non-covalently associated. The alpha subunit is responsible for the interaction with the ECM, while the beta subunit is responsible for the interaction with the cytoskeleton. Integrins are activated by a variety of stimuli, including growth factors, cytokines, and mechanical forces.

Integrins are critical for cell adhesion and migration. They are involved in the regulation of cell survival, proliferation, and differentiation. Integrins are also involved in the regulation of the immune system, as they are expressed on immune cells and mediate the interaction between immune cells and the ECM.

The process of invasion and metastasis is a complex and multi-step process that involves the interaction of cancer cells with the ECM and the immune system. The ECM is a highly dynamic and heterogeneous structure that provides a physical and biochemical barrier to the spread of cancer cells. The ECM is composed of a variety of proteins, including collagens, laminins, fibronectin, and proteoglycans. These molecules interact with the cell surface receptors, including integrins, to mediate cell adhesion and migration. The interaction of integrins with the ECM is regulated by various factors, including growth factors, cytokines, and mechanical forces.

Integrins are important for the development of metastatic disease, as they are involved in the dissemination of cancer cells to the bloodstream. The interaction of cancer cells with the ECM is mediated by integrins, which are critical for cell survival and migration. The integrins are activated by a variety of stimuli, including growth factors, cytokines, and mechanical forces. The activation of integrins is important for the development of metastatic disease, as it is necessary for the dissemination of cancer cells to the bloodstream.
tended extravasation. Metastatic cells extrava- 
sate by breaking the capillaries in which they are 
embedded. A second cell-scare mechanism 
that allow migration across the capillary wall is 
as a result of mechanical disruption of capillar-
is by expanding tumour峨. Only into 
the other ano, tumour cells are confronted with 
a different microenvironment in which they must 
Survive. A landmark, the loss of E-cadherin expres-
demonstrates the difficulty of invasion and metastasis 
Assessment of whether the EMT is a result of 
generally accepted in advanced or 
are assumed by the metastatic cells, 
such as bone marrow-derived progenitor cells and other 
local cells that provide a permissive “niche” for 
metastatic cancer. 
which, in turn, allows growing metastases to 
shut down recruitment of organ-specific components of 
the tumour microenvironment, such as the activa-
tion of bone-resorbing osteoclasts by breast 
cancer cells during osteolytic metastasis [22]. Full 
metastatic colonisation can occur by immediate 
growth of cancer cells upon their extravasation, 
or after a prolonged period of micrometastatic 
dormancy.

Epidermal-mesenchyme transition and the concept of metastatic cancer stem cells

Metastatic solid tumours start with an epithelial phe-
totype. However, during tumour progression, 
this phenotype becomes altered and some cells 
undergo a transition to assume a more mesenchy-
mal phenotype. These mesenchymal-like cancer 
cells acquire a high migratory capacity and may 
represent one of the main forms into which cancer cells 
undergo metastasis generation and entry. 
Conversely, at the time of extravasation, 
these cells undergo a reverse mesenchymal-epithelial transition which regenerates high proliferative 
status and allows formation of a metastasis with 
a morphology that resembles the primary tumour. 
It has emerged that this process closely resem-
bles Epidermal-Mesenchyme Transition (EMT), a 
mechanism that is vital for morphogenesis during 
embryonic development [20,24]. During gradu-
ation in mammals, cells migrate from primitive epi-
thelial structures to spatially reorganise and 
form one of the three main embryonic layers, the 
mesoderm. In this process, epithelial cells acquire 
blast-like properties, show reduced adhe-
sion to ECM and increased motility, exactly like 
metastatic cancer cells. 

EMT is essential for many morphogenetic events 
such as organogenesis, wound healing tissue 
remodelling and heart development. A landmark, 
the loss of E-cadherin expression in advanced 
cancers is assumed by the metastatic cells, 
and metastatic cancer cells transform into an 
epithelial phenotype. These mesenchymal-like cancer 
cells with stem cell properties, including 
self-renewal in vitro and asymmetric divi-
sion. In normal tissue, stem cells are present only 
in proliferative areas such as the basal layer of 
quamous mucosa or crypts of glandular mucosa. 
Such stem cells become embedded within solid, 
early cancers mass as static cancer stem cells 
(SCSC) [2]. These SCSCs are, to a large extent, 
susceptible to sustain production of daughter 
cancer cells which assume an epithelial pheno-
type and constitute the bulk of the tumour mass. 
In certain conditions, SCSC can undergo EMT 
and become mobile, migrating cells while retain-
ing their capacity for self renewal. The signals 
that trigger this EMT may correspond to a form 
of disrupted wound healing response generated 
by the breakdown of local basement membranes 
and increased severity of the tissue lesion caused by 
the tumour.

Mobile, migrating cancer stem cells (MCSC) 
may actually represent only a small fraction of 
the cells that are shed in the bloodstream. But 
their stem status endows them with the capacity 
to survive during migration as well as to re-di-
ferentiate into epithelial-like cells upon extravasation 
and colony formation into distant organs. Upon 
entry into the stroma of a target organ, MCSC 
may locally recruit normal fibroblasts and other 
cells to constitute an appropriate niche for 
undergoing mesenchymo-epithelial transition and 
growing rise to rapidly growing metastases.

The choice of treatment depends upon many 
factors, principally the type of the cancer, 
number and localisation of metastases, the 
cancer cell phenotype and condition of the patients, and 
the treatments the patient has already received in 
the case of secondary metastatic cancer. In many 
instances, available treatments are not capable 
to provide a complete cure for metastatic cancer, 
although they can induce remission, improve quality of life, and significantly increase survival 
after diagnosis. Finding new, efficient and better 
tolerated treatments for metastatic cancer is a major challenge in current cancer research and 
clinical trials.

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cells that form the wall of endothelial vessels mediate 
cells that form the wall of endothelial vessels mediate 
cells that form the wall of endothelial vessels mediate 
cells that form the wall of endothelial vessels mediate 
cells that form the wall of endothelial vessels mediate 
cells that form the wall of endothelial vessels mediate 
Chapter 3.6: Emerging Technologies

Proteomics

Proteomics is a general term that covers a variety of conceptual and technological targets ranging from protein expression and function, often in high-throughput format. Proteomics provides a window to biological function and regulation that is strongly complementary to those provided by genomics and expression profiling.

MicroRNAs (miRNAs) and small interfering RNAs (siRNAs) are small, double-stranded RNA molecules that regulate gene expression and can be used as a powerful research tool for understanding gene function and are thought to have important therapeutic potential.

High density array technologies have been steadily increasing in sophistication and assay density since the mid-1990s. Currently, the three main applications of these technologies are expression profiling (used to measure the expression of many genes simultaneously), array CGH (used to search for DNA duplications or deletions in tumor samples at high resolution), and high-density SNP genotyping (used for genome-wide SNP association studies).

Proteomics

Proteomics is the study of the proteome, the protein complement of the genome in a biological system at a given point in time. The terms proteomics and proteome were first introduced in the late 1980s but also on a multitude of translational controls and on regulation of protein degradation [2].

The proteome is a dynamic protein level depends not only on the corresponding transcript level, but also on a multitude of translational controls and on regulation of protein degradation [2]. Proteomics, in contrast to genomics, also has the potential to explore large-scale measurements of protein modifications and their quantitative changes following cell perturbations, which are often as important for protein activity as protein expression levels [3].

Completion of the Human Genome Project was critical for the large-scale development of proteomics not only because the genome sequence provides a full list of possible protein coding sequences, but also because the Human Genome Project changed the paradigm for large-scale biological projects. Just as the human genome project spawned many other projects, the Human Proteome Organization (Hupo) has launched initiatives on human organ and cell systems, established standards, and created antibody (Human Protein Atlas) and mouse models to overcome current limitations of proteomics.

The rapid development of proteomics as a field has depended upon substantial technological advances in many specific areas including gel-based or gel-free protein separation and sequencing techniques (shotgun sequencing), protein chips (SELDI-MS, protein-, tissue-, and sequencing techniques), gel-based or gel-free protein separation and sequencing techniques (shotgun sequencing), protein chips (SELDI-MS, protein-, tissue-, and antibody arrays), mass spectrometry (MS) (sensitivity, resolution, speed and throughput), and bioinformatics [4-5]. Currently, there is no technique that can cover the large number of single proteins contained in a complex sample and the wide dynamic range in the abundance of the individual protein species [5], but large-scale studies of protein complexes are emerging that show how the cell organizes to deliver function at the molecular level.

Proteomics projects generate enormous quantities of data, and public domain databases have been developed to manage and assemble this information. Examples of existing databases include PRIDE (http://www.ebi.ac.uk/pride/), PeptideAtlas (http://www.peptideatlas.org/), and MEXP (http://mexp.scripps.edu/index.html). A critical consequence of the use of these databases is that the need for standardized nomenclature, after publication of manuscripts so that other investigators can re-analyze original data or incorporate the original data into new studies.

Proteomics provides an attractive approach to large scale disease-driven transition studies. Clinical proteomics has focused on the discovery of low abundance, disease-associated proteins or biomarkers with a particular focus on biomarkers that can be assayed from easily available samples such as blood or urine. However, disease-driven marker discovery (or marker validation) studies are in many respects more difficult than basic science studies. The main difference is that basic science studies can proceed from relatively small numbers of samples gathered under carefully controlled laboratory conditions, while marker validation studies require large numbers of samples gathered from human subjects under different conditions. For example, many studies have reported serum peptide signatures associated with specific cancer groups, such as prostate cancer, breast cancer, lung cancer, or melanoma cancer, etc. (for examples, see [7,11]). However, none of these signatures yet enjoy the level of replication that has been achieved for, for example, RNA expression profiling of breast tumours. The difficulty in extracting replicable disease-associated serum proteomics profiles can in part be attributed to the intrinsic difficulty of the research goal. However, that difficulty also raises challenges, including creation of suitable biological resource centres that contain large numbers of well-documented biopspecimens of the correct type and in the correct state of physical preservation to support specific proteomics studies, validation of candidate biomarkers in large, well-characterised cohorts (depending on biological resource centres), and reduction of validated proteomics-based biosignatures to robust and efficient procedures that will work in the clinic.

MicroRNAs

In 1993, Lee and Ambros discovered that lin-4, a gene known to control the timing of C. elegans’ larval development does not code for a protein but instead produces a pair of small RNA [12]. They demonstrated that these small lin-4 RNAs base pair with the 3’ untranslated region of the lin-14 mRNA and result in translational repression of the mRNA. The importance of this discovery did not become evident until several years later, when other small RNA molecules with regulatory functions were found [13]. Since then, about 4000 small regulatory RNAs, termed microRNAs (miRNAs), have been identified in a variety of animals, plants, and viruses and have been deposited in publicly available databases, such as miRBase [http://microrna.sanger.ac.uk].

It is clear now that miRNAs together with small interfering RNAs (siRNAs) are members of a widespread class of small, evolutionarily conserved, non-coding, double-stranded RNA (dsRNA), with regulatory functions. miRNA and siRNA differ in terms of their origin and processing. Once in their single-stranded form, either can regulate the expression of downstream genes by binding to a target messenger RNA (mRNA) at a specific complementary target sequence and guide the targeted mRNA to the double-stranded RNA-induced silencing complex (RISC), responsible for its cleavage or its translational inhibition (Figure 3.6.1). Up to 30% of protein-coding genes may be regulated by miRNA [14], including transcription factors, oncogenes and tumour suppressor genes. Therefore miRNAs play an essential role in multiple disease processes.

Moreover, miRNA expression has been shown to be deregulated in a number of cancers [15-17]. miRNAs are easily designed, synthesized in vitro, and can be delivered into cells, that can be used to regulate the expression of experiment-specific target genes in a laboratory setting. Consequently, miRNA have been used as powerful experimental tool to explore gene function. However, it is becoming increasingly evident that the potential applications of RNA interference go much further. miRNAs, both naturally occurring and synthetic, microarrays and beads have enabled the discovery of numerous miRNAs that are differentially expressed in normal tissues compared with tumours and are associated with cancer development, diagnosis, and prognosis [17]. miRNAs have also become targets for development of anticancer gene therapy; antisense molecules that can inhibit miRNA activity are currently being tested for their anti-tumour activity [18].

The discovery of viral encoded microRNAs indicates that viruses also use this mode of gene regulation to play an important role in regulating both the viral life cycle and the interaction between viruses and host cells, and therefore microRNAs may act as critical modulators of viral mediated oncogenesis. In addition, viral gene-specific miRNA expression patterns may act as antiviral inhibitors and have been examined in a broad range of medically important viruses.

Without a doubt, the phenomenon of RNA interference has been harnessed to create enormously powerful research tools. RNA interference has clear potential to become an important partner in fighting cancer. Future applications of miRNA-related technologies will become even more powerful as new miRNA targets are identified and miRNA expression and regulatory mechanisms better understood.

Fig. 3.6.1 Erika Check (2007) Nature 448, 855-858
Natural deoxyribonucleic acid (DNA) molecules are mixed polymers of the 4 deoxyribonucleotides deoxyadenosine (dA), deoxythymidine (dT), deoxyguanosine (dG) and deoxycytidine (dC). Single-stranded DNA molecules have the very useful characteristic that they hybridise with DNA molecules complementary to their sequence, forming stable double stranded DNA duplexes. In these oligonucleotides, single-stranded DNA is then attached to a solid support such as a nitrocellulose filter in a way that the features on the array are either parts of specific DNA sequences or biological processes of DNA replication, transcription of DNA into RNA, and translation of RNA to make protein. In addition, complementary base pairing is fundamental to the biological processes of DNA replication, transcription of DNA into RNA, and translation of RNA to make protein. One family of these protocols is high-density array hybridisation. The key concept behind filter hybridisation is that a mixed population of DNA molecules can be hybridised, denatured to single stranded DNA, and then utilised as a solid support such as a microtitre filter in a way that preserves positional information from the fractionation. It is a substantially pure preparation of labelled probe (radioactive or fluorescent or biotinylated, etc.) is then hybridised in solution to the filter, the probe will hybridise to and be positionally concentrated at its target DNA sequence on the filter, under suitable conditions, the signal may also reveal the sequence of its complement on the filter. This is the idea behind high-density array hybridisation.

Over the last 15 years, a number of technical development-oriented labs and biotechnology companies have competed to develop useful high-density array hybridisation applications. Many of the popular applications have fallen into one of three categories: expression profiling, comparative genome hybridisation and array CGH, genome-wide SNP genotyping and whole-genome association studies.

For expression profiling, the DNAs affixed at the features on the array are either parts of specific cDNA clones or DNA oligonucleotides that correspond to the sequence of specific RNA transcripts. RNA or cDNA prepared from a particular sample (cell line, tissue, tumour tissue, et cetera) is labelled and then hybridised to the array. After hybridisation, the signal present at each feature of the array provides information about the expression level of individual genes or, if oligos are used as probes, even individual exons [34]. Many of the experimental results achieved by expression profiling have been recapitulated by array CGH. For example, Berghaus et al recently demonstrated that the breast cancer subtypes identified by expression profiling can also be identified by array CGH [25]. Moreover, array CGH has the advantage over expression profiling that its substrate DNA is much more stable than the RNA required for expression profiling—potentially an important advantage for clinical applications.

Genome-wide SNP association studies (GWAS) seek associations between common SNPs and risk of one or another disease, without having to rely on prior hypotheses of which genes or genetic pathways are involved in the disease. These trends have merged to make such studies possible: (1) the human SNP haplotype mapping project has mapped and measured allelomorphs between more than 3 000 000 common human SNPs and in so doing showed that genotyping about 500 000 well-selected SNPs captures much of the information present in the full set of 3 000 000 [26]; (2) the total number of features that could be hybridised on to a high-density DNA hybridisation array increased from the low thousands to several hundred thousand (as of early 2008, more than 1 million), making it possible to genotype a genome-wide representative set of DNA in a single experiment; and (3) epidemiology research groups have joined into consortia that can assemble series of 5000 or more cases and controls, sufficient to overcome the statistical multiple testing problems inherent in association studies that seek to test hundreds of thousands of independent hypotheses.

The combined result has been that in 2007 and 2008, international research consortia announced results from GWAS studies in breast cancer, colon cancer, lung cancer and prostate cancer [27,28]. It is also very likely that GWAS studies of some of the less common cancers will be completed over the next few years.

Beyond providing irrefutable proof that inheritance of common SNPs does influence the risk of common cancers, what are some of the most interesting results that have emerged from these studies? Perhaps the most intriguing new information is that SNPs isolated across a small fragment of chromosome 8q, not far from the oncogene MYCC (c-myc), influence the risk of breast cancer, colon cancer and prostate cancer. A second result has been the finding that that very few SNPs with frequencies of 0.1% to 0.2% are medically useful.

Around the world, scientists and engineers continuously invent new technologies or improve on old technologies. A small fraction of these inventions open whole new avenues of research, leading to important advances in medical science. Another overlapping fraction lead to important improvements in clinical medical practice. Thus today’s relatively new technologies become commonplace as we look forward to tomorrow’s new technologies.
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Biomarkers at a Crossroads: Implications for Early Cancer Detection and Diagnosis

Chapter 3.7: Biomarkers at a Crossroads: Implications for Early Cancer Detection and Diagnosis

Carcinogenesis is a complex process requiring the coordinated interactions of numerous genes, proteins, signaling pathways and cell types. As a result of extensive studies on the molecular carcinogenesis of cancer, we are making significant strides in understanding and targeting these pathways and networks have been identified. These pathways have revealed several unique aspects, marked by stochastic modifications to cells and the expression of genes and proteins that accompany oncogenic transformation. This implies a morphological and molecular signatures change during cancer development. By discerning these changes accurately with the help of biomarkers, we can improve the early detection and diagnosis of individual cancers. Biomarkers are the molecular signposts that indicate the presence of a disease. This chapter will travel across the network or pathway leading to the development of a tumour. Biomarkers are the major measures by which future medical discoveries will be personalised for individuals, and prevention or treatment will be based on unique target-specific therapies, as opposed to standard systemic infusions of toxic chemotherapy agents [1].

Definition of biomarkers

There is no standard definition for “biomarker” that is universally used. In 1999, the US National Institutes of Health/Food and Drug Administration Working Group drafted a definition of a biomarker as a construct that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention [2]. However, this definition is broad and many researchers include the general public. Biomarkers may be defined as quantifiable molecules, including DNA, RNA, proteins, and metabolites, that are found in body fluids or tissues at an abnormal level that signal a pathologic condition, such as cancer. A biomarker might be a molecule that is altered by or a marker of an altered state of the body, such as cancer. Alterations in gene sequence or expression and in protein structure and function have been associated with more than 400 cancers and 300 investigational agents, has established guiding principles, commonly known as the five-phase approach, for developing, evaluating and validating biomarkers [3]. These guidelines are used to facilitate the transition of biomarkers toward clinical applicability. The five phases provide the principles and study designs for validating biomarkers headed for clinical use in risk assessment and early detection of cancer [4]. The discovery phase, which includes exploratory study to identify potentially useful biomarkers. In Phase 2, the validation phase, biomarkers are thoroughly analysed and verified to determine their capacity for distinguishing between people with cancer and those without. Phase 3 focuses on the capacity of a biomarker to detect precancerous disease by testing the marker against tissues collected from participants in a less invasive manner than organ biopsies. Phase 4 comprises prospective screening studies. In Phase 5, large-scale population-based collection of information on the biomarker for detection of cancer, and the overall impact of screening on the population and the healthcare system. This chapter provides information for novel technologies for diagnosing cancers.

The coupling of high-throughput technologies enables samples from hundreds of patients to be screened in parallel, and these technologies have greatly advanced the field of proteomics, the study of the structure and function of proteins including the way they work and interact with each other inside cells, genomics (the study of the organisation of genes and the molecular sequences of the component genes), and transcriptomics (the study of genes transcribed from DNA within living cells to molecules of messenger RNA) and their derivatives [5]. As a result, a number of candidate biomarkers have been identified for various cancer types. The next challenge is how to pick the right biomarkers from among the hundreds of promising candidates.

Selecting the right biomarker

The US National Cancer Institute’s Early Detection Research Network [4], a consortium of more than 40 laboratories and 300 investigators, has established guiding principles, commonly known as the five-phase approach, for developing, evaluating and validating biomarkers. These guidelines are used to facilitate the transition of biomarkers toward clinical applicability. The five phases provide the principles and study designs for validating biomarkers headed for clinical use in risk assessment and early detection of cancer [4]. The discovery phase, which includes exploratory study to identify potentially useful biomarkers. In Phase 2, the validation phase, biomarkers are thoroughly analysed and verified to determine their capacity for distinguishing between people with cancer and those without. Phase 3 focuses on the capacity of a biomarker to detect precancerous disease by testing the marker against tissues collected from participants in a less invasive manner than organ biopsies. Phase 4 comprises prospective screening studies. In Phase 5, large-scale population-based collection of information on the biomarker for detection of cancer, and the overall impact of screening on the population and the healthcare system. This chapter provides information for novel technologies for diagnosing cancers.

In the context of cancer biomarker testing, the sensitivity of a biomarker refers to the proportion of individuals with cancer who will test positive for the biomarker. Specificity refers to the proportion of control subjects (individuals without disease) who test negative for the biomarker. An ideal biomarker test would have 100% sensitivity and specificity, that is, everyone with cancer would have a positive test, and everyone without cancer would have a negative test. The lower the sensitivity, the more often individuals with cancer will not be detected. The lower the specificity, the more often someone without cancer will test positive. None of the currently known biomarkers achieve 100% sensitivity and specificity. For example, prostate specific antigen (PSA), currently the best clinical indicator for identifying prostate cancer, has high sensitivity (greater than 90%) but low specificity (only 25%), which results in many men having biopsies when they do not have detectable prostate cancer [6]. The sensitivity and specificity of cancer biomarkers are important factors that are considered when using a biomarker for clinical decision-making. In general, a biomarker with high sensitivity and low specificity is useful for screening purposes, while a biomarker with high specificity and low sensitivity is useful for diagnostic purposes.

The sensitivity and specificity of a biomarker are influenced by several factors, including the prevalence of the disease, the prevalence of the biomarker in the general population, the population being tested, and the clinical setting. For example, a biomarker with high sensitivity and low specificity is more useful for screening purposes in a population with a high prevalence of the disease, while a biomarker with high specificity and low sensitivity is more useful for diagnostic purposes in a population with a low prevalence of the disease.

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Biomarkers at a Crossroads: Implications for Early Cancer Detection and Diagnosis
Panel 15 microsatellite markers, in detecting bladder cancer in patients requiring cytoscopy. This technique will be compared to the diagnostic standard of cytoscopy, as well as to urine cytology.

To determine the temporal performance characteristics of microsatellite analysis of urine sediment.

- To determine which of the 15 individual markers or combinations of markers that make up the microsatellite analysis test are most predictive of the presence of bladder cancer.

Three populations will be included in this study. The three populations will include participants (100 each) without bladder cancer (controls). The control population will include two cohorts: (1) a cohort of 100 participants without a history of current urologic disease or devices and with a normal analysis and urine cytology examination, referred to as Control Group I, and (2) a cohort of 100 participants with one of four urologic processes and a cytology at baseline along with microsatellite analysis test are most predictive of the presence of bladder cancer.

To determine which of the 15 individual markers or combinations of markers that make up the microsatellite analysis test are most predictive of the presence of bladder cancer.

The accrual is now complete and follow-ups are underway. This first-ever study will provide evidence as to whether or not microsatellite analysis should be used alone or in combination with urine cytology and cytoscopy to monitor the progression of bladder cancer.

A number of other validation studies are underway for markers for pancreatic, lung, mesothelioma, prostate and bladder cancers (Table 3.7.1).

Future directions

Because a single biomarker may not have sufficient sensitivity and specificity to be useful for early detection, there is interest in multiplexing biomarkers (that is, developing a panel of them for concurrent use) that would probably perform better than a single diagnostic marker. Flexible technology platforms are being developed to simultaneously analyse a panel of protein or nucleic acid biomarkers or more than one kind of biomarker. The multiplexing approach can eliminate time-consuming manual processing of samples, making it faster, efficient and more convenient and allowing for routine data acquisition and efficient sample comparison. Another important innovation in biotech technology is the microfluidic chip-based immunoassay, which can analyse the expression of serum proteins comparable to commercial enzyme-linked immunosorbent assays, a method using antibodies to quantify levels of a biological marker. However, multiplexing can be a confounding task when optimizing the assay conditions, and there is still need for the development of efficient tools for analysing such high dimensional and high throughput data.

With continued attention, support and open cross-disciplinary, multi-institutional collaborations, the challenges of finding and developing accurate and useful biomarkers for early cancer detection and cancer risk will fade and new, long-awaited, less invasive tools brought into clinical use.

Table 3.7.1 List of clinical biomarker candidates transitioning through the five-phase approach established by the Early Detection Research Network

<table>
<thead>
<tr>
<th>Candidate/Panel</th>
<th>Organ</th>
<th>Status</th>
<th>Part of Multiplex</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanin 1, 179, 1, 16-3-5Nrb</td>
<td>Lung Adenocarcinomas</td>
<td>Phase II</td>
<td>yes</td>
<td>(1)</td>
</tr>
<tr>
<td>LCN2, TGF, REG1A, REG3 and IGFR1</td>
<td>Pancreatic</td>
<td></td>
<td>yes</td>
<td>(2)</td>
</tr>
<tr>
<td>SPINK1, PCA3, G0PH2, TMSS2-erG</td>
<td>Prostate</td>
<td></td>
<td>yes</td>
<td>(3)</td>
</tr>
<tr>
<td>CA-125, MF-1, prostatic, oatp1a1, OATP1A2, and leptin</td>
<td>Ovary</td>
<td></td>
<td>yes</td>
<td>(14)</td>
</tr>
</tbody>
</table>

REFERENCES

Stem Cells and Cancer Stem Cells

Summary

Stem cells constitute a distinct population of cells characterized by the ability to renew themselves indefinitely through mitotic division and to differentiate into a diverse range of specialized cell types.

The two broad types of mammalian stem cells are: the embryonic stem cells that are found in early embryos, and the adult stem cells that are found in many adult tissues.

The main properties of stem cells are self-renewal, essential for maintenance of the stem cell pool, and the ability to differentiate into different lineages required for the integrity and function of tissues.

Cancer stem cell (CSC) is an operational term to functionally define a distinct subpopulation of tumour cells with unlimited renewal potential. Cancer stem cells share many key properties with embryonic stem cells, including the intrinsic proliferation potential and the capacity to invade tissues and organs.

Research on stem cells and cancer stem cells holds great promise to advance the design of novel strategies in cancer therapy.

Embryonic and tissue-specific stem cells

Every cell in the body is a descendant of a single cell (fertilized egg or zygote). The life of an organism starts with fertilization of an egg, and from this moment until death involves the passage through several developmental stages. Each of these stages is associated with a specific set of properties (Figure 3.8.1). Multiplication of fertilized eggs gives rise to different cell types. This process involves generation of populations of stem cells that can be propagated indefinitely in culture under appropriate conditions. These cells are called the embryonic (ES) cells that are able to give rise to any cell type and to reconstitute the entire embryo. In addition, many adult tissues contain a discrete population of undifferentiated cells with properties of stem cells. These cells are known as tissue-specific stem cells (a.k.a. adult stem cells). Hematopoietic stem cells are the best-characterized tissue-specific stem cells that generate all blood lineages and mature blood elements. The adult stem cells are identified in many other tissues such as brain, skin, and liver. While only a few tissue-specific stem cells have undergone a rigorous identification and characterization, it is likely that stem cells are present in any tissue that undergoes renewal.

Tissue-specific stem cells also have the capacity to give rise to differentiated cells while maintaining their potential to give rise to various lineages. This characteristic is shared by embryonic stem cells. These cells have the potential to form all types of differentiated cells while retaining the capacity to give rise to different cell types.

The two characteristics of stem cells that distinguish them from all other cell types is their self-renewal and pluripotency. Self-renewal is the capacity of stem cells to multiply and produce identical daughter cells that can maintain their properties for extended periods of time. Pluripotency is the capacity of stem cells to differentiate into any cell type.

Cancer stem cells

Stem cells have been discovered a quarter of a century ago and have been exploited extensively for the generation of genetically modified animal models (for example, knockout mice), an essential tool in cancer research. However, the identification of the first human stem cells and in particular so-called cancer stem cells triggered unprecedented attention of the cancer research community. It has long been accepted that most tumours are derived from a single cell that has been transformed into a cancer-initiating cell through acquisition of a series of genetic and epigenetic lesions. These initial events allow expansion of transformed cells and formation of a population of cancer cells (clonotypes) with capacity to grow and divide in defiance of normal cellular control. Continuation of selection of “fitter” and more aggressive cancer cells results in a generation of cancer clones capable of invading and destroying neighbouring tissues and migrating to distant organs to form secondary tumours (metastasis). It is now believed that many human cancers arise from deregulated control of stem cells (Figure 3.8.2).

Cancer stem cells may involve more than one mechanism. First, cancer stem cells may be derived from normal stem cells. Second, cancer stem cells may arise as a result of abnormal behaviour and properties of stem cells. These hypotheses are not mutually exclusive, and the genesis of cancer stem cells may involve more than one mechanism.

Gene wiring that instructs stem cell identity

Although the features that distinguish stem cells from all differentiated cells have been known for a long time, the molecular mechanisms that determine the fate of stem cells are largely unknown.
for many decades, it was not until recently that we have begun to understand the genetic basis of stem cell identity. The development of powerful tools in genomics for genome-wide screens allowed the identification of genes and gene networks that keep stem cells in a special state. Using these tools, scientists have discovered a handful of genes that are necessary and sufficient to maintain self-renewal and pluripotency, two distinguishing features of stem cells. These genes are known as “masters of stemness.” The genes Oct4, Sox2, and Nanog belong to this privileged club [12]. These genes encode for specialised proteins known as transcription factors whose duty is to control the transcription of other genes (Figure 3.8.3). This forms a kind of genetic wiring that instructs stem cell behaviour, function, and identity. When these genes are inactivated or mutated, stem cells may differentiate into specialised cells and stem cell pool may be rapidly depleted. This can impede regeneration and integrity of normal tissues leading to degenerative diseases [13].

The discovery of stem cell master genes enabled another even more tantalising adventure: the reversal of specialised (differentiated) cells into immature pluripotent (stem) cells, the process known as de-differentiation—in other words, making specialised cells such as neurons or muscle fibre become cells with stem cell properties that would allow the generation of just about any type of cell. This would solve important ethical issues associated with the use of embryos as a source of stem cells. Recent studies demonstrated just that [1,14,15]. Several laboratories showed that the introduction of as few as 4 of master genes into differentiated cells (from patients) or other cells, including stem cells, could convert them into pluripotent cells with the potential for multi-lineage differentiation. This allowed the identification of genes and gene networks that are necessary and sufficient to maintain self-renewal and pluripotency, two features of stem cells that are controlled by epigenetic mechanisms. Self-renewal and pluripotency represent opposing patterns without changes in the genomic code (Figure 3.8.3). This forms a kind of genetic wiring that instructs stem cell behaviour, function, and identity. When these genes are inactivated or mutated, stem cells may differentiate into specialised cells and stem cell pool may be rapidly depleted. This can impede regeneration and integrity of normal tissues leading to degenerative diseases [13].

In contrast, the potential for multi-lineage differentiation requires plasticity of the genome allowing multiple differentiation decisions. The apparent dichotomy of stem cells is reflected by the presence of specific patterns in DNA methylation (epigenetic modification of DNA molecule which does not involve changes in genetic code) and histone modifications (markings of special proteins which ensure protection and compaction of DNA chain)[9]. Therefore, it is quite plausible that deregulation of epigenetic mechanisms may lead to an altered potential of stem cell self-renewal and expansion of epigenetically modified stem cell pools. Stem cells modified in this manner exhibit no genetic changes, yet they may represent a precursor to tumourigenesis and is a contributing factor to the apparent dichotomy of stem cells but also differentiated cells (Figure 3.8.2). The discovery of stem cell master genes enabled another even more tantalising adventure: the reversal of specialised (differentiated) cells into immature pluripotent (stem) cells, the process known as de-differentiation—in other words, making specialised cells such as neurons or muscle fibre become cells with stem cell properties that would allow the generation of just about any type of cell. This would solve important ethical issues associated with the use of embryos as a source of stem cells. Recent studies demonstrated just that [1,14,15]. Several laboratories showed that the introduction of as few as 4 of master genes into differentiated cells (from patients) or other cells, including stem cells, could convert them into pluripotent cells with the potential for multi-lineage differentiation. This allowed the identification of genes and gene networks that are necessary and sufficient to maintain self-renewal and pluripotency, two features of stem cells that are controlled by epigenetic mechanisms. Self-renewal and pluripotency represent opposing patterns without changes in the genomic code (Figure 3.8.3).
Fig. 3.8.4 Conventional therapies may reduce tumours by killing mainly differentiated cancer cells. If the putative cancer stem cells are the cancer to these therapies, then they will become viable after therapy and re-establish the cancer. By contrast, if the therapies can be targeted against cancer stem cells, then they might more effectively kill the cancer stem cells, rendering the tumour unable to maintain themselves or grow. Thus, even if cancer stem cell-directed therapies do not shrink tumours initially, they may eventually lead to cures [7].

REFERENCES

Biobanks are at the centre of recent advances in cancer research. A "biobank" is an infrastructure to store biospecimens, e.g. blood samples or tissues, and to make them available for laboratory analyses. The term "Biological Resource Centre" (BRC) is used to identify specialised units that handle the acquisition, quality control, storage, processing and distribution of biospecimens. Biobanks are a large-scale biological analysis with bio-computing, involving many actors at different levels. In this chapter, the authors explain how biobank data can be used to study the relationship between disease patterns in different parts of the world and the prevalence of diagnostic laboratories, and to develop effective strategies for managing these diseases. The chapter also discusses the importance of networking and the development of appropriate methods to obtain and store biospecimens. It is recommended that the institution develop biobanks, which can be of constant, controlled quality, independent of their origin. The authors stress that the development of biobanks can be made strongly comparable.
Proprietary and Confidential Information

Chapter 3.9. Biobanks and Biological Resource Centres

Chapter 3.9.1. Principles of sustainable Biological Resource Centres

Chapter 3.9.2. Infrastructure and facilities

Chapter 3.9.3. Management and staff

Chapter 3.9.4. Life and the environment

Chapter 3.9.5. Access to biobanks and BRCs

Chapter 3.9.6. Biological hazards

Chapter 3.9.7. Environment and alien biological species

Chapter 3.9.8. Records and documentation

Chapter 3.9.9. Forms of participation and communication

Chapter 3.9.10. Legal and moral requirements

Chapter 3.9.11. Appropriateness of the mechanisms of carcinogenesis

Chapter 3.9.12. Lessons learned

Chapter 3.9.13. Conclusions

Chapter 3.9.14. References

Chapter 3.9.15. Acknowledgements

Chapter 3.9.16. Glossary
The critical temperature for sensitive tissues, including the biochemical and physical properties of water, cryopreservation and formation of water crystals. Table 3.9.1 lists the most commonly accepted cryopreservation standards for human tissue and body fluids. It should be noted that specific applications (e.g., proteomics or development of primary cultures) may require more complex cryopreservation procedures. General information on the principles of cryopreservation may be found at http://www.cryobiology-systems.com/CBS/Cryobiology/cbs_ads.asp (Figure 3.9.3).

Specimen freezing is generally performed by placing the specimen in a sealed container, and by immersing the specimen into a rapid freezing medium. The ideal medium for rapid freezing is isopentane, which has been cooled to its freezing point (-130°C). To achieve this, the vessel containing the specimen must be introduced into another container of liquid nitrogen. The freezing point approximately corresponds to the moment when opaque drops begin to appear in the isopentane. Direct contact of the specimen with liquid nitrogen should be avoided, as this damages tissue structures.

Other fixation and preservation methods. Formalin fixation and paraffin embedding may be used as an alternative method to preserve tissues at relatively low cost when adequate freezing procedures and storage facilities are not available. Fixed paraffin blocks may be stored in the dark at 2°C in a correctly ventilated cupboard (Figures 3.9.4 and 3.9.5).

Tissues fixed according to strict protocols may be used for DNA extraction. The DNA is usually fragmented but remains suitable for PCR-based analysis of short DNA fragments (up to 10 kb). However, fixed tissues are of limited usefulness for RNA extraction. RNAlater cannot be further used for pathological analysis.

Working with Liquid Nitrogen

Where liquid nitrogen (LN) refrigeration is employed, an adequate supply of refrigerant must be maintained. The supply maintained in the liquid phase storage, including the risk of simultaneous leakage of N2 from the cryostat and LN2 in the vapour phase. Use of vapour phase nitrogen can lead to simultaneous leakage of N2 from the cryostat and LN2 in the vapour phase. Use of vapour phase nitrogen can lead to simultaneous leakage of N2 from the cryostat and LN2 in the vapour phase.

When bulk storage and piping systems are used, other fixation and preservation methods. Formalin fixation and paraffin embedding may be used as an alternative method to preserve tissues at relatively low cost when adequate freezing procedures and storage facilities are not available. Fixed paraffin blocks may be stored in the dark at 2°C in a correctly ventilated cupboard (Figures 3.9.4 and 3.9.5).
Readily available to all laboratory personnel. The SOP manual should specifically include:

- Specimen handling policies and procedures including supplies, methods and equipment
- Laboratory protocol for testing and any delays or other specimen processing
- Policies and procedures for shipping and receiving specimens
- Records management policies
- Quality assurance and quality control policies
- Procedures for supplies, equipment, instrument, reagents, labels, and processes employed in sample retrieval and processing
- Emergency and safety policies and procedures, including reporting of errors, complaints and adverse outcomes
- Policies and procedures and schedules for equipment inspection, maintenance, repair and calibration
- Procedures for disposal of medical and other hazardous waste
- Policies and procedures describing requirements of training programs for BRC staff

BRCs should have an appropriate QA and QC programs regarding equipment maintenance and repair, staff training, data management and recordkeeping, and adherence to Good Laboratory Practice. Each BRC must be subjected to regular audits. The timing, scope and outcome of these audits should be documented. QA is an integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. QC is the system of technical activities that measures the attributes and performances of a process, or item, against defined standards, to verify that the stated requirements are fully met.

Records Management
BRCs must develop a record management system that permits detailed records to be made concurrently with the performance of each step in the collection, processing and banking of specimens. This may include but is not limited to: informed consent, procurement, processing, preservation, quarantine, testing, record review, releasing, labeling, storage, distribution and quality control of specimens. Records shall be created and maintained in a manner that allows steps to be clearly traced. Record security systems should be adequate to ensure confidentiality and safety. Record management should be regularly audited. Records should be kept for at least 10 years after expiration of specimen storage or specimen distribution. Electronic records should be adequately protected (regular back-ups, an appropriate media, intrusion-proof management system).

The BRC should be inventoried at regular intervals (e.g. every two years) to assess the concordance between stored specimens and records. The specific position of every stored aliquot should be tracked. Each freezer, refrigerator or room temperature storage cabinet should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as, each location within the container. The biospecimen database should be updated each time a biospecimen is moved within or out of the biospecimen database.

Specimen labelling
Each specimen should be labelled in such a manner that the labelling will survive all potential storage conditions, in particular dry ice and liquid nitrogen.

- Ink used on the label should be resistant to all common laboratory solvents.
- Labels should be printed with a linear bar-code if possible, thus providing a direct link to database software. However, it is also important to include human-readable indicators of contents.
- Suggested information for the label is the tissue bank’s unique identifier number, sample type and date of collection/banking, plus a barcode if available (Figures 3.9.8 and 3.9.9).

Specimen collection, processing, storage
The methods used to collect biospecimens will vary depending on how the specimens will be processed and what is intended to be the end use. This paragraph provides general recommendations for collection of blood, solid tissues, urine and wide blood cells. These recommendations are derived from those described in the Biospecimen Protocols developed by the Australasian Biospecimen Network [6].

Collection of Blood
Detailed instructions and protocols for collection of blood specimens are given in the Protocols section. The following general guidelines should be considered:

- All blood should be treated as potentially infectious. It is recommended to take tissue bank blood samples concurrently with routine clinical blood samples, so as to limit exposure to prisoners, prison staff and BRC staff. Blood may be collected into EDTA, ACD (Acid Citrate Dextrose), lithium heparin, or into a chilled tube containing anticoagulant gel. Either EDTA and ACD tubes can be used. ACD tubes can be used to extract DNA. It is recommended that lymphocyte cell lines be made, however, ACD is more appropriate if there is to be an extended time lapse between blood collection and processing. Lithium heparin is generally only used if cytology studies are being performed. If DNA is to be extracted from the blood, an aliquot of cell lines be made, collecting into lithium heparin is not recommended [7].
- Tubes should be clearly labelled (Figure 3.9.10).
- The amount of blood usually collected varies for different diseases. In most cases, 2 tubes (18 ml) of blood is a good collection amount. The volume collected is guided by ethics clearance. Reduced volume of blood in a tube containing additives should be noted so as to avoid confounding of results with tissue processing.
- Time of blood and time of freezing should be recorded, as well as any variations to the processing.
- Blood should be transported at room temperature, unless otherwise specified for particular applications (for some proteomic applications require transport on dry ice).
- All blood should be processed within 24 hours of collection. Cell viability decreases rapidly after 24 hours, resulting in poor cell culture and quality control of specimens. The methods used to collect biospecimens will vary depending on how the specimens will be processed and what is intended to be the end use. This paragraph provides general recommendations for collection of blood, solid tissues, urine and wide blood cells. These recommendations are derived from those described in the Biospecimen Protocols developed by the Australasian Biospecimen Network [6].

Collection of Solid Tissues
Solid tissues are collected by biopsy or during surgical procedures. Collection should be core needle biopsy, preferably with cryopreservation of the tissue. The pathologist should be present in surgery when selecting the tissue to be processed and what is intended to be the end use. This paragraph provides general recommendations for collection of blood, solid tissues, urine and wide blood cells. These recommendations are derived from those described in the Biospecimen Protocols developed by the Australasian Biospecimen Network [6].

- Blood sample identification
- Blood sample identification

- Blood spot collection should be considered as alternative to whole blood when protocols call for easier collection and room-temperature storage. [8]. Guthrie cards are made from pure cotton and can be used for the extraction of DNA (Figure 3.9.11).

Collection of Solid Tissues
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- Collection of Solid Tissues
- Collection of Solid Tissues

- Collection of Solid Tissues
can be frozen in a Dewar of liquid nitrogen or on dry ice at the time of collection – When dry ice/liquid nitrogen is not readily available, tissue collectors into RNA/AlteR may be a good alternative provided that this tissue is not required for diagnosis and cleanup is given by the pathologist.

Collection of other specimens

Urine

Urine is easy to collect and is suitable source of proteins, hormones, metabolites and DNA from exfoliated bladder cells. However, storage of urine specimen is space-consuming. Urine should be stored at 0°C or in liquid nitrogen vapors.

Buccal cells

The collection of buccal cells is not difficult and does not require highly trained staff. Buccal cell collection should therefore be considered when non-invasive, self-administered or mailed collection protocols are required [8]. Donors who do not give blood may also be asked to donate a buccal cell specimen; however, buccal cell collection will yield only limited amounts of DNA in comparison to blood. A collection kit containing mouthwash, 50 ml plastic tube, plastic biohazard bottle, andコース (containing mouthwash, 50 ml plastic tube, plastic biohazard bottle, and courier packaging) may be mailed or given to the participant, along with an instruction sheet.

Specimen annotations, data collection

It is recommended that BRC adopt standardised systems for annotating the characteristics of collected specimens as well as data on the patients or subjects who are the source of these specimens. The nature and extent of data collection may vary depending upon the project in which the specimens are collected as well as depending upon the type of cancer and nature of specimen collected. The paragraphs below provide a brief outline of the structure of minimal annotation datasets.

Annotations on patients/subjects

– Local Patient Case Code

– Local BRC inventory code

– Disease condition (tumour/non-tumour/interference)

– Preservation protocol

– Time (in min) elapsed between tissue removal and fixation/freezing

– Duration of storage and record of storage incidents

– History of freezing/thawing

– Amount of tissue collected and amount left over in storage

Specimen shipping and sending

Human biospecimens are considered as “dangerous goods” that is, “articles or substances which are capable of posing a risk to health, safety, property, the environment”. According to UN regulations, dangerous goods meet one or more of nine UN hazard classes (see links to references below). The relevant class for biological specimens is Class 6, division 6.2: Infectious substances. It consists of three layers, as follows:

– Primary receptacle: a primary watertight, leak-proof receptacle containing the specimens, packaged with enough absorbent material to absorb all fluids in case of breakage.

– Secondary packaging: a second, durable, waterproof, leak-proof packaging to enclose and protect the primary receptacle. Several primary receptacles may be placed in one secondary packaging but additional absorbent material should be used in case of breakage.

– Outer packaging: an outer shipping packaging of suitable cushioning material, protecting the contents from outside influences while in transit (Figures 3.9.14 and 3.9.15).

Use appropriate insulation, e.g. for +8°C to 20°C use gel packs, for 80°C use dry ice and if samples need to be kept at -150°C, transport them in a dry shipper containing liquid nitrogen. Ensure enough refrigerant is included to allow for a 24-hour delay in shipping.

The triple packaging system also applies to Exempt Human Specimens such as paraffin-embedded samples (that should be shipped at room temperature in insulated packaging to protect from extreme fluctuations in temperature). Collection cards that are shipped in watertight plastic bag or histopathological slides (that need to be cushioned to prevent breakage) in all cases should be used for samples sensitive to humidity.

Labelling

All outer packages must bear United Nations packaging specification marking according to the category in which the specimens fall. For category A, the packaging instruction P650 applies. For category B, the relevant packaging instruction is P650. Detailed instructions are described in the IATA “Infectious Substances and Diagnostic Specimens Shipping Guidelines 2005” (www.iata.org).

WHO [World Health Organization]

Transport of infectious substances 2005


When preparing to transport biospecimens, it is important to consider shipping time, distance, climate, method of transport, and regulations as well as the type and number of biospecimens to be sent and their intended use. Below are some general guidelines:

Regulations

Infectious substances fall into two categories:

– Category A: Substances which are transported in a form that, when exposure to them occurs, are capable of causing permanent disability or life-threatening or fatal disease to humans or animals. Category A specimens include, but are not restricted to, specimens contaminated by highly pathogenic viruses (Bola, Hantaan, Marburg, Lassa, etc.) or cultures of viruses such as Dengue, Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV). The proper shipping name for such substances is UN2814: “Infectious substances affecting humans” or UN2900: “Infectious substances affecting animal only”.

– Category B: Substances that do not meet the above criteria. Most human specimens such as blood samples, tissues, exfoliated cells or urine, not contaminated by highly pathogenic viruses, will fall into Category B. The proper shipping name for such substances is UN3373: “Biological Substance, Category B”.

Biopspecimens or derived products that have been specifically treated to neutralize infectious agents, or for which there is a minimal likelihood that pathogens are present, are not subject to these regulations. The proper shipping name for such substances is “Exempt Human or Animal Specimen”.

Packaging

The basic triple packaging system applies to all substances. It consists of three layers, as follows:

– Primary receptacle: a primary watertight, leak-proof receptacle containing the specimen, packaged with enough absorbent material to absorb all fluids in case of breakage.

– Secondary packaging: a second, durable, waterproof, leak-proof packaging to enclose and protect the primary receptacle. Several primary receptacles may be placed in one secondary packaging but additional absorbent material should be used in case of breakage.

– Outer packaging: an outer shipping packaging of suitable cushioning material, protecting the contents from outside influences while in transit (Figures 3.9.14 and 3.9.15).

Use appropriate insulation, e.g. for +8°C to 20°C use gel packs, for 80°C use dry ice and if samples need to be kept at -150°C, transport them in a dry shipper containing liquid nitrogen. Ensure enough refrigerant is included to allow for a 24-hour delay in shipping.

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All outer packages must bear United Nations packaging specification marking according to the category in which the specimens fall. For category A, the packaging instruction P650 applies. For category B, the relevant packaging instruction is P650. Detailed instructions are described in the IATA “Infectious Substances and Diagnostic Specimens Shipping Guidelines 2005” (www.iata.org).

When shipping biospecimens overseas, be aware of the receiver country’s requirements prior to the initiation of the shipment, and ensure that the consignee adheres to these regulations.

Access to stored materials and data for research purposes

Access to human biospecimens for research purposes can be crucial for most fields of research. However, the access to the consignment adheres to these regulations.
There are many types of BRC. Tumour banks, which often are hospital-based collections, are a typical example of such a large collection of tissues which are ‘leftovers’ from diagnostic or surgical procedures. Many collections are also developed in the context of clinical trials: the patients recruited in these trials donate blood or tissue specimens, the analysis of which often enrich the results of the trial by allowing a better understanding of the parameters that determine good or bad responses to a treatment. But the largest collections are formed when the more systematic collections are those associated with large cohort studies developed in molecular epidemiological contexts. Typically, in such cohorts, healthy subjects are recruited, donate specimens at the time of recruitment for (for example, blood, urine, saliva, or exfoliated cells from the buccal cavity) and are then followed up for a period of time that can extend over several decades. With time, a proportion of these subjects develop chronic diseases, including cancer (and also diabetes, heart diseases, or many other medical conditions) and are then used to carry out molecular studies using the specimens collected at recruitment, to identify biomarkers that predict or explain why these individuals developed the disease under study.

The EPIC (European Prospective Investigation into Cancer) is a typical example of such a large cohort study. It was developed by the IARC as a long-term, multicentric prospective study in Western Europe to investigate the relationships between nutrition and cancer, taking advantage of the vast range of cancer rates observed in European countries. At the time of recruitment, healthy subjects were invited to participate either by mail or in person. Individuals who agreed to participate signed an informed consent agreement and were mailed a questionnaire on diet and a questionnaire on lifestyle. Most participants completed these questionnaires at home and were then invited to a study centre for an examination that included collection of the completed questionnaires, blood donation, anthropometry and measurement of blood pressure. The enrolment of subjects took place between 1992 and 2000. The cohort participants are now followed over time for the occurrence of cancer and other diseases, as well as for overall mortality. The study has recruited 319,978 participants in 23 centres located in 10 European countries.

Constructing and running a large BRC: The example of the EPIC biobank

There are many types of BRC. Tumour banks, for example, often are hospital-based collections of tissues which are ‘leftovers’ from diagnostic or surgical procedures. Many collections are also developed in the context of clinical trials: the patients recruited in these trials donate blood or tissue specimens, the analysis of which often enrich the results of the trial by allowing a better understanding of the parameters that determine good or bad responses to a treatment. But the largest collections are formed when the more systematic collections are those associated with large cohort studies developed in molecular epidemiological contexts. Typically, in such cohorts, healthy subjects are recruited, donate specimens at the time of recruitment for (for example, blood, urine, saliva, or exfoliated cells from the buccal cavity) and are then followed up for a period of time that can extend over several decades. With time, a proportion of these subjects develop chronic diseases, including cancer (and also diabetes, heart diseases, or many other medical conditions) and are then used to carry out molecular studies using the specimens collected at recruitment, to identify biomarkers that predict or explain why these individuals developed the disease under study.

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Blood was obtained by venipuncture and sepa- rated into plasma, serum, white blood cells and erythrocytes. They were collected from 385 ML of the 519 978 EPIC study partici- pants. To make storage easier, blood samples were aliquoted into 28 plastic straws containing 0.5 mL each. Thus, tropomyosin and two mirror halves of 14 aliquots each. One set was stored at +4°C and the other was trans- ported to IARC to be kept in liquid nitrogen in a central biorepository located at IARC, where the specimens are kept under N2 liquid phase. The biobank contains about 3.8 million straws, labelled with the participant’s ID and colour-coded to indicate its contents.

The EPIC provides a framework for addressing a wide range of questions relevant to cancer. When biological samples are involved, studies mostly use the nested case–control approach. Typically, cases are subjects who developed a particular pathology after they were recruited in the cohort (incident cases) and had not been diagnosed with cancer before or at the time of recruitment. Controls are usually chosen at random among all cohort members who were alive without cancer at the time of recruitment of the case. The logistical tasks related to speci- men handling include sample management, labelling and distribution are handled by the team of Laboratory Infrastructure and Resources (LIR) and IARC. Based on lots of specimens and on their known position in the biorepository, the LIR technicians develop an ordered retrieval plan that minimise the time of opening of each LN2 tank. Specimen retrieval is performed manually. It takes about 5 minutes to access one specific storage position and to retrieve either one or several straws of materials from the same subject. Standard operating proce- dures include double checking of 10% of all retrieved specimens to minimise the risk of individual errors. On average, a trained techni- cian can retrieve specimens for about 150 sub-

The future of biobanking

The EPIC example shows the importance of developing large biobanks by networking the efforts of scientists in different countries. There is indeed a huge benefit in networking. Cancer diseases are very diverse and have complex relationships with both the genetic makeup of individuals and their lifestyles, so comparisons across different countries, ethnic groups and cultural backgrounds are extremely informative. Through biobanking, large biobanks such as EPIC can be made of networks and hubs, interconnecting many collection centres and making it possible to access large series of specimens for research. By networking, it is possible to share the burden of invest- ing into large biobanks as well as the benefits of research. Today’s cancer research is a vast, collective endeavour, in which scientists and doctors have to team-up in powerful networks, capable of delivering the best of human’s mind creativity to the bedside of cancer patients.
According to WHO 2002 mortality estimates, cancer is the fourth-ranked cause of death in the Eastern Mediterranean and North African Region (EMRO), after cardiovascular diseases, infectious/parasitic diseases and injuries. It is estimated that cancer kills 272,000 people each year in the EM Region, more than HIV/AIDS, tuberculosis and malaria combined (241,000 deaths per year). Although cancer incidence in the EM region is still much lower than in other parts of the world, the largest increase in cancer incidence among the WHO regions in the next 15 years is likely to be in the EM region, in which projected modelling predicts an increase of between 100% and 1815% (Rastogi et al. 2004). At present, resources for cancer control in the EM region as a whole are not only inadequate but directed almost exclusively to treatment. However, the impact of preventive measures on incidence is not fully exploited, while the lack of approaches to earlier diagnosis results in a reduced value of therapy. The curability of cancer is directly related to its stage at the time of diagnosis, and in the majority of EM countries, cancer is generally diagnosed when at a relatively advanced stage (Table 1).

In response to the above situation, WHO/EMRO has developed a regional strategy for the prevention and control of cancer in its Member States, a draft of which was presented and discussed in a consultative meeting in Marrakesh, Morocco, November 2007 and will be finalised and formally launched in a meeting planned in April 2008. A Regional Alliance Against Cancer, bringing together various NGOs and interested parties working in EM Member States, was formally created during the Marrakesh meeting under the leadership of WHO and in collaboration with the Lalla Salma Association Against Cancer and H.R.H. Princess Lalla Salma, Patroness of Prevention and Care for cancer in the Eastern Mediterranean Region.

The strategy lays a foundation for the development of a coordinated approach that seeks to take advantage of the strengths of some of the regional resources to overcome some of the weaknesses that exist in the Region. An important function of the strategy resides in its twin goals of sensitising all of Member States to the pressing need to control cancer more effectively, while at the same time providing technical guidance and is a foundational formula for regional cooperation in this endeavour. The strategy encourages countries to develop their National Cancer Control Programmes (NCCPs) on essential first step towards more effective cancer control.

The EM regional strategy is in keeping with the WHO Global Action Plan against Cancer (GAPAC) and pursues the same goals, which are to:

- Prevent Preventable Cancers (through avoiding or reducing exposure to risk factors, e.g. prevention strategies);
- Cure Curable Cancers (early detection, diagnostic and treatment strategies);
- Relieve Pain and Improve Quality of Life (Palliative care strategies); and
- Manage for Success (strengthening health care systems, management, monitoring and evaluation of interventions).

WHO/EMRO continues to assist countries to develop their NCCPs, and in 2007 participated in two missions to Yemen and Syria in collaboration with IAEA’s PACT Programme.

The pattern of cancer in EM Region is shown in Table 2. Data are obtained from the GLOBOCAN database and updated, for many countries, directly by national focal points based on latest information from their cancer registries. Breast cancer has the highest incidence rate in most countries, while cervical cancer is the leading type of cancer in Djibouti and Somalia.

REFERENCES


Table 1. Stage at diagnosis in breast and cervical cancer as reported by a population based registry in Saudi Arabia [National cancer registry report, 2002], Tanta Cancer registry (Gharibiah 2000-2002, Egypt), and US [SEER, 9 Registries 1988-2003].

<table>
<thead>
<tr>
<th>Country</th>
<th>1st cancer</th>
<th>2nd cancer</th>
<th>3rd cancer</th>
<th>4th cancer</th>
<th>5th cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>Breast</td>
<td>Stomach</td>
<td>Esophagus</td>
<td>Lung</td>
<td>Oral Cavity</td>
</tr>
<tr>
<td>Bahrain</td>
<td>Breast</td>
<td>Lung</td>
<td>Colon</td>
<td>Bladder</td>
<td>Leukaemia</td>
</tr>
<tr>
<td>Djibouti</td>
<td>Cervix</td>
<td>Liver</td>
<td>Breast</td>
<td>Esophagus</td>
<td>Kaposi</td>
</tr>
<tr>
<td>Egypt</td>
<td>Breast</td>
<td>bladder</td>
<td>NHL</td>
<td>Liver</td>
<td>Lung</td>
</tr>
<tr>
<td>Iran</td>
<td>Breast</td>
<td>Stomach</td>
<td>Colon</td>
<td>Bladder</td>
<td>Esophagus</td>
</tr>
<tr>
<td>Iraq</td>
<td>Breast</td>
<td>Leukaemia</td>
<td>Lung</td>
<td>Brain and CNS; Larynx</td>
<td>Bladder</td>
</tr>
<tr>
<td>Jordan</td>
<td>Breast</td>
<td>Colon</td>
<td>Lung</td>
<td>Bladder</td>
<td>NHL</td>
</tr>
<tr>
<td>Kuwait</td>
<td>Breast</td>
<td>Lung</td>
<td>Colon</td>
<td>NHL</td>
<td>Leukaemia</td>
</tr>
<tr>
<td>Lebanon</td>
<td>Breast</td>
<td>Lung</td>
<td>Bladder</td>
<td>Cervix</td>
<td>Larynx</td>
</tr>
<tr>
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<td>Breast</td>
<td>Lung</td>
<td>Colon</td>
<td>Head &amp; neck; Cervix</td>
<td>Bladder</td>
</tr>
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<td>Morocco</td>
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<td>Lung</td>
<td>Cervix</td>
<td>Prostate</td>
<td>Lymphoma</td>
</tr>
<tr>
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<td>Stomach</td>
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<td>Lung</td>
<td>NHL</td>
<td>Liver</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Breast</td>
<td>Oral Cavity</td>
<td>Lung</td>
<td>Esophagus</td>
<td>Bladder</td>
</tr>
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<td>Breast</td>
<td>Colon</td>
<td>Bladder</td>
<td>Liver</td>
</tr>
<tr>
<td>Saudi Arabia</td>
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<td>NHL</td>
<td>Liver</td>
<td>Colon</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Somalia</td>
<td>Cervix</td>
<td>Liver</td>
<td>Esophagus</td>
<td>Breast</td>
<td>NHL</td>
</tr>
<tr>
<td>Sudan</td>
<td>Breast</td>
<td>Cervix</td>
<td>Oral Cavity</td>
<td>Esophagus</td>
<td>Colon</td>
</tr>
<tr>
<td>Syria</td>
<td>Breast</td>
<td>lung</td>
<td>NHL</td>
<td>CNS</td>
<td>Bladder</td>
</tr>
<tr>
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<td>Lung</td>
<td>Breast</td>
<td>Bladder</td>
<td>Colon</td>
<td>NHL</td>
</tr>
<tr>
<td>UAE</td>
<td>Breast</td>
<td>Colon</td>
<td>Blood Leukaemia</td>
<td>Lymphomas</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Yemen</td>
<td>Breast</td>
<td>NHL</td>
<td>Colon</td>
<td>NHL</td>
<td>Esophagus</td>
</tr>
</tbody>
</table>

Table 2. Commonest 5 cancers in EM countries
Tobacco Control

Summary

- The main benefit from quitting smoking arises from avoiding the more pronounced increase in risk that would result from continuing to smoke.
- Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers.
- The WHO Framework Convention on Tobacco Control (WHO FCTC), a public health treaty conceived to reduce tobacco use and supply, is widely supported, encompasses a series of stipulations designed to control tobacco use and supply.
- Comprehensive tobacco-free and tobacco-pricing policies, two of the WHO FCTC-endorsed policies, have been effective in reducing exposure to secondhand smoke, diminishing cigarette consumption, and increasing quitting smoking.
- There are pharmacologic and non-pharmacologic tobacco dependence treatment options, varying in effectiveness, available to aid those who want to quit smoking.

Risk reduction

For smoking-induced morbidity and mortality to disappear, smoking initiation in the young must cease. Ironically, it would take many decades for morbidity and mortality trends to reflect the effects of such intervention, mainly due to the long time expected before observed health consequences in prevalent smokers will continue to do so. However, if current smokers quit, the risks of developing smoking-related diseases would diminish even if stopping after decades of smoking. An assessment of changes in cancer risk and of other diseases caused by smoking with smoking cessation was conducted by an International Expert Group of experts convened at IARC in Lyon on March 13-19, 2006 [12]. The assessment addressed three questions:

- Is the risk of developing cancer, for each of the 13 tobacco-associated cancers considered reduced, lower in former smokers than in otherwise similar current smokers?
- Are otherwise similar former smokers, is the risk of disease lower with more prolonged abstinence?
- Does the risk return to that of never smokers after a long period of abstinence?

Conclusions by the Working Group on the effects of smoking cessation on the risk of developing and dying from lung, laryngeal, and oesophageal cancers are shown in Tables 4.1.1 and 4.1.2, indicating a lower risk of cancer at these sites in those who quit as compared to those who continue to smoke [2].

Tobacco control interventions

To arrest the global tobacco epidemic, intervention must be prevented and cessation encouraged at the population level (e.g. smoking restrictions in public places) and the latter often effective in reducing exposure to secondhand smoke, diminishing cigarette consumption, and increasing quitting smoking.

Tobacco control interventions are directed at preventing tobacco use, decreasing tobacco use and supply. The body of policies stipulated in the treaty became binding international law on 27 February 2005. Of the 38 articles, articles 6 to 14 cover policy interventions directed at preventing tobacco use, decreasing consumption, reducing toxicity, protecting non-smokers and diminishing tobacco use. Intervention Articles 15 to 17 relate to measures controlling the availability of tobacco [Table 4.1.3] [3]. The concerted adherence of countries to the treaty among the world will make it a global response to the tobacco epidemic. An issue in each of the policy interventions included in the WHO FCTC will depend on the way effectively countries formulate and implement these policies. As of November 2005, 160 countries have signed the treaty [Figure 4.11][13]. IARC convened a group of international tobacco control policy experts in March 2007 to propose a framework for guiding the evaluation of tobacco control policies expected to be formulated worldwide in response to WHO FCTC. This framework and its scientific and policy bases will aid tobacco control policy authorities to assess if intended targets are fulfilled [4].

Comprehensive tobacco control programs are more likely to be successful in reducing tobacco use than programs relying in few interventions. Jassim and Raw [3] have proposed a scale to quantity the implementation of tobacco control interventions at country level. Their work is based on a baseline survey conducted in 2005 in 30 European countries. Tobacco control policies taken into account in the scale included price of cigarettes and other tobacco products, smoke-free work and other public places on July 1, 2005, spending on public information campaigns in 2004, comprehensive bans on advertising and promotion on July 2005, large health warning labels on July 1, 2005; and taxation services in place. Tobacco control performance varied greatly worldwide, from countries accruing 270 points (Croatia, Spain, Iceland and Norway) to countries accumulating <30, with results by type of intervention indicating areas where future efforts could be concentrated.

Protection from exposure to SHS. Countries enacting laws banning smoking in public places have shown high compliance and significant decrease in SHS exposure. The banning of smoking in pubs and restaurants in Scotland started in March 2006, with pre-ban concentration levels of particulate matter [PM] 1.0 are

Benefits of quitting smoking on risk of developing and/or dying from lung cancer

Table 4.1.1 provides data on the risk difference in developing and/or dying from lung cancer in comparison with an otherwise similar individual who has never used tobacco.

Table 4.1.2 Benefits of quitting smoking on risk of developing and/or dying from lung cancer

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The majority of smokers desire to quit smoking, but the path from intention to actual cessation is long and fraught with many obstacles. There are pharmacologic (i.e. nicotine replacement therapy, NRT, Table 4.1.4) and non-pharmacologic interventions (Fig. 4.1.3) available to aid smokers quit their dependence on nicotine, the addictive component of tobacco, and both types are often prescribed together. One year after the Scottish ban a significant decline in cotinine concentrations (i.e. smoking biomarkers) was higher for individuals living in households where the household (and cars) as a source of exposure to SHS [7]. This systematic review found an overall reduction in smoking prevalence (3.5%, 95% CI: 2.9–4.2%) and percentage of cigarettes smoked daily in continuing smokers (3.1 cigarettes, 95% CI: 2.4–3.8) with total smoking bans. Price and tax measures to reduce demand. The impact of similar price increments (10%) on tobacco use in low/middle-income countries approached, smoking restrictions on the population studied and the income level referred to (3.4–6.5% in China; 13.3% and 5.2% in lower and higher income respectively in Bulgaria) [11] long-term reduction in tobacco consumption at a per capita price increase of a 1.25 to 2.65ld over placebo, blupofusin, an anti- depressant and smoking cessation aid involves 3 daily doses of 2 over placebo, and varenicline, a nicotine receptor partial antagonist that reduces nicotine withdrawal symptoms (odds ratio of quitting of 3-fold over placebo) [14,15]. The characteristics of these therapies are compared in Table 4.1.4. These products have been tested in clinical trials where psychological, behavioral and emotional supports have been available to trial participants. Since approximately 70% of smokers want to stop smoking, it is imperative that smokers become aware of the existence of these pharmacologic approaches and that healthcare providers use every opportunity possible to assess patient’s desire to quit, provide information on quitting aids, advise additional support of non-pharmacologic interventions for the treatment of nicotine dependence, and try to identify possible follow smokers in their quitting attempts (Table 4.1.5). More recently, vaccine technology has been used to produce antibodies against nicotine as an approach to prevent exposure in former smokers and to allow quitting smoking. Several vaccines have been formulated and tested in animals and humans with cessation success has been observed in those mounting strong anti- body responses [16]. At present, 3 vaccines have been tested in Phase II clinical trials, each using a different antigen (nicotinic) presentation approach. MucVax® (Celtic Pharma, Harlington, Buckingham) binds nicotine to recombinant cholera toxin B; NicQb (Cytos Biotechnology, Zurich, Switzerland) employs virus-like particles from the bacteriophage Qb; and NicVax® (Pfizer Pharmaceuticals, Boca Raton, Florida, USA) uses recombinant exoprotein A [15]. The nicotine vaccine can also bring about a reduction in the amount smoked by making the metabolism of nicotine slower and reducing its effect to last longer, hence reducing craving. The duration of the vaccine immunity is, however, unknown at present. Dosing and administration schemes are being formulated in order to treat smokers on Phase II clinical trials that will reveal vaccine efficacy. The potential use of this secondary prevention approach is very promising given the number of smokers who wish to quit and the number of former smokers who desire to remain abstinent.

### Discussion

Two WHO FCTC-endorsed policies with impact at the population level and several approaches to tobacco dependence in the population. Such policies in achieving reductions in tobacco use and protection in nonsmokers will depend on a more complex array of factors than those included in this chapter, such as total or partial ban of smoking restrictions in work and public places, enforcement of restrictions, tax avoidance, smuggling of tobacco products and/or proliferation of lower priced alternative tobacco products, and both types are often prescribed together. Nicotine replacement therapy has been shown to modulate tobacco use in adolescents and adults. Lung cancer rates are influenced by smoking initiation and smoking cessation in the population. At present, there are many countries showing increasing trends in lung cancer mortality in younger age groups where there are no evident trends in decreasing smoking initiation and/or...
increasing smoking cessation. If these smoking trends remain unaltered, projected lung cancer incidence and mortality will grow rather than decrease. Policies leading to smoking cessation and preventing smoking initiation must be fostered and maintained. Also important, smokers and former smokers can and should be assisted in their attempts to quit and remain abstinent by receiving pharmacologic and non-pharmacologic intervention treatments within the healthcare system or as advised by the principal healthcare provider. However, smokers tend to avoid clinic-based smoking cessation programmes but on the other hand respond to environmental prescriptions such as smoking bans. Hence the importance of policy-based interventions designed to deter tobacco use and eventually leading to the denormalisation of this behaviour.

<table>
<thead>
<tr>
<th>Table 4.1.4 Pharmacologic treatment of tobacco dependence. Adapted from Le Foll and George, 2007[14]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Nicotine replacement therapy</td>
<td>Dose is adjusted to level of nicotine dependence and is decreased progressively over treatment period</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>Initial dose: 21–42 mg/d, then decreased progressively</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>8–10 pieces (2 or 4 mg each) per day</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>4–6 puffs per day</td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>9–20 lozenges per day</td>
</tr>
<tr>
<td>Bupropion, sustained release (Zyban)</td>
<td>150 mg/d for first 3 days, then 300 mg/d</td>
</tr>
<tr>
<td>Varenicline (Champix)</td>
<td>0.5 mg/d for first 3 days, then 0.5 mg twice daily for the next 4 days and 1 mg twice daily thereafter</td>
</tr>
</tbody>
</table>

**Table 4.1.5 Nonpharmacologic interventions for the treatment of tobacco dependence and their estimated efficacy. Adapted from Le Foll and George, 2007[14]**

*Note: CI = confidence interval.
REFERENCES

Over the past 50 years, the number of occupa-
tionally induced cancers has likely decreased in high-resource countries [3]. This is due to several different trends. The decline in blue-
collar heavy industry and the corresponding growth of white-collar knowledge indus-
ties has served to decrease the number of workers in particularly “dirty” occupations. At the same time, many industries have insti-
tuted procedures and processes that provide much cleaner work sites than in the past [2]. The motivations for this are complex and multi-
dimensional. In part, this is a byproduct of epidemiologic research carried out in the past [3,4]. In many countries the identifica-
tion and characterisation of occupational carcinogens triggers regulatory actions intended to reduce the permissible exposure levels. Such actions may range from substitution of one substance in an industrial process for another, modifica-
tion of industrial procedures or ventilation, emission control procedures, or the use of protective equipment by workers. But the real benefits of such regulations may be quite non-
specific. That is, while regulations concerning a particular carcinogen may be expected to reduce the risk of cancer in relation to that carci-
gen, cleaning up an industrial process induces reduction in exposure to many substances, some of which may be in the hidden part of the iceberg of occupational carcinogens.

It is impossible to estimate how many occupa-
tional cancer cases have been prevented, but it is certainly a partial success story. In addi-
tion, there has been a growing realisation on the part of many industries that good industrial hygiene makes good business sense. The caution-
tary tales of companies that have suffered from regulatory or legal opprobrium, as well as compensation costs, as a result of being identified as a ‘cancer-causing company’, might have served as an incentive for other companies to clean up.

Setting standards for regulatory purposes is a di-
ficult task that relies on epidemiologic, toxicologic and after data [5,6]. Historically, these standards have usually been based on consid-
erations of acute toxicity; increasingly, however, cancer has become a key endpoint. The main problem with setting standards aimed at reducing carcinogen exposure is the lack of reliable epidemiologic data on dose-response relationships. For the most part, the regulators must rely on animal data, with complex math-
ematical models used to translate the animal experiments into terms that are relevant for human risk assessment. One approach, which can only be imple-
mented if a known cancerogen has not yet been intro-
duced into industrial practice, is to ban its introduction. On occasions when an agent has been used and shown to be carcinogenic in one country that information can then be used by other countries. For example, following reports from the United States on the increased bladder cancer risk among workers exposed to 4-aminobiphenyl, its introduction was banned in the United Kingdom [7]. Substitution of prod-
ucts known to be carcinogenic has been used successfully, as in the example of asbestos and man-made mineral fibers. More common, however, have been attempts to reduce exposure levels to known or suspect carcinogens. Successful examples include the virtual elimination of radiation related cancer risk among nuclear industry workers [8], the significant decrease in liver cancer risk among workers in the vinyl chloride industry following recognition of its carcinogenicity in the 1970s [9], the significant decrease in lung cancer risk among American workers exposed to chloromethyl ethers fol-
lowing recognition of its carcinogenicity in the 1950s [10], and the significant decrease in lung cancer risk among Norwegian nickel refinery workers following recognition of cancer risks in the 1930s [11].

Table 4.2.1 1993 - acting for prevention

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Butadiene concentration (mg/m3)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1991</td>
<td>22 (Probable human carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Belgium</td>
<td>1991</td>
<td>22 (Probable human carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>1991</td>
<td>20</td>
<td>Ceiling</td>
</tr>
<tr>
<td>Denmark</td>
<td>1993</td>
<td>22 (Potential occupational carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Finland</td>
<td>1998</td>
<td>22 (Potential occupational carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>France</td>
<td>1993</td>
<td>36</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Germany</td>
<td>1998</td>
<td>34 (Human carcinogen)</td>
<td>Technical exposure limit</td>
</tr>
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<td>Hungary</td>
<td>1993</td>
<td>10 (Potential occupational carcinogen)</td>
<td>Short-term exposure limit</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1996</td>
<td>46</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>The Philippines</td>
<td>1993</td>
<td>2200</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Poland</td>
<td>1997</td>
<td>100</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Russia</td>
<td>1991</td>
<td>100</td>
<td>Short-term exposure limit</td>
</tr>
<tr>
<td>Sweden</td>
<td>1991</td>
<td>20 (Suspected of having a carcinogenic potential)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 (Suspected of having a carcinogenic potential)</td>
<td>Ceiling</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1991</td>
<td>11 (Suspected of being a carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>Turkey</td>
<td>1993</td>
<td>2200</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1991</td>
<td>22</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACGIH (Threshold Limit Value)</td>
<td>1997</td>
<td>4.4 (Suspected human carcinogen)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>NIOSH (Recommended Exposure Limit)</td>
<td>1997</td>
<td>(Potential occupational carcinogen: lowest feasible concentration)</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>OSHA (Permissible Exposure Limit)</td>
<td>1996</td>
<td>2.2</td>
<td>Time-weighted average</td>
</tr>
</tbody>
</table>

Limits and guidelines from International Labour Office (1991); United States Occupational Safety and Health Administration (OSHA, 1996); American Conference of Governmental Industrial Hygienists (ACGIH, 1997); United States National Library of Medicine (1997); Deutsche Forschungsgemeinschaft (1998); Ministry of Social Affairs and Health (1998) * Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

Table 4.2.2 International occupational exposure limits and guidelines for butadiene (what is stated by IARC as an established human carcinogen, Group 1).

The decrease in exposure to occupational carci-

nogens may be due to reduced emissions, improved ventilation or use of personal protec-
tion by the workers. As a general rule, the first two approaches are more efficient in achieving a durable reduction in exposure than is the use of protective equipment. Reduction of emissions can be easily achieved for chemicals produced under controlled conditions, such as intermedi-
ates formed during chemical manufacturing processes. However, reduction of exposure at the sources might be difficult to achieve for sub-
stances that are used under less controlled condi-
tions, such as motor exhausts.

Screening of occupationally exposed workers has been proposed as an additional measure to prevent cancer deaths. However, for none of the cancers for which it has been proposed is there evidence of efficacy. This is the case in particular for lung cancer and mesothelioma among asbestos-exposed workers, and bladder cancer among workers exposed to aromatic amines [12,13].
There has been significant improvement in occupational hygiene conditions in large industries in high-resource countries [2]. The challenge is to extend this improvement to smaller enterprises and to medium- and low-resource countries, where there remain significant problems of exposure to such agents as asbestos, crystalline silica and pesticides [14].

### Table 4.2.3: Means to either prevent or determine the level of exposure to occupational carcinogens

<table>
<thead>
<tr>
<th>Compound</th>
<th>Average ambient air concentration [mg/m³]</th>
<th>Cancer associated</th>
<th>IARC classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde</td>
<td>5</td>
<td>Nasal tumours in rats</td>
<td>2B</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>0.01 – 16</td>
<td>Lung cancer in workers</td>
<td>2A</td>
</tr>
<tr>
<td>Arenic</td>
<td>(1 – 30) x 10⁻⁶</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Benz(a)pyrene</td>
<td>No data</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Bis(2-chloroethyl)ether</td>
<td>No data</td>
<td>Epitheliomas in rats</td>
<td>1</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.5–10</td>
<td>Kidney tumours in rats</td>
<td>2B</td>
</tr>
<tr>
<td>Chromium VI</td>
<td>(5 – 2000) x 10⁻⁶</td>
<td>Lung cancer in workers</td>
<td>1</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>0.07 – 4</td>
<td>Tumour formation in rodents</td>
<td>2B</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>1.0 – 10.0</td>
<td>Lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Nickel</td>
<td>1 – 180</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>(1 – 10) x 10⁻⁶</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>0.1 – 0.7</td>
<td>Hepatocellular carcinomas in mice</td>
<td>3</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1 – 10</td>
<td>Cell tumours in tissues of rats</td>
<td>2A</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>0.1 – 10</td>
<td>Haemangiosarcoma in workers</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 4.2.4: WHO guidelines (1999) for air pollutants with carcinogenic health endpoints. These substances have been classified by IARC as either human carcinogens (Group 1), probable human carcinogens (Group 2A) or possible human carcinogens (Group 2B).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Average ambient air concentration [mg/m³]</th>
<th>Cancer associated</th>
<th>IARC classification</th>
</tr>
</thead>
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</tr>
<tr>
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<td>0.01 – 16</td>
<td>Lung cancer in workers</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>2B</td>
</tr>
<tr>
<td>Chromium VI</td>
<td>(5 – 2000) x 10⁻⁶</td>
<td>Lung cancer in workers</td>
<td>1</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>0.07 – 4</td>
<td>Tumour formation in rodents</td>
<td>2B</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>1.0 – 10.0</td>
<td>Lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Nickel</td>
<td>1 – 180</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>(1 – 10) x 10⁻⁶</td>
<td>Lung cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>0.1 – 0.7</td>
<td>Hepatocellular carcinomas in mice</td>
<td>3</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1 – 10</td>
<td>Cell tumours in tissues of rats</td>
<td>2A</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>0.1 – 10</td>
<td>Haemangiosarcoma in workers</td>
<td>1</td>
</tr>
</tbody>
</table>

### REFERENCES

Chapter 4.3: Vaccination

Summary

- Hepatitis B virus (HBV) vaccine has proven its broad global effect in preventing chronic hepatitis and hepatocellular carcinoma.
- Twenty-five years after having been licensed, HBV vaccination programs are now carried out in at least 158 countries. However, they have yet to achieve high genetic protection in many high-risk areas, such as sub-Saharan Africa.
- Two human papillomavirus (HPV) vaccines were licensed in 2007 and show high efficacy in the prevention of precancerous lesions of the cervix uteri in young women who have not already been infected by the HPV types included in the vaccine.
- The duration of the efficacy of the HBV vaccine and the need for a booster are not yet known, and the vaccine price is currently unaffordable in medium- and low-income countries.
- The development of vaccines against infections other than HBV and HPV has been very difficult. A more realistic goal for vaccines against hepatitis C virus (HCV), human immunodeficiency virus (HIV) may be in the prevention of chronic hepatitis and disease as opposed to reducing complete protection against primary infection.

The most important implication of our understanding that a high fraction of cancer may be caused by chronic infections [19] is the possibility of preventing the onset of these cancers through vaccination. Mass immunization, when it has proved feasible, has reached in some of the greatest medical successes in human history. Vaccination programs have been implemented even in the poorest countries of the world and in fact can lead to substantial cost-saving, something that is rarely expected of healthcare interventions. The renewed interest in vaccines that has been seen in the past few years, including those meant to prevent certain cancers, is greatly encouraging. However, there are also some major limitations in vaccine research, development and distribution in different parts of the world, which will be explored briefly in this chapter.

Cancer-causing chronic infectious agents include DNA viruses, RNA viruses, bacteria and parasites. Two vaccines against two DNA viruses, HBV and HPV, have shown efficacy in preventing the corresponding chronic infection, as well as precancerous lesions of the affected sites (liver and cervix). Progress in the design of vaccines against RNA viruses that are associated with increased chronic (HBV and HIV) and chronic infection (hepatitis B surface antigen, HBsAg).

HBV vaccine

An epidemic of jaundice due to HBV infection since childhood have a 5% incidence of hepatocellular carcinoma. It has been estimated that adults who have had chronic HBV infection since childhood have a 5% incidence of hepatocellular carcinoma per decade. HBV vaccines were first licensed in the United States in 1981. Formerly, they were plasma-derived and composed of purified HBsAg. Nowadays, HBV vaccines are predominantly produced by recombinant DNA technology. The vaccine is administered in a three-dose series and has resulted in high immunogenicity and efficacy, which to date has been monitored using shorter immunization series (i.e., reduction in acute HBV infection and seroconversion studies in vaccinated populations). Declines in incidence and mortality rates from hepatocellular carcinoma have been reported only in children and adolescents in Taiwan, which established the first HBV immunization program in 1984 [4]. A better estimate of the decrease in the cancer burden will be possible in approximately a decade in the two large-scale randomized trials. HBV was first started in 1986 in the Gambian [5] and in 1990 in Qidong, China [6]. Despite decreases in anti-HBcV titers, to date, relatively low, immunocompetent vaccinated individuals have not developed chronic hepatitis A infection in 10–20-year follow-up. Vaccine protection within 12–24 hours after birth, followed by a 3-dose vaccine series, is effective in preventing vertical transmission, and the safety of the vaccine has been demonstrated in large studies. Concerns were expressed about the possibility of the vaccine having caused some cases of multiple sclerosis, diabetes mellitus and demyelinating diseases, but an expert panel dismissed these for lack of an association [7]. In addition, breakthrough infections by HBV mutant escapes among successfully-vaccinated persons have been excluded.

In 1992, the World Health Organization (WHO) recommended the integration of the HBV vaccine into national immunization campaigns. As shown in Figure 4.3.1, the number of countries that introduced the vaccine and implemented global infant coverage grew steadily from 17 in 1989 to 96 in 2000. By 2005, 158 of the 192 WHO Member States had infant HBV vaccination programs in place, with over half of these countries (62%) reporting ≥80% coverage by their programs ([4.3.2]. The 34 countries that have not yet introduced infant HBV vaccination notably include several high-endemic countries in sub-Saharan Africa. Several high-resource countries with low HBV endemicity, including the United Kingdom, Scandinavian countries and Japan, do not routinely vaccinate children, but have instead chosen to target high-risk groups (e.g., immigrants from high-endemicity areas, adolescents, and adults with risk factors for HBV infection). Priorities for the future are clearly to expand the number of high-endemicity countries that

Figure 4.3.1: Number of countries that introduced hepatitis B virus (HBV) vaccine in children and global infant HBV vaccine coverage, 1989–2005.

include HPV vaccination in infant immunisation schedules (Fig. 4.3.1) and to improve coverage in countries that have already opted to do so (Fig. 4.3.2). The drop in the price of the HPV vaccine and the efforts of vaccine - developing organisations should help to make these targets possible. In addition, as polio of selective immunisation of high-risk individuals are seldom effective, routine HPV vaccination is now also advocated in low-endemicity coun - tries on the grounds that whenever a potentially devastating disease like hepatitis B can - cina is easily preventable, steps should be taken to achieve this outcome.

### HPV Vaccine

HPVs are DNA viruses that infect epithelial (skin or mucosal) cells. There are more than 100 known mucosal HPV types, and at least 13 of them, called high-risk types, can cause cancer of the cervix [8]. HPV16 and 18 are found in over 70% of cervical cancer world - wide and also predominate in cancer sites other than the cervix (i.e. anus, vulva, vagina, penis, and a small fraction of cancers of the head and neck). The discovery that cervical cancer was associated with sexual contact paved the way to an understanding of the role of HPV infection, which is predominantly sexu - tally transmitted [8].

The two currently available HPV vaccines [9,10] include HPV16 and 18 and are based on L1 virus-like particles (VLPs), i.e. empty viral capsids. They were therefore expected, as has been subsequently confirmed, to be effective, as they include neither viral oncogenes nor low - attenuated virions. They have been licensed since 2007 for use in women aged 9–26 years in the United States, European Union and in a number of other countries. In clinical trials that included approximately 40,000 women, both vaccines were at least 90% effective in pre - venting persistent HPV infection and 95% effec - tive in preventing type-specific precancerous lesions (i.e. cervical intraepithelial neoplasia [CIN]) grade 2 and 3, and in situ adenocarcinoma of the cervix. One of the two vaccines also includes low-risk HPV types 6 and 11, and is therefore able to prevent genital warts, in addition to cervical HPV infections.

Available vaccines did not, however, prevent development of CIN3 and 3 women who had been infected by HPV16 and 18 before immunisation, or CIN2 and 3 caused by other HPV types in clinical trials. [9]. Therefore, in the analyses by intention to treat, the efficacy diminished from 98% to 100% (95% confidence interval: 7–29%) when all CIN2 and 3 lesions were considered [Table 4.3.1]. This efficacy profile obliges us to: 1) concentrate on the vac - cination of girls before they become sexually active; 2) try to increase the number of high-risk HPV types present in the vaccine, and 3) make every possible effort to match immunisation with high-quality organised screening programs [11]. Although data on all high-risk types present in CIN2 and 3 have not yet become available, some cross-protection against persistent infec - tion from high-risk types other than HPV16 and 18 has been reported [Table 4.3.2] [10].

However, successful prevention of cervical cancer through immunisation promotes enor - mous challenges. The greatest of these are the lack of information on the duration of vaccine efficacy, which at this point has been evaluated for no more than five years, and by the vaccine price that is unaffordable in many medium- and low-income countries. In addition, reaching girls before puberty or in their early teens may be more difficult than delivering vaccines to newborns and infants, especially in low-resource countries. Cultural barriers and misinformation may also burden HPV vaccine acceptance.

For the moment, no plan exists to expand the use of the HPV vaccine to boys, as if efficacy of the vaccine in the prevention of HPV infection in men is not yet proven, and 2) if good coverage is achieved, a sexually transmitted infection like HPV should be greatly reduced even by vac - cinating one gender only.

### Vaccines against other cancer-causing chronic infections

Research into new prophylactic and therapeutic vaccines is also ongoing for at least three addi - tional infections that are responsible for a large portion of the cancer burden worldwide: HCV, HIV and Hp. Although the first two agents are RNA viruses and the third is a bacterium, they all - have in common some characteristics that have greatly endeared past efforts to produce efficacious vaccines: 1) they display high genetic and antigenic diversity and mutate very rapidly in the host; 2) they induce, after natural infec - tion, strong humoral and cellular responses that seem, however, unable to eliminate the infection or prevent reinfection; and 3) small animal model or cell culture systems were available up until recently to help vaccine developments.

Several candidate vaccines (e.g. virus-like par - ticles, recombinant vaccines) are increasingly important cause of liver cancer, were tested in chimpanzees [12], and induced a strong cellular-immune response. Vaccination did not prevent the chimpanzees from becoming infected, but the course of the infection was apparently attenuated.

A Gram-negative flagellate bacterium that is present in the stomach of more than half of the global population, is the leading cause of chronic gastritis, peptic ulcer disease and gastric adenocarcinoma and lymphoma (see

---

**Table 4.3.1** Efficacy of quadrivalent vaccine against human papillomavirus (HPV) 16/18

<table>
<thead>
<tr>
<th>Vaccine / Control</th>
<th>HPV type</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol</td>
<td>Against HPV 16/18</td>
<td>Against any HPV type</td>
</tr>
<tr>
<td>HPV-negative</td>
<td>99 (92–100)</td>
<td>98 (89–100)</td>
</tr>
<tr>
<td>CIN3/2 or AIS</td>
<td>99 (92–100)</td>
<td>98 (89–100)</td>
</tr>
<tr>
<td>CN2</td>
<td>100 (99–100)</td>
<td>99 (92–100)</td>
</tr>
<tr>
<td>CN3</td>
<td>98 (89–100)</td>
<td>97 (89–99)</td>
</tr>
<tr>
<td>AIIS</td>
<td>100 (99–100)</td>
<td>97 (89–99)</td>
</tr>
</tbody>
</table>

**Table 4.3.2** Efficacy of bivalent vaccine against human papillomavirus (HPV) 16/18

<table>
<thead>
<tr>
<th>Vaccine / Control</th>
<th>HPV type</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol</td>
<td>Against HPV 16/18</td>
<td>Against any HPV type</td>
</tr>
<tr>
<td>HPV-negative</td>
<td>92 (85–99)</td>
<td>92 (85–99)</td>
</tr>
<tr>
<td>CIN2 or more severe</td>
<td>2 / 21</td>
<td>90 (83–99)</td>
</tr>
<tr>
<td>CIN3 or more severe</td>
<td>3 / 28</td>
<td>90 (83–99)</td>
</tr>
<tr>
<td>Persistent infections (12 months)</td>
<td>3 / 28</td>
<td>90 (83–99)</td>
</tr>
<tr>
<td>HPV16/18</td>
<td>11 / 46</td>
<td>76 (69–84)</td>
</tr>
<tr>
<td>Other high-risk types</td>
<td>100 / 137</td>
<td>72 (57–84)</td>
</tr>
<tr>
<td>All high-risk types</td>
<td>112 / 180</td>
<td>38 (18–54)</td>
</tr>
</tbody>
</table>

---

**Fig. 4.3.2** Course of human immunodeficiency virus infection in vaccinated persons and the hypothetical course of infection in unvaccinated persons

Panel A shows the course of infection in unvaccinated persons. The primary stage of HIV infection (yellow) starts with a burst of viremia, dissemination of the virus, early seeding and destruction of gut-associated lymphoid tissue, and establishment of a latent component (window of vulnerability). HIV levels in plasma then decline to a set point that lasts from months to years. Eventually, in the absence of effective therapy, the virus escapes immune control and AIDS results (red). Panel B shows the hypothetical course of infection in vaccinated persons. A true vaccine might decrease the burst of viremia and dissemination that occurs in primary infection (yellow), preserving gut-associated lymphoid tissue, decreasing viral levels at the set point, and increasing the length of time that viral loads are controlled (blue). From Johnston and Fauci, 2007.
under one year old in the Gambia for a review). A few vaccination studies have not provided satisfactory results such as recombinant urease, which is the target of the virus, but later their attention moved to vaccines able to enhance T-cell immu-
nity. However, Tollcl mediated control of infection may not prove to be complete. Deciding whether the level and duration of-mediated protection observed in clinical trials are sufficient to seek or grant vaccine licensing will challenge vaccine developers and regulators alike. At the same time, whether the level and durability of moderated protective vaccines such as recombinant urease, killed whole bacteria in infected participants [14].

A unique feature of HIV is that a pool of latently infected lymphocytes (resting CD4+ T cells) is the target of the virus, but later their attention moved to vaccines able to enhance T-cell immunity. However, Tollcl mediated control of infection may not prove to be complete. Deciding whether the level and duration of-mediated protection observed in clinical trials are sufficient to seek or grant vaccine licensing will challenge vaccine developers and regulators alike. At the same time, whether the level and durability of moderated protective vaccines such as recombinant urease, killed whole bacteria in infected participants [14].

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Chemoprevention is the reduction of cancer risk through the use of pharmaceuticals or other agents such as micronutrients. Chemoprevention is an appealing low-cost and easy cancer control method, mainly for subject having an inherited predisposition to certain cancers.

Randomised trials using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence on cancer risk, although these ordinary doses seem to reduce mortality.

Vitamin A and retinoids

Compounds related to vitamin A comprise preformed vitamin A compounds, essentially retinol and retinyl esters. These compounds were initially shown to modulate differentiation in many experimental systems [10,11]. No significant effects on mortality rates were observed for supplementation with combination of retinol and zinc [12]. beta-carotene and retinol A [5]. One large randomised trial of a vitamin A analogue, bemetretex, showed no impact on occurrence of secondary breast cancer in breast cancer survivors [13]. Vitamin A and retinoids may antagonise the physiological action of vitamin D, mainly on bone. Two studies have reported doubling of hip fracture rates among women with high retinol intakes from food or supplements (>1.5 mg per day) [14,15].

In 1998, a systematic review by an IARC Expert Group concluded that there was inadequate or limited evidence for anti-cancer activity of nine different retinoid acid compounds, and some of them are teratogenic in humans or in animals [Table 4.4.1] [11].

Retinoids are a class of compounds structurally related to vitamin A. In 1999, a systematic review by an IARC Expert Group concluded that there was inadequate or limited evidence for anti-cancer activity of nine different retinoid acid compounds, and some of them are teratogenic in humans or in animals [Table 4.4.1] [11].

Vitamin C

Vitamin C is thought to be a free-radical scavenger, and high intakes of foods rich in vitamin C (e.g. citrus fruits) could play a role in decreasing gastric cancer incidence. Double-blind randomised trials of supplementation with ascorbic acid, vitamin E, selenium and beta-carotene of populations at high risk for gastric cancer in China and Venezuela did not result in higher rates of regression of dysplastic lesions in the stomach [16,17].

Vitamin E

Vitamin E exists in eight different isomers, and alpha-tocopherol is the most biologically active. Vitamin E has anti-oxidant properties that have been deemed to play a role in control of cellular oxidative damage. In the ATBC study [5], the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However, deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women’s Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk [18].

A meta-analysis of vitamin E supplementation including 16 randomised trials suggested that high doses of vitamin E supplementation that were deemed to play a role in control of cellulite oxidative damage. In the ATBC study [5], the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However, deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women’s Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk [18].

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Selenium
Selenium is involved in defence mechanisms against oxidative stress through the selenoproteins. Selenium at high doses is known to be toxic. A randomised placebo-controlled trial of doses around 200µg per day was thought to prevent non-melanoma skin cancer, and colorectal and prostate cancer. Selenium has been part of several trials, but often mixed with vitamins, making it difficult to isolate an effect specific to this compound. The Nutritional Prevention of Cancer (NPC) Trial [20] was a placebo-controlled randomised trial to test whether selenium supplements could reduce the incidence of non-melanoma skin cancer. The incidence of non-melanoma skin cancer remained the same in the intervention and in the placebo groups. However, the group that received the supplement had statistically significant reductions of 40% and 50% in overall cancer incidence and cancer mortality, respectively. Main reductions in incidence were observed for prostate, colorectal and lung cancer. Separate follow-up of lung cancer and prostate cancer showed reduction of the incidence of these two cancers in subjects who had low serum selenium levels at baseline, and not in subjects with higher levels at baseline [21,22]. A meta-analysis of the data showed that all the protective effect was confined to males, and that selenium supplements decreased cancer risk in subjects with low serum selenium levels at baseline, whereas these supplements seemed to increase cancer risk in subjects with high serum levels at baseline [21].

A randomised trial organised within the NPC Trial failed to show reduction of colon polyps with selenium supplementation [23], but again a significant decrease was noticeable among subjects with low serum selenium levels at baseline, while in subjects with high serum selenium level at baseline, the frequency of polyps was greater, although statistically non-significant.

Recent results of the Third National Health and Nutrition Examination Survey (NHANES III) cohort study in the USA call for caution with use of this compound, as the study suggests a U-shaped curve in associated risk with serum selenium levels and all-cause and cancer mortality, with higher mortality in subjects with low or with high serum levels of selenium, and lower reduction in overall mortality compared to optimal serum levels [24]. Hence, supplementation with selenium has little influence on cancer risk, and instead can be detrimental for subjects who have high levels of serum selenium.

Microorganisms in subjects with poor nutritional conditions

One large trial tested a combination of beta-carotene, vitamin E, selenium and trace elements (e.g. in a poorly nourished Chinese population [12]). After 5 years, the treated group experienced a statistically significant 9% reduction in total mortality, mainly as a result of a statistically significant 21% lower stomach cancer mortality rate. There was no significant reduction in oesophageal cancer, the primary endpoint of the study. Indirect evidence that beta-carotene may protect from stomach cancer in high-risk subjects comes from the randomised, controlled double-blind chemo-prevention trial in subjects with gastric dysplasia in the area with a very high gastric cancer incidence in Colombia. Gastric biopsies taken at baseline were compared with those taken after 72 months; daily use of 30mg beta-carotene (combined with vitamin C) resulted in a statistically significant increase in the frequency of regression of preneoplastic lesions of the stomach [25].

Multivitamin preparations

A systematic review conducted under the auspices of the US National Institute for Health found that multivitamin preparations could reduce cancer risk [26]. A possible role of vitamin D in colorectal cancer is suggested by cohort studies [30]. But the randomised trials that found no impact at all of ordinary doses of vitamin D supplements [33,34] on colorectal and all-cancer risk. The trial by Trivedi et al [33] had as its primary objective the reduction of fracture risk and used 800 IU vitamin D alone per day, while the WHI trial [34] used 400 IU vitamin D per day and 50 mg elemental calcium.

Methyl donation: Folic acid

Folic acid plays an important role in DNA repair, synthesis and methylation reactions. Two randomised placebo-controlled trials showed that folic acid supplements may in reality increase the risk of colorectal and prostate cancer, and of adenomas of the polype [28-30]. A possible role of vitamin D in colorectal and prostate cancer is suggested by cohort studies [30]. Also, arguments in the placebo group severely undermined the trial’s findings [37].

A meta-analysis of randomised trials on intake of vitamin D and calcium supplements found that 500–600 IU per day of vitamin D i.e., doses similar to those tested in the WHI and in the trial by Trivedi et al [33] decreased all-cancer mortality [38]. This result is in sharp contrast to trials on antioxidants showing increasing all-cancer mortality. The biological mechanisms underlying the gain in life expectancy remains obscure but in probability not mediated by a reduction in cancer risk.

The question remains whether higher doses of vitamin D supplements would have more beneficial effects than ordinary doses, on cancer risk, on the risk of other non-cancerous diseases, and on mortality. The associations between high intakes or high baseline serum levels of several compounds and higher or reduced mortality are not well explained. However, studies on high-dose vitamin D supplements may in reality increase the risk of colorectal and prostate cancer, and of adenomas of the polype. The WHI trial’s findings [37] support the view that high-dose vitamin D, such a schedule should first be tested by large-scale double-blind placebo-controlled randomised study [32].

Nonsteroidal anti-inflammatory drugs (NSAIDs)
Numerous observational epidemiological studies have found that long-term users of aspirin or other NSAIDs have a lower risk of colorectal adenomas and polyps and colorectal cancer than non-users [90, 95]. The biological mechanisms may stem from anti-cancer properties of NSAIDs. For instance, NSAIDs suppress inflammation, apoptosis and angiogenesis, and so are potential candidates for cancer prevention. Increasing latitude has been equated with a decrease in vitamin D status due to less sun exposure and thus less endogenous synthesis of vitamin D in the skin. Vitamin D levels in the skin and subcutaneous tissues, including the generation of cytoprotective prostaglandins. Inflammatory stimuli induce COX-2, which is also highly expressed in colorectal neoplasia in the absence of stimulation.
cyclooxygenase (COX)-2 inhibitor celecoxib, effectively inhibit the growth of familial adenomatous polyposis (APC) [44, 45]. However, randomised trials in patients with sporadic adenomatous polyps reduced the possibility of using this class of drug for cancer prevention because of significant cardiovascular toxicity despite effectiveness in preventing sporadic polyps [43, 44]. Administration of celecoxib did not result in regression of adenomatous polyps [43, 44]. Trials showed that celecoxib and raloxifene had a similar ability to reduce breast cancer incidence. Raloxifene induced fewer thrombembolic events, but seemed to increase the incidence of in situ breast cancer. Death rates among women taking tamoxifen or raloxifene were similar.

Omega-3 fatty acids

Omega-3 fatty acids are mainly found in oily fish, and were deemed to protect against oxidative reactions involved in cancer and cardiovascular diseases. Systematic reviews of prospective cohort studies and of randomised trials found no evidence for a protective effect of these fatty acids on either cancer (including colorectal and breast cancer) or cardiovascular diseases [54, 55].

Dietary fibre (see also chapter on diet and cancer)

A systematic review of 13 prospective cohort studies found no effect of dietary fibre intake on colorectal cancer incidence [56]. In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas [57-60]. The randomised trial by Bonnithon-Kopp et al. [58] found that subject assigned in the intervention arm (300g/hukka 3.5g per day) had a 17% increase in kidney stone formation in the WISHL trial [54].

Conclusions

Most of these trials testing chemopreventive properties of many compounds found to possibly have anti-cancer properties in observational studies turned out to be negative or to show serious adverse events. Therefore, no recommendation for use of a compound (even “natural substances” found in the diet) for cancer chemoprevention should be made before a large randomised trial (preferably double-blind and placebo-controlled) has evaluated both the efficacy as well as adverse effects of ingestion of the compound.

In healthy subjects living in well-nourished communities, current evidence does not support recommendations for any agent for chemoprevention. In communities with sub-optimal nutritional status, supplements with anti-oxidants may serve to mitigate toxicity.

Randomised trials conducted so far using ordinary doses of vitamin D (i.e. 400-600 IU per day) have shown no influence of vitamin D supplements on colorectal cancer risk. However, these ordinary doses seem to reduce all-cause mortality. The effects of intakes of high doses of vitamin D (≥1500 IU per day) over the long term are unknown, and such schedule should be hot tested by a placebo-controlled randomised study [42].
REFERENCES


In most developed countries, cytological screening (Pap test) has led to a significant reduction in the incidence of and mortality from cervical cancer, particularly in countries that have implemented population-based screening programmes. In countries with lower participation compliance and a less developed healthcare system, screening has been much less effective in reducing mortality.

In developing countries, the cost of infrastructure and initial investments for organised cytological screening may be prohibitive. Alternative methods such as visual inspection with acetic acid (VIA) or with Lugol's iodine solution (VILI) are effective in preventing cervical cancer in low-resource countries.

HPV testing is an alternative but currently expensive method for screening and preventing cervical cancer. There is a need to develop simple, affordable and accurate methods of HPV testing with comprehensive guidelines for its use in screening programmes.

Screening should be implemented in the context of an organised programme following comprehensive quality assurance guidelines, with adequate attention paid to planning and training, resources for management of detected lesions and coordination, monitoring and evaluation of performance and effectiveness.

Invasive cervical cancer is preceded for several years by asymptomatic and slowly progressing precancerous lesions such as high-grade cervical intraepithelial lesions (CIN grade 2 and 3) or adenocarcinoma in situ. The early detection of CIN by screening and their effective treatment leads to prevention of invasive cervical cancer. Following the introduction of cervical screening programmes in many developed countries a decline in incidence of and mortality from cervical cancer has been observed in the past 5 decades (Figure 4.5.1).

Persistent infection with one or more of the oncogenic types of human papillomaviruses (HPV) is the cause for cervical neoplasia (1), and cervical cancer is a rare long-term outcome of a common viral infection of the cervical epithelium. This knowledge has opened up new avenues of prevention such as HPV vaccination and HPV testing for cervical screening. While HPV vaccination is an exciting and emerging preventive option in the long run, currently screening remains the principal strategy to prevent cervical cancer globally. CIN 2–3 lesions represent a ‘precancerous’ stage of cervical squamous-cell carcinoma that has high prevalence and is detectable in the course of population-based screening. On the other hand, screening is often not effective in detecting the pre-invasive glandular lesions of the cervical canal. HPV screening has instead proved to be effective in preventing adenocarcinoma of the cervix.

Conventional cervical cytology (Pap smear, Figure 4.5.2), the most commonly and widely used cervical screening test, has been largely responsible for the early detection of cervical precancerous lesions and subsequent decline of invasive cervical cancer incidence and mortality in many developed regions of the world where successful screening programmes have been established. However, certain limitations of the Pap smear, in terms of the subjective nature of the test, resources required and low sensitivity in most routine settings, have led to the development and evaluation of alternative screening tests such as liquid based cytology, HPV testing and visual screening tests.

The efficacy of Pap smear screening

Cytology screening involves collection of cervical cells from the cervical epithelium using a wooden spatula or a brush, preparation and fixation of the smear by a doctor or a nurse followed by staining and reading and reporting of the results by a cytootechnician and a cytopathologist. Cytology requires a laboratory infrastructure, with internal and external quality control measures to process slides and microscopy, and a system to communicate the results to the women. High-quality training, continuing education and proficiency testing of personnel are essential to ensure reliable and efficient testing. Population-based Pap smear screening programmes were initiated in British Columbia in 1949 and in regions of Norway in 1959 and Scotland in 1960. Since then, programmes have been introduced in many developed countries. These programmes vary in their organisation, differing in the balance between public and private health care, whether the programme is systematic and population-based or opportunistic (based upon self-referral), the age range of the women to whom screening is offered, the recommended interval between successive screens and the follow-up and management of women found to have cervical abnormalities.

In most routine settings, Pap smear has a wide range in sensitivity in detecting cervical neoplasia. The sensitivity to detect CIN 2 and 3 lesions ranged from 47–92% and the specificity from 65–95% in reviews of several studies [2,3]. The sensitivity of Pap smear ranged from 31–78% and the specificity from 91–96% in studies in developing countries [4].

Large-scale population-based cytology screening programmes have resulted in a marked reduction in the incidence of and mortality from cervical cancer in the past few decades in the developed countries of Europe, North America, Japan, Australia and New Zealand [4]. Organised screening with systematic call, recall, follow-up and surveillance systems have shown the greatest effect [e.g. Finland, Iceland], while using fewer resources than the less organised programmes [e.g. USA, France]. In the UK,
cervical cancer incidence rates started declining after coverage for screening was improved (Figure 4.5.3). Cervical cancer incidence has been reduced by as much as 80% where the cytology screening quality, coverage and follow-up of women are high. The highest reduction in cervical cancer incidence was in the 30–49 age group, where the focus of screening was the most intense.

Pap smear screening has been very sparsely implemented in most developing countries. Establishing quality-assured cytology screening programmes with national coverage is a challenging task in many developing countries, in view of the infrastructure for testing, trained personnel for reading, quality assurance and the resources and organization required. Cytology screening programmes in Latin American countries such as Cuba, Brazil, Mexico, Peru and Colombia, among others, have not resulted in a significant reduction in the cervical cancer burden in these countries [5]. Possible reasons for the lack of success in these countries include a combination of sub-optimal cytology testing, lack of quality assurance, poor coverage of women at risk and inadequate follow-up of screen-positive women with diagnosis and treatment. A critical appraisal of reasons for the sub-optimal performance of cytology screening in low- and medium-resourced countries has prompted the reorganisation of programmes in many Latin American countries and the evaluation of alternative screening tests, such as HPV DNA testing, visual screening with 3–5% acetic acid or Lugol’s iodine, and paradigms of HPV DNA testing, visual screening with 3–5% acetic acid or Lugol’s iodine, and paradigms that require one or two visits to complete the screening and diagnosis/treatment processes [6]. Following the reorganisation of the Pap smear programme in Chile, incidence and mortality started to decline [7].

Liquid-based cytology

Liquid-based cytology (LBC) relies on a uniform thin-layer of cervical cells (Figure 4.5.4) without debris prepared from processing a fluid medium containing the cervical cells, leading to improved sample adequacy and microscopic readability of the smear. It is a more expensive test than conventional cytology, and requires additional instrumentation to prepare the smears. Although earlier reviews claimed improved sensitivity to detect high-grade CIN [3,8], results from a recent review [9] and a randomised trial [10] do not support claims of better performance by LBC.

HPV testing

The fact that cervical neoplasia are caused by persistent infection with oncogenic types of HPV has led to the evaluation of HPV testing as a primary screening test for cervical neoplasia. HPV testing is the most objective and reproducible of all currently available cervical screening tests. In several cross-sectional studies the sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66–100% and the specificity varied from 62–90% [4,11,12]. The sensitivity of HPV testing reported by studies in developing countries has been somewhat lower than that reported by studies in developed countries. Recently reported randomised trials indicate that HPV testing has higher sensitivity for the detection of CIN as compared with Pap smear [13–15].

Although self-sampling for HPV DNA testing seems to be a viable screening option, and potentially promising for use in under-resourced areas or for women who are reluctant to participate in screening programmes, further definitive research is needed to provide a solid evidence base to inform on the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened [16].

In low-resource settings, where repeated screening of women is not feasible, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease [4]. However, it is currently more expensive ($35–$80) than other screening tests and requires sophisticated laboratory infrastructure including testing equipment, storage facilities for samples, and trained technicians. Further developments in terms of less expensive testing and less sophisticated infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings. Efforts are now under way to develop simple, affordable, rapid and accurate HPV testing methods for use in low- and medium-resource settings.

In summary, compared to cytology, HPV testing is substantially more sensitive for prevalent CIN 2 or worse lesions, but significantly less specific. Whether this gain represents overdiagnosis or protection against future high-grade CIN or cervical cancer is not clear. Reduced incidence

Table 4.5.1 Cervical cancer incidence and mortality in the cluster randomized controlled trial in Tamil Nadu, India. S. Sankaranarayanan et al. (2007) [24], M. Quinn et al. (1999) [29], B.J. Willoughby et al. (2006) [30]

<table>
<thead>
<tr>
<th>Eligible individuals</th>
<th>Cancer causes</th>
<th>Cervical cancer incidence mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>30,958</td>
<td>Cervical cancer incidence</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>0.34 (0.18–0.66)</td>
</tr>
<tr>
<td>30–49 years</td>
<td>Overall</td>
<td>1.00</td>
</tr>
<tr>
<td>40–49 years</td>
<td>1.00</td>
<td>0.62 (0.49–0.94)</td>
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<tr>
<td>50–59 years</td>
<td>1.00</td>
<td>0.82 (0.55–1.24)</td>
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<td></td>
<td>50–59 years</td>
<td>1.00</td>
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</tbody>
</table>

Table 4.5.2 Cervical cancer incidence and mortality in the cluster randomized controlled trial in Tamil Nadu, India. S. Sankaranarayanan et al. (2007) [24]

<table>
<thead>
<tr>
<th>Cancer deaths</th>
<th>Hazard ratio (95% CI)</th>
<th>92</th>
<th>83</th>
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<tbody>
<tr>
<td>Overall</td>
<td>Overall</td>
<td>1.00</td>
<td>0.65 (0.47–0.89)</td>
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<tr>
<td>30–49 years</td>
<td>1.00</td>
<td>0.34 (0.18–0.66)</td>
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<tr>
<td>40–49 years</td>
<td>1.00</td>
<td>0.52 (0.31–0.92)</td>
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<tr>
<td>50–59 years</td>
<td>1.00</td>
<td>0.99 (0.58–1.76)</td>
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</tbody>
</table>
of or mortality from invasive cervical cancer among HPV-screened subjects compared with cytologically-screened subjects has not yet been demonstrated; this issue is being addressed in a randomised trial in India [17]. Interim results from this trial show similar detection rates of CIN 2 and 3 lesions per 1000 screened women among those screened by cytology, HPV testing or visual screening with 4% acetic acid. HPV testing reportedly does not add significant psychological distress when combined with cytology in routine primary cervical screening [18].

### Visual inspection

Visual screening is carried out after application of dilute acetic acid or Lugol's iodine solution. Visual inspection with acetic acid (VIA) involves naked-eye inspection of the cervix using a bright torch light or a halogen focus lamp, 1–2 minutes after the application of 3–5% acetic acid using a cotton swab or a spray. A positive test is characterised by well-defined acetowhite areas close to the squamo-columnar junction (SCJ), to the external os, on the entire cervix or a cervical growth turning acetowhite (Figure 4.4.5) [19]. Immediate results following VIA allow diagnostic investigations and/or treatment in the same session as screening. However, VIA is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for VIA are yet to be standardised and assuring consistent high performance can be challenging under field conditions, requiring constant monitoring and frequent re-training of test providers. The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37–95% and the specificity varied from 49–97% in several cross-sectional studies in developing countries [4]. The wide range in the accuracy of VIA underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used to establish the true positive disease. When Pap smear was concurrently evaluated, the sensitivity of VIA was found to be higher than or similar to that of Pap smear, but had lower specificity. It appears that a good quality VIA has an average sensitivity of around 50% and specificity of around 85% to detect high-grade CIN in experimental study settings.

The immediate availability of test results following visual testing has opened up the option of “screen and treat” or “single-visit” approach to ensure a high compliance to the treatment of screen-positive women, in which those women with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. The safety, acceptability and feasibility of combining VIA and cryotherapy in a single-visit approach have been demonstrated in rural Thailand [20], Ghana [21], Guatemala [22] and South Africa [23]. In a randomised controlled trial in South Africa, VIA followed by cryotherapy resulted in 37% and 46% lower prevalences of CIN 2–3 lesions at 6 and 12 months follow-up compared with a control group [23]. Cryotherapy for HPV test-positive women resulted in much higher declines in the prevalence of CIN 2–3 at 6 and 12 months [77% and 71%, respectively] in this study.

Currently, the efficacy and effectiveness of VIA screening in reducing cervical cancer incidence and mortality are being addressed in randomised controlled trials in India [17, 24]. A 25% reduction in cervical cancer incidence and a 33% reduction in mortality have been observed 7 years from the beginning of VIA screening in one of the trials (Table 1)[24].

Visual inspection with Lugol's iodine

Visual inspection with Lugol's iodine (VILI) involves naked-eye examination of the cervix to identify mustard-yellow lesions in the transformation zone after application of Lugol's iodine (Figure 4.4.6) [19]. The sensitivity of VILI varied from 44–92% and specificity from 75–85% in cross-sectional studies [25–27].
Conclusions

Cervical cancer reflects sinking global health inequities, resulting in deaths of women in their most productive years, resulting in devastating effects on the society at large. It is the largest single cause of years lost to life in cancer in the developing world. The major barrier to prevention of cervical cancer is failure to be screened at all.

Organised screening is generally considered to be substantially more effective and efficient than opportunistic screening. The long national history of cervical cancer presents several opportunities in terms of prevention, screening, early detection and treatment of CIN to prevent invasive cancer. Both screening and vaccination have the potential to save many lives. At the public health level, health care infrastructure, affordability and capacity to initiate and sustain vaccination and screening programmes are critical factors in cervical cancer control. Substantial evidence now exists on implementation of screening programs based on cytology, visual screening tests or HPV testing, and such action has the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

To screen successfully in low-resource settings, such action has the potential for profound social impact and the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

Screening programmes based on cytology, visual screening tests or HPV testing, and such action have the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

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Criteria for Screening

Screening for Breast Cancer

Summary

Breast cancer is the most frequent cancer in women and accounts for over one in five new cancer cases in women worldwide. Due to an overall aging of the world population, the number of cases is expected to increase in the coming years.

The large randomised trials performed from 1976–1990 have shown that an invitation to breast cancer screening based on mammography can reduce mortality from breast cancer among women averaging 23% in women aged 50–69 years. More recently, analysis of population-based service screening programmes in women aged 40–69 years has demonstrated that regular mammography screening attendance can provide 40–45% reduction in breast cancer mortality.

There is only indirect evidence that screening by clinical breast examination will reduce the number of breast cancer deaths.

Screening should be implemented in the context of an organized, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation.

Cancer of the breast is the most common cancer in women worldwide, and in many regions it is the most common cause of death from cancer in women. Breast cancer is characterized by a preclinical detectable phase lasting from 1–7 years, depending on the specific disease subtype. Mammography (X-ray examination of the breast) can detect preclinical cancer that is detectable before it is palpable and before it causes symptoms. Tumours detected and treated at an early stage are associated with better survival rates than those detected symptomatically. Early diagnosis may permit breast-conserving surgery (Stage I disease), reduce the need for adjuvant therapy and decrease complications related to intensive treatment and recurrence [1–3].

The impact of screening

The incidence of breast cancer worldwide has been on the rise for at least the past half-century. Factors such as diminished and delayed childbearing are partly responsible for this increase. Improved diagnostic methods are also generally considered to influence the increase. However, the introduction of screening mammography occurred several decades after the documented increase in incidence and can account for only a minor part of the increase. On the other hand, the marked increase in the incidence of in situ breast carcinoma appears to be directly related to the availability of mammography, as this form of breast cancer is difficult to detect by clinical methods [4–6].

In many developed countries mortality rates have been rather stable despite the steady increase in incidence. No clear overall decline in mortality was observed in any place before the late 1980s, when a gradual downturn in mortality was observed in any place before the late 1980s, when a gradual downturn in mortality was observed.

Screening programmes target the age group 50–69 years for mammography screening. The younger age targeted for screening is generally 40 years. Some opportunistic programmes do not set an upper age limit for eligibility, whereas some population-based screening programmes target women up to age 74 or, in at least one case (the Netherlands) age 73. The upper age limit for three-yearly population-based invitation to attend the NHS Breast Screening Programme in the United Kingdom is 70 years; older women can also request to attend screening. Most screening programmes have adopted a two-year screening interval, short intervals of 12 or 18 months have been adopted by programmes targeting women under age 50 which is consistent with the shorter mean sojourn time of breast tumours in younger women [11].

Mammography screening is performed on large numbers of predominantly asymptomatic women. The potential harm caused by mammography includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost, and use of ionizing radiation. The strongest possible emphasis on quality assurance occurred in Europe, North America and Australia. These decreases in breast cancer mortality have been attributed to a combination of earlier detection and improved treatment, but the relative contribution of each has not been determined [1,4,7,8].

Protocols for screening

Breast cancer screening is delivered in a variety of ways, including organized programmes and “opportunistic” activities which involve referral to mammography facilities by clinicians and self-referral by women themselves. Organised programmes are recommended because they include an administrative structure responsible for implementation, quality assurance, and evaluation. The screening process begins with information and invitation of the eligible women to attend screening and extends from performance of the screening test (in most cases mammography) to the diagnostic assessment of women with suspicious test results and, if necessary, treatment of women with screen-detected lesions. Overall screening outcome and quality depend on the performance at each step in the screening process. Population-based programmes generally require a high degree of organization in order to identify and personally invite each woman in the eligible target population. The population-based approach to programme implementation is recommended because it provides an organizational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimization of invitation to screening and for evaluation of screening performance and impact.

By the mid-1990s at least 22 countries had established national, sub-national or pilot population breast cancer screening programmes [9]. Currently, most of the 27 member states of the European Union are running or establishing population-based breast cancer screening programmes based on mammography [10]. Many programmes target the age group 50–69 years for mammography screening. The youngest age targeted for screening is generally 40 years. Some opportunistic programmes do not set an upper age limit for eligibility, whereas some population-based screening programmes target women up to age 74 or, in at least one case (the Netherlands) age 73. The upper age limit for three-yearly population-based invitation to attend the NHS Breast Screening Programme in the United Kingdom is 70 years; older women can also request to attend screening. Most screening programmes have adopted a two-year screening interval, short intervals of 12 or 18 months have been adopted by programmes targeting women under age 50 which is consistent with the shorter mean sojourn time of breast tumours in younger women [11].

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Chapter 4.6: Screening for Breast Cancer

Numerous countries have adopted regulations and guidelines on quality assurance of mammography screening [13]. In the United States, the Mammography Quality Standards Act (MQSA) has made certification of mammography facilities mandatory [15]. Comprehensive multidisciplinary guidelines for quality assurance in breast cancer screening and diagnosis have been developed by experts and published by the European Commission [16]. The Council of the European Union has recommended implementation of population-based breast cancer screening programmes according to the EU guidelines to all EU member states [16].

There is currently insufficient evidence from studies in high-resource countries to support the efficacy of clinical breast examination or the teaching of self-examination of the breast as a public health strategy to lower the number of breast cancer deaths in the population. These methods are being evaluated for screening in low-resource countries in which most patients currently present for treatment at very late stages [17]. A study aiming to reduce the proportion of newly diagnosed advanced stage breast cancer by promoting breast self-awareness, breast self-examination, clinical breast examination and centralised assessment of abnormalities is currently underway in India.

Cancers diagnosed in the interval between two routine screening examinations, or within the time period corresponding to the regular screening interval after a negative screening examination, are known as “interval” cancers. Mammographic breast density appears to be a major risk factor for interval cancer, with the highest risk being associated with extremely dense breasts [18]. Clinical examination and self-examination, whilst not proven to show a benefit in terms of reduction in breast cancer mortality [19], may aid in the detection of interval cancers in mammography-based screening programmes, as well as standards of multidisciplinary management of lesions detected in screening. False-negative mechanisms should be established to ensure that all women with abnormalities are contacted and recalled or referred for diagnostic assessment, which may involve repeat screening and/or more comprehensive mammography, clinical breast examination, ultrasonography and biopsy, if suspicion of malignancy cannot otherwise be ruled out (Figure 4.6.3). Independent double reading of mammograms with a protocol for resolution of discrepant interpretations, and use of two views (mediolateral oblique and craniocaudal) is recommended to increase accuracy in detection of lesions [10,14]. It is also essential to adhere to adequate standards of diagnostic assessment of women with abnormal results of the initial screening examination and physicists-technique quality, control is recommended to maintain an appropriate balance between harm and benefit of screening. The evaluation of individual mammograms requires appropriate expertise and performance standards (Figure 4.6.4). Independent double reading of mammograms with a protocol for resolution of discrepant interpretations, and use of two views (mediolateral oblique and craniocaudal) is recommended to increase accuracy in detection of lesions [10,14]. It is also essential to adhere to adequate standards of diagnostic assessment of women with abnormal results of the initial screening examination and physicists-technique quality, control is required to maintain an appropriate balance between harm and benefit of screening. The evaluation of individual mammograms requires appropriate expertise and performance standards (Figure 4.6.4).

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Combined) corresponded to a mortality reduction of 27% (screened and non-screened women). In an average follow-up period of 13 years, the analysis was restricted to women <70. Screening to women in the age range 70-74, from regions with invitation to screening in the age range 40-69 and approximately one third was needed to screen to save one life ranged from 40–45% in the women actually screened (Figure 4.6.5). Effective quality management, screening should be implemented in the context of coordination, monitoring and evaluation. Due to the favorable prognosis of breast cancer in high-resource countries, long-term follow-up is required to assess the full impact of service screening programmes (24,10).

**REFERENCES**

In 2002, the worldwide burden of colorectal cancer (CRC) was estimated to be 550,000 new cases and 278,000 deaths for men and women combined. In North America, Australia, New Zealand, and Western Europe, the number of new colorectal cancer (CRC) cases is estimated to be 550,000 (90% accurate) to optical colonoscopy for the detection of large adenomas and cancers over 1 cm in diameter [22].

**REFERENCES**

1. Ferlay J, Bray F, Pisani P, et al., eds. (2004). GLOBOCAN 2002: Cancer incidence, prevalence, and mortality worldwide. IARC CancerBase No. 5: Version 2.0. Lyon: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/Depos/Annual_Visual_According to recent evidence from non-randomised studies that have undergone colonoscopy. This high rate of colorectal cancer mortality is due to the fact that colorectal cancer is one of the leading causes of death worldwide. The importance of screening for colorectal cancer cannot be overstated, as timely detection can lead to improved outcomes for patients. The benefits of screening include:

- Reduction in colorectal cancer mortality
- Detection and removal of precancerous polyps
- Improved quality of life for affected individuals

Despite these benefits, colorectal cancer screening is not without challenges. Factors such as patient acceptance, compliance, and cost can impact the effectiveness of screening programs. Ongoing research and developments in technology are aimed at improving the accuracy and efficiency of colorectal cancer screening methods. Future challenges include the development of more effective and less invasive screening technologies, as well as strategies to improve patient adherence to screening recommendations. Overall, colorectal cancer screening remains an essential component of cancer control efforts worldwide.
Screening for Oral Cancer

4.8

Summary

1. Oral cancer and its precancerous lesions can be readily detected by visual inspection of the oral cavity by health care providers.

2. Oral cancer screening leads to the diagnosis of an increased proportion of early stage oral cancers and improves 5-year survival.

3. A statistically significant 33% reduction in oral cancer mortality follows oral visual screening has been demonstrated in a large population-based randomised controlled trial.

4. The assessment of the oral cavity during routine health care interactions and improved awareness among health care providers and seekers provide excellent opportunities for implementing oral cancer screening.

Oral cancer is a major health problem worldwide, accounting for 274,000 new cases and 143,000 deaths annually, of which two thirds occur in developing countries. [1] Oral cancer is often preceded by precancerous lesions such as leukoplakia, erythroplakia, lichen planus and submucous fibrosis. Oral leukoplakia refers to the presence of flat, predominantly white lesions in the lining of the mouth that cannot be characterised as any other disease. White lesions in a uniform smooth, corrugated or warty texture are referred to as non-homogeneous types and those located on the tongue or the floor of the mouth, presence of candida albicans and presence of epithelial dysplasia.

The proportion of leukoplakia which regresses has been reported to vary between 5% and 20% per year. It is difficult to determine to what extent the above findings are due to variations in case selection or are a true reflection of the natural history.

Early detection of oral cancer

Early oral cancers clinically present as small indurated ulcers, surface thickening, nodules (Figure 4.8.6), reddish velvety areas (Figure 4.8.7) or ulceroproliferative growths (Figure 4.8.8). Early detection such as mouth self-examination, systematic naked eye visual inspection of the oral cavity, and referral among screen-positive subjects was shown to be a sensitive and specific test to detect oral precancerous lesions and early asymptomatic oral cancers in several studies, the sensitivity of visual examination for detecting, oral lesions varied from 58 to 94% and the specificity from 70 to 98%.[3-10] The frequency of positive screening tests ranged between 1.3% and 7.3% in screen subjects and the frequency of adherence to referral among screen-positive subjects was sub-optimal, ranging from 54% to 72%.

An oral cancer screening programme in Cuba, initiated 1994, involved annual oral examination of subjects aged 15 and above by dentists. Although the proportion of stage I cancers increased from 24% in 1983 to 49% in 1989, no reduction in oral cancer mortality has been observed since the introduction of screening, due to sub-optimal coverage of target population both for participation and treatment.[11] A case-control study in the context of the programme revealed a 33% reduction (odds ratio 0.67 [95% CI: 0.46-0.95]) in the risk of advanced oral cancer.[12] The programme has been recognised to cover subjects aged 30 years and above with oral visual inspection once in 3 years and with an improved referral pathway for diagnosis and treatment.

In a community-based cluster randomised controlled oral cancer screening intervention trial involving three rounds of oral visual inspection at 3-year intervals provided by trained health workers during 1995–2004 in Trichinopoly, South India, a shift towards early stage at diagnosis (41% vs. 23%) and a higher 5-year survival frequency (50% vs. 34%) were observed.
oral cancer mortality rate (per 100 000)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&lt;2 cm)</td>
<td>51 (23%)</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>II (2-4 cm)</td>
<td>34 (17%)</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>III (&gt;4 cm)</td>
<td>37 (18%)</td>
<td>35 (22%)</td>
</tr>
<tr>
<td>IV (adjacent structures involved)</td>
<td>67 (33%)</td>
<td>70 (44%)</td>
</tr>
<tr>
<td>No known</td>
<td>16 (8%)</td>
<td>16 (10%)</td>
</tr>
</tbody>
</table>

Total 205 (100%) 186 (100%)

Table 4.8.1 Oral cancer cases according to stage (and percentage distribution), detected during an Indian screening trial (1990-1995), compared with an uncontrolled population.

There is very little information on self-screening for oral cancer or on health education to promote self-scrutiny. There does not appear to be any consensus or equality as to how self-screening is being practised. There is very little information on self-screening for oral cancer or on health education to promote

Conclusions Based on the findings from the large Indian cluster-randomized controlled trial, routine use of oral visual screening among tobacco and/or alcohol users is an effective method of reducing oral cancer mortality in addition to primary prevention efforts to reduce tobacco and alcohol use. The very low risk of oral neoplasia among non-users of tobacco or alcohol or both justifies the restricted use of screening among high-risk individuals. Health education messages and information on the usefulness of oral visual inspection through mass media and posters in health centres, dispensaries, and other health care establishments are conducive to improving awareness among at-risk individuals to help them avoid themselves of early detection services. Considering the fact that oral cavity assessment is an integral part of a general physical examination, awareness among health care providers of the effectiveness of oral visual inspection is critical in the early detection of oral neoplasia.

REFERENCES
Screening for Stomach Cancer

**Summary**
- Stomach cancer screening has been practiced in certain high-risk areas such as Japan and the Republic of Korea.
- The efficacy and effectiveness of such screening has not been shown in a randomized trial.

Stomach cancer screening has been practiced in Japan since 1963 and has been public health policy in the Republic of Korea since 1996. Screening is based on early detection of stomach cancer, with surgical resection of the stomach if a tumor is detected. The two techniques used for detection are X-ray examination, after the patient swallows a barium contrast medium, and endoscopic examination, with biopsies taken to confirm the presence of cancer. Gastric cancer screening is rare in less-developed countries, although pilot schemes based on the Japanese model have been conducted in Venezuela, Chile, and Costa Rica.

It is difficult to judge the efficacy of stomach cancer screening in reducing mortality from stomach cancer. No randomized trial of stomach cancer screening has ever been conducted, though case-control studies with mortality from stomach cancer as an endpoint have been carried out. However, these studies were subject to several sources of bias that reduce the quality of the evidence they provide on screening efficacy. Recently, some prospective studies have shown important reductions in mortality from gastric cancer among participants in screening programmes in Japan and Costa Rica [1-3]. These studies are not subject to the recall bias that affects case-control studies. However, since these are observational studies, they still have the problem of self-selection: individuals who choose to participate in the screening programme may have a cancer risk that differs from that of non-participants. Therefore these studies cannot substitute for randomized trials.

**REFERENCES**
Screening for Prostate Cancer

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Among several methods that have been proposed to screen for prostate cancer, case-control studies have found conflicting results for digital rectal examination. Prostate-Specific Antigen (PSA) measurement, obtained from a simple blood sample, has been widely proposed as an additional screening test for prostate cancer. The PSA test was first approved in 1986 for monitoring prostate cancer. The side effects of radical therapy for all forms of prostate cancer have been well known for many years, so whether to recommend screening depends on whether any moderate reduction in mortality is offset by a decreased quality of life for the men treated [8]. In a random sample of patients in the USA, Forsythe found a rate of serious adverse events (30-day postoperative mortality, incontinence, wearing pads at 6 months, pain at 12 months) to be 0.7% for rectal bleeding that required intervention, 80.6% for continuation at 3 months and 95.1% for continuation at 12 months [5]. Randomised, controlled trials evaluating the effectiveness of PSA and digital rectal examination in reducing prostate cancer mortality are under way [3,5], but the results are not available for several years. Furthermore, the identification of these trials may be compromised if they were not randomised. screen-adherent group is extensive, i.e. widespread contamination of statistical power of these trials could be considerable. Overall, these results from Tyrol confirm that, in the best of circumstances, a programme of PSA testing and early detection and treatment can be effective. A paradox seen in many studies in the USA is that men diagnosed with prostate cancer live as long as, or longer than, men who have not been given such screening. Force [15] claimed that men with a life expectancy of less than 10 years are unlikely to benefit from screening even under favourable assumptions, concluding that “although potential harms of screening for prostate cancer can be established, the presence or magnitude of potential benefits cannot. Therefore, the net benefit of screening cannot be determined.” They recommended that physicians opt to perform screening for an individual patient only after they have discussed the uncertainties and possible hazards of screening.

Even if the results of ongoing trials are not in conflict, the issue of non-adherence to the intervention needs to be addressed. Even these randomised trials may be compromised if they were not randomised. The prevalence of non-adherence to the assigned intervention is extensive, i.e. widespread contamination of statistical power of these trials could be considerable.
The real impact and tragedy of widespread prostate cancer testing is the doubling of the lifetime risk of a diagnosis of prostate cancer without any effect on the risk of dying from this disease. In 1985, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% risk of dying from prostate cancer [16]. Twenty years later, in 2005, an American man had a 17% lifetime risk of being diagnosed with prostate cancer and a 3% risk of dying from prostate cancer [17]. Despite this, the increase in PSA testing will be impossible to stop.

Trial results for and against testing have always been contentious among supporters and opponents of screening. In the case of breast cancer, even with data available from nine randomized trials with reasonable methods, claims have been made that there is no evidence to support mammographic screening. With fewer trials available for evaluating prostate cancer screening and with contamination rates in the control group likely to be very high, questions will undoubtedly be posed about the reliability of the findings.

REFERENCES

Screening for Ovarian Cancer

Summary

1. There is at present no established method for early detection of ovarian cancer.
2. Methods proposed to date yield many false-positive results requiring unnecessary laparotomy or are not sensitive enough for detection of ovarian cancer when in an early stage of development.
3. Randomised trials of potential screening methods are underway.

Ovarian cancer is the fourth most common cancer in females, with annual incidence rates ranging between 8.5 and 21.5 per 100,000 in female populations of European countries. The International Agency for Research on Cancer estimated that in 2002 there were 204,499 ovarian cancer cases and 124,860 ovarian cancer deaths worldwide [1]. Ovarian cancer is a heterogeneous group of malignancies that can remain asymptomatic despite being at an advanced stage, or cause non-specific symptoms. In about 70% of patients, ovarian cancer is diagnosed at an advanced stage, leading to a poor prognosis in Europe, the average 5-year survival of ovarian cancer patients is around 40% [2].

The ability to non-invasively distinguish between non-cancerous and cancerous ovarian processes and to detect ovarian cancers at an earlier stage would be major benefit in the management of women with symptomatic pelvic conditions. Many methods, used alone or in combination, for distinguishing between non-cancerous and cancerous ovarian process have been investigated, including transvaginal sonography (TVS), Doplpter ultrasonography, measurement of serum CA 125, computed tomography scan (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) and positron emission tomography (PET) scan [3-7]. However, for a number of reasons, from lack of sensitivity or specificity to cost issues, TVS remains the major detection tool. The use of the Risk of Malignancy Index (RMI), which incorporates menopausal status, CA 125 and TVS, has also been proposed. The RMI version developed by Jacobs and co-workers has a pooled sensitivity of 78% (95% CI 72–84%) and pooled specificity of 90% (95% CI 81–95%), with an inverse correlation between sensitivity and specificity [8-9]. Other computerised expert systems and a variety of scoring systems based on the combination of ultrasound image characteristics, serum CA 125 level and various other clinical and patient-related parameters have also been tried, but have proven to be less effective than TVS [7] or TVS performed by expert ultrasonographers [10].

Various serum biomarkers have been proposed, like the CA 125, or some blood protein profiles that would represent biological signatures of ovarian cancer; but none of these biomarkers has shown superiority to echography, and furthermore their large-scale application leads to many false positive results and unnecessary laparotomy procedures [11].

On-going trials in the USA [12] and in the UK [13] are at assessing the value of ultrasound and biomarker-based tests. Their results will not be available for several years. In the meantime, currently available methods prove quite unable to detect ovarian cancer early [13], and new technologies are eagerly awaited.

REFERENCES

Screening for Lung Cancer

Summary
- Lung cancer is a good candidate for screening, but early attempts based on X-rays and cytology did not prove to be effective.
- The search for serological biomarkers for early detection of lung cancer is an active area of research.
- Pulmonary spiral CT-scan results in the identification of early lesions with good prognosis, but the possibility of lead-time bias and over-diagnosis cannot yet be ruled out.
- Currently, no methods can be recommended for population-based screening of lung cancer.

Lung cancer has one of the poorest survival rates of all cancers, mainly due to the lack, in the majority of patients, of symptoms and signs during the early phases of neoplastic growth. This fact, together with the high risk in specific groups of the population, namely smokers (the cumulative risk at age 75 reaches 15% or more in continuous smokers [3]), workers exposed to occupational carcinogens, and women exposed to high-level indoor air pollution, make lung cancer a good candidate for targeted pre-clinical detection.

Effective efforts to identify an effective approach to screening pre-clinical cases of lung cancer concentrated on X-ray examinations, search of abnormal cells in sputum, and the combination of the two [2] for a review). Unfortunately, although screen-detected cases had a longer survival than clinically detected cases, the difference was accounted for by lead-time bias, that is, the fact that an earlier detection of a cancer would generate a longer survival even if the natural history of the disease is not altered (i.e. mortality is not affected), and by over-diagnosis, that is, the fact that the screening detected slow-growing lessons that by their nature have a long survival [2].

In the past decade, two new approaches have been proposed for screening lung cancer in high-risk populations. First, efforts are being made to identify disease biomarkers, typically in serum, using novel molecular techniques, notably proteomics (i.e. the systematic analysis of proteins and protein fragments). Although promising, this approach has not yet led to the identification of a valid biomarker [3].

The second approach relies on CT-scanned, low-energy X-rays, notably the so-called spiral CT-scan, which generates a high-resolution, three-dimensional image of the lungs. Non-randomized studies of spiral CT scan in high-risk populations have resulted in the identification of a relatively large number of nodules in the lungs, which can be removed surgically, and in the majority of cases, are shown to be early forms of lung cancer [4]. The survival of the patients whose early cancers are removed is excellent, but two issues remain to be elucidated before one can conclude that spiral CT scan should be implemented in population-based screening [5]. First, the occurrence of spiral CT scan-detected nodules is higher than that of clinically diagnosed cancers in a comparable population, suggesting that a proportion of the nodules are ‘false positives’, i.e. represent slow-growing neoplastic lesions that would not have become clinically relevant (so-called over-diagnosis). Second, a reduction in mortality in a screening population has not yet been demonstrated (i.e. the possibility of lead-time bias has not been excluded). These two possible biases are illustrated in Figure 4.12.1.

Randomised trials ongoing in the United States and Europe should provide the final evidence on the effectiveness of spiral CT scan as screening method for lung cancer. In the meantime, national and international authorities generally recommend against the implementation of population-based screening programs for lung cancer [6].

REFERENCES
Screening for Cutaneous Melanoma

Summary

- The goal of screening is to prevent deaths from cutaneous melanoma through detection of the cancer at an early, curable stage. The common methods for early detection of melanoma are whole-body skin examinations (WBSE) and skin self-examination (SSE).

- The common-controversies regarding population screening for cutaneous melanoma, no randomized trial has ever shown that such screening could save lives or indicated how many. Other factors fuel the apparent simplicity of screening at an early stage may guarantee cure with time available for such screening.

- Many individuals will have new or in situ melanoma removed instead of invasive melanoma, and this will contribute to further increasing costs of screening, lead to disfiguring scars and finally negatively impact quality of life.

- Many screen-detected cutaneous melanoma will consist of indolent cancer that would most probably never have become life-threatening.

- Mortality from cutaneous melanoma concentrates in the elderly, mainly in men over 60 years of age, because of delay to consult a doctor when a pigmented lesion develops, or because the melanoma develops on a hidden skin area such as the back and the shoulders. Also, it is known that elderly men would have low compliance to skin screening.

- Evaluation of pilot programmes have shown that individuals attending screening often constitute a selected fraction of the population that are more concerned about their health, and also are healthier than non-attenders.

- Following logically from the previous point, costs of screening may be considerable in comparison to eventual health benefits. It may appear more appropriate to test the efficacy of screening for melanoma in a subset of high-risk subjects, for instance individuals with a strong family history of cutaneous melanomas, or siblings of melanoma patients, or of patients with numerous nevi or atypical nevi, or sun-sensitive individuals living in sunny climates. It remains to be shown (ideally via randomized trials) whether a targeted screening strategy may be efficient in Queensland, Australia, where the incidence of cutaneous melanoma is the highest in the world, a randomised trial of WBSE is ongoing (6,7). This trial devotes much effort toward having men 50 years old and older participating in the screening programme (8).

- A form of screening requiring fewer resources than WBSE is the promotion of regular skin self-examination (SSE) for self-detection of changes in new appearance (9). Promotion of SSE requires ensuring rapid accessibility to medical services for checking (and eventually removing) self-detected suspected lesions. Simply disseminating a message about SSE and the importance of early detection without providing opportunities to have lesions examined and excised will seriously hamper preventive efforts and lead to reduced reliability in health messages given to the population. One case-control study found that SSE could reduce the development of advanced cutaneous melanoma (10), but results on screening efficacy from this kind of study design require verification by more robust designs such as a randomised trial.

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Chapter 4.14: Genetic Testing

Summary

Genetic testing of high-risk cancer susceptibility genes is becoming an important part of clinical cancer genetics in some high-income countries, but is not available in middle- or low-income countries.

The main beneficiaries of the genetic information gleaned from this type of genetic testing are the unaffected relatives of the individuals who are tested.

The most commonly tested high-risk susceptibility genes are BRCA1 and BRCA2 (primarily for breast and ovarian cancer) and MSH2 (primarily for colon and endometrial cancer). However, there are many other genes for high-risk cancer susceptibility under the Bethesda Guidelines [22,23].

Genetic testing of high-risk cancer susceptibility syndromes is often referred to as Hereditary Breast-Ovarian Cancer Syndrome (HBOC). The genes were first characterised in 1994 and 1995, respectively [3-5]. Although the absolute risks conferred by inheritance of high-risk susceptibility genes have been estimated, what is controversial is a combined analysis of 22 studies estimated that BRCA1 mutation carriers have a cumulative risk of colon cancer of 15% at age 70. For BRCA2 carriers, the cumulative breast cancer risk is approximately 11%, and 15% for ovarian cancer risk by age 70 [3]. These risks are age-related as the relative contribution of breast and ovarian cancers to the overall cancer risk varies with age. It is logical demanding and relatively expensive. In order to maximize testing efficiency, the first individual from an at-risk family to be tested will usually be a cancer case considered to have a high probability of carrying a mutation based on age at diagnosis, family history, and family tumour genetics. If the index case is found to be a mutation carrier, the genotype information may influence their subsequent medical and surgical management.

Two further consequences flow from the identification of a specific mutation in an index case. First, it must be understood and emphasized that the main beneficiaries of the genetic information will be the unaffected relatives of the index case. This is because for unaffected mutation carriers there are two main medical and surgical interventions that can either reduce the risk of disease or aid in early detection thus improving survival. Second, with an increasing number of these interventions, the at-risk relatives of the index case need only be tested with a specific test targeting the exact mutation that was identified in the index case. Mutation-specific tests are much less expensive, and have higher sensitivity and specificity, than the non-‘genetic’ whole-genome tests.

Breast cancer

The principal high-risk breast cancer susceptibility genes are BRCA1 and BRCA2, predisposition to inherited mutations in either of these genes is often referred to as Hereditary Breast-Ovarian Cancer Syndrome (HBOC). The genes were first characterised in 1994 and 1995, respectively [3-5]. Although the absolute risks conferred by inheritance of high-risk susceptibility genes have been estimated, what is controversial is a combined analysis of 22 studies estimated that BRCA1 mutation carriers have a cumulative risk of colon cancer of 15% at age 70. For BRCA2 carriers, the cumulative breast cancer risk is approximately 11%, and 15% for ovarian cancer risk by age 70 [3]. These risks are age-related as the relative contribution of breast and ovarian cancers to the overall cancer risk varies with age. It is logical demanding and relatively expensive. In order to maximize testing efficiency, the first individual from an at-risk family to be tested will usually be a cancer case considered to have a high probability of carrying a mutation based on age at diagnosis, family history, and family tumour genetics. If the index case is found to be a mutation carrier, the genotype information may influence their subsequent medical and surgical management.

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### Dominant Inheritance

<table>
<thead>
<tr>
<th>SYNDROMES</th>
<th>GENES</th>
<th>GENE SYMBOLS</th>
<th>CHROMOSOMAL LOCATION</th>
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</thead>
<tbody>
<tr>
<td>Familial retinoblastoma</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>Rb1</td>
<td>13q14</td>
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<td>Colorectal cancer</td>
<td>ApC</td>
<td>5q21</td>
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<td>Hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>Colorectal, endometrial, ovarian, and gastric cancer</td>
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<td>3p</td>
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<tr>
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<td>Msh2</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Msh6</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pms1</td>
<td>2q</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer (HBOC)</td>
<td>Breast, ovarian, prostate, and colon cancer</td>
<td>Brca1</td>
<td>17q</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>Sarcomas, breast cancer, brain tumors, leukemia</td>
<td>Tp53</td>
<td>17p13</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome 2 (LFS2) [the syndrome assignment controversial, however, increased cancer risk is clear]</td>
<td>Breast cancer ± weak LFS-like spectrum</td>
<td>Chek2</td>
<td>22q12</td>
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<tr>
<td>Cowden syndrome and Bannayan-Riley-Ruvalcaba-Riley syndrome</td>
<td>Breast, thyroid</td>
<td>Pten</td>
<td>10q22</td>
</tr>
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<td>Neurofibromas, leukemias, soft-tissue sarcoma, bone tumors</td>
<td>Nf1</td>
<td>17q11</td>
</tr>
<tr>
<td>Neurofibromatosis, type 2</td>
<td>Neurofibromas, meningiomas</td>
<td>Nf2</td>
<td>22q2</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia (MEN) type 1</td>
<td>Pancreatic islet cell cancer, parathyroid, hyperplasia, pituitary adenomas</td>
<td>Men1</td>
<td>11q13</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia (MEN) type 2a and 2b</td>
<td>Medullary thyroid cancer; pheochromocytoma</td>
<td>Bct</td>
<td>10q11</td>
</tr>
<tr>
<td>Von Hippel-Lindau syndrome (VHL)</td>
<td>Renal cancer, vascular tumors</td>
<td>Vhl</td>
<td>3p25</td>
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<tr>
<td>Familial melanoma</td>
<td>Melanomas, other tumors</td>
<td>Nm22a</td>
<td>9p</td>
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<td>Goltz syndrome</td>
<td>Basal cell carcinoma</td>
<td>Cdk4</td>
<td>6q</td>
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<td>Hereditary leiomyomatosis and renal cell cancer (HLRCC)</td>
<td>Leiomyomas, renal cell tumors</td>
<td>Ph</td>
<td>1q42.3-3q43</td>
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<td>Peutz-Jeghers syndrome</td>
<td>Gastrointestinal hamartomatous polyposis, gastric, colon, breast, ovarian cancer</td>
<td>Stk11</td>
<td>19p</td>
</tr>
</tbody>
</table>

Table 4.14.1 | Cancer susceptibility syndromes and underlying high-risk susceptibility genes

### Recessive Inheritance

<table>
<thead>
<tr>
<th>SYNDROMES</th>
<th>GENES</th>
<th>GENE SYMBOLS</th>
<th>CHROMOSOMAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td>Lymphoma, leukemia, breast cancer</td>
<td>Atm</td>
<td>11q22</td>
</tr>
<tr>
<td>MYH associated polyposis</td>
<td>Colon</td>
<td>Myh</td>
<td>3p22-34</td>
</tr>
<tr>
<td>Miyagi hereditary polyposis</td>
<td>Lymphoma, leukemia, breast cancer, prostate cancer</td>
<td>Nhbs1</td>
<td>8p11</td>
</tr>
<tr>
<td>Bloom’s syndrome</td>
<td>Solid tumors</td>
<td>Blm</td>
<td>15q26</td>
</tr>
<tr>
<td>Familial Wilms tumor</td>
<td>Kidney</td>
<td>Wt1</td>
<td>11q</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Basal cell carcinoma, squamous-cell carcinoma, melanoma (skin)</td>
<td>Xpa</td>
<td>9p34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xpb</td>
<td>2q12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xpc</td>
<td>3p23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xpf</td>
<td>10q13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ddb2 (xpe)</td>
<td>11p11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ercc1 (xpf)</td>
<td>16p13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xpg</td>
<td>13q22-33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xpf (pol n)</td>
<td>19q13</td>
</tr>
</tbody>
</table>

| Fanconi Anemia | Fana | 16q24 |
| | Fancb | 9p22 |
| | Fancd2 | 9p22 |
| | Fancd1 | 9p22 |
| | Fancd2 | 9p22 |
| | Fancg | 9p22 |
| | Fancg | 9p22 |
| | Bmf1 (fancj) | 17q22-34 |
| | Fanci | 11p13 |
| | Xlp | 11p13 |

Table 4.14.1 (cont.)
REFERENCES


In Thailand, the WHO collaborative work includes assessment of exposure to occupational carcinogens, development of an occupational and environmental cancer surveillance system, networking of community health personnel and volunteers and strengthening of communities and local authorities to assess and tackle environmental threats. Also, in other Member States of the SEA Region, including Bangladesh, Bhutan, DPR Korea, Maldives and Sri Lanka, WHO country offices are providing technical support in development of NCCPs and in implementing specific cancer control activities.

Visit: www.searo.who.int

**Figure 1.** Minimum incidence of all cancers in India (men)
Source: Cancer Atlas (ICMR)

**Figure 2.** IEC poster produced jointly by the Ministry of Health and WHO in Myanmar

Technical support of WHO at the national level is being executed in close collaboration with the ministries of health, in line with long-term WHO country cooperation strategies, and focuses on strategic planning, capacity building, advocacy, networking and research. In support of the National Cancer Control Programme (NCCP), the WHO India Country Office provides technical support in the area of cancer surveillance (see the Atlas of Cancer in India), development of training manuals, guidelines and awareness materials, demonstration programmes for community-based cancer control, and capacity building of health personnel. It supports initiatives for pain relief and palliative care and facilitated oral morphine availability in India. The Country Office is supporting the revision of NCCP strategy to achieve an optimal mix of preventive, curative and palliative care and will continue to support the implementation and evaluation of comprehensive cancer control in India.

In Indonesia, WHO is helping to develop national policy and strategy on cancer prevention and control by bringing together policymakers, professionals and NGOs. It supports the development of hospital-based cancer registries in Jakarta and also has facilitated the development and use of guidelines for comprehensive cervical cancer prevention. In Myanmar, WHO’s support focuses on providing fellowships to various categories of health professionals in the areas of surveillance, prevention, early detection, effective treatment and palliative care. WHO’s collaborative work includes also development of information, education, and communication (IEC) materials (Figure 2) and creating community awareness on early detection of cancer. Technical support to epidemiological research on cancer is also provided.

*and Thailand. Currently, WHO is supporting Maldives and Thailand in engaging in the research project on delivery of HPV vaccine to adolescents.*

Childhood immunisation against hepatitis B is the most cost-effective strategy to prevent adult mortality from liver cancer. Following 1992 World Health Assembly Resolution WHA45.17, most countries of the SEA Region have introduced hepatitis B vaccine in their routine national immunisation programmes. This process was further accelerated by the Global Alliance for Vaccines and Immunization (GAVI).

A majority of countries of the SEA Region already have national cancer control programmes in place. Most of these programmes are at the early stage of development. WHO is supporting the national governments in strengthening their capacity to prevent and control cancer. This is being done through advocacy for and technical support in development and strengthening of cancer control programmes and plans encompassing cancer prevention, early detection, management, palliative care and surveillance and research. Member countries are being supported in setting up surveillance systems (cancer registries) and in addressing major behavioural risk factors of cancer in line with ITC and DPAS. Technical assistance is provided in implementing the hepatitis B immunisation and cervical cancer prevention programmes. WHO is involved in cancer control partnerships such as the Programme of Action on Cancer Therapy (PACT), aimed at strengthening diagnostic and treatment capacity of cancer in developing countries.

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<table>
<thead>
<tr>
<th>Area</th>
<th>Indicator</th>
<th>No. of countries (total 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy/programme</td>
<td>National health policy addresses cancer and other major NCDs</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>National plan/programme for cancer control</td>
<td>8</td>
</tr>
<tr>
<td>Infrastructure</td>
<td>Presence of a NCD unit or department in ministry of health</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Presence of national cancer reference centre</td>
<td>9</td>
</tr>
<tr>
<td>Legislation/regulation</td>
<td>Anti-tobacco</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Food and nutrition (related to NCDs)</td>
<td>5</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Surveillance systems for major cancers</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Population-based cancer registries</td>
<td>3</td>
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<td></td>
<td>Hospital-based cancer registries</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>NCD risk factor (STEPS) surveys conducted</td>
<td>9</td>
</tr>
<tr>
<td>Management</td>
<td>Availability of guidelines for cancer management</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Anti-neoplastic medicines accessible and affordable for low-income groups</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. Capacity of SEA Member countries to prevent and control cancer: select indicators
Modified from “Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Capacity for noncommunicable disease prevention and control in countries of the South-East Asia Region: results of a 2006-2007 survey.” SEA/RC60/9 -INF DOC1

<table>
<thead>
<tr>
<th>Country/site</th>
<th>Current smokers (%)</th>
<th>Current consumers of alcohol (%)</th>
<th>Proportion (% eating &lt; 5 servings of F &amp; V</th>
<th>Proportion (%) physically inactive</th>
<th>Proportion (%) overweight and obese</th>
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<tbody>
<tr>
<td>Bangladesh – R</td>
<td>25.3</td>
<td>NS</td>
<td>NR</td>
<td>NR</td>
<td>8.6</td>
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<tr>
<td>Bangladesh – U</td>
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<td>NS</td>
<td>NR</td>
<td>NR</td>
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<td>India – R</td>
<td>17.8</td>
<td>26.4</td>
<td>84.6</td>
<td>10.0</td>
<td>13.3</td>
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<tr>
<td>India – U</td>
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<td>20.7</td>
<td>81.4</td>
<td>23.8</td>
<td>39.4</td>
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<td>Indonesia*</td>
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<td>94.5</td>
<td>7.8</td>
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<td>3-41</td>
<td>81-99</td>
<td>4-24</td>
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</table>

Table 2. Prevalence of select behavioural risk-factors in the SEA Region (age 25–64, both sexes)
Source: “Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Risk factors: results from surveys using the STEPS approach.” SEA/RC60/9 -INF DOC2
*Only national surveys, other are sub-national surveys; F & V – fruits and vegetables; NR – not reported; NS – not studied; R – rural; U – urban
Cancer Site by Site
and very light drinkers, the risk in heavy drinkers head and neck cancer. Relative to abstainers alcoholic beverages also increases the risk of the hypopharynx and larynx than smoking of low-tar cigarettes. Cigar and pipe smoking also pose a risk, while stopping smoking is followed by a decrease in risk [3]. Smoking of very high-tar cigarettes. Cigar and pipe smoking cancer, and the risk is higher for heavy smokers, squamous-cell carcinoma (SCC) in histology, Southern Asia as well as parts of Central and Regions with a high incidence include much of 400 000 cases of cancer of the oral cavity and Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. Each year there are approximately 400 000 cases of cancer of the oral cavity and pharynx, with 160 000 cases of the larynx, resulting in approximately 300 000 deaths [2]. Reasons for a high incidence include much of Southern Asia as well as parts of Central and Southern Europe. The majority of head and neck cancers are squamous-cell carcinoma (SCC) in histology, and the main risk factors for these cancers are tobacco and alcohol use. Tobacco smoking is the most important risk factor for head and neck cancer, and the risk is higher for heavy smokers, long-term smokers and smokers of black tobacco or high-tar cigarettes. Cigar and pipe smoking also pose a risk, while stopping smoking is followed by a decrease in risk [3]. Smoking of bidis (small cigarettes common in parts of Asia) appears to have a higher risk for cancer of the hypopharynx and larynx than smoking of Western type cigarettes [4]. Consumption of alcoholic beverages also increases the risk of head and neck cancer. Relative to abstainers and very light drinkers, the risk in heavy drinkers is in the order of tenfold. This increased risk is unlikely to be related to alcohol consumption per se, but instead it may be caused by exposure to acetaldehyde, which is an intermediate metabolite of ethanol and is a known animal carcinogen [5]. Although the effect of alcohol and tobacco may vary slightly according to the different subsites, the combined effect of both exposures accounts for the majority of all head and neck cancers that occur globally. A recent pooled analysis from the INHANCE consortium based on over 10 000 cases and 15 000 controls, shows that approximately 75% of such cancers can be explained by these two exposures, ranging from 65% for oral cavity cancer (51% for women and 65% for men) to 86% for larynx cancer (79% for women and 86% for men). Furthermore, the proportion of these cancers caused by alcohol and tobacco was reduced with decreasing age, being just 32% for cancers diagnosed prior to age 45. Strong interaction between the two exposures was also apparent (Figure 5.1.1). Other risk factors for these cancers are therefore clearly important. Established risk factors specifically for oral cavity cancer are betel quid and areca nut in India and Taiwan [6]. Several occupational substances or circumstances such as inorganic arsenic, inorganic arsenic, are suspected risk factors for laryngeal cancer [7]. Poor oral health and frequent use of mouthwash is also a potential risk factor for oral cancer, although it is unlikely to be relevant for other head and neck cancers [8]. Human papilloma virus (HPV) is a recognised cause of some head and neck cancers, with substantial evidence for a role of HPV16A from large case-control studies. The evidence comes primarily from several large epidemiological studies that have analysed associations of various HPV markers. HPV markers studied comes were [4] HPV DNA in biopsy tissues or oral cell scraping analysed by southern blotting or highly sensitive PCR methods, [4] antibodies to HPV 16 capsid proteins, and [4] antibodies to HPV 16 capsid proteins [11,12]. HPV 16 is a marker of different states of disease in the oral cavity [6]. Treatment and survival Primary treatment varies with the anatomic subsite and stage of disease. For most early cancers, surgical resection is the standard treatment. Occasionally, chemotherapy may be used in addition to radiotherapy. Following diagnosis of oral cavity and pharynx cancer, 5-year relative survival is close to 40% in the United States and in Europe, although it varies substantially among countries. Moreover, the prognosis is generally better for women and for malignancies of the oral cavity than for those arising in the hypopharynx. In Europe, 5-year relative survival rates remained virtually identical from 1983 to 1994, suggesting that no major progress has been made [11].
Genetic susceptibility to aerodigestive cancers

Genetic susceptibility studies for aerodigestive cancers have focused primarily on genes related to alcohol metabolism. A pooled analysis of 6 studies comprising over 3800 cases and 5000 controls has however provided extremely strong evidence for a protective effect for the ADH1B R48H variant (OR=0.54, 0.46–0.65, p=10^-12), and the ADH7 A92G variant (OR=0.68, 0.60–0.77, p=10^-9).

Furthermore, the effect of both variants was significantly modified by alcohol consumption. These results indicate that interactions between environment and genetics may be critical to the ADH1B variant genotype [20]. Subsequent analysis based on a collaboration of 3 large studies comprising over 3800 cases and 5000 controls has however provided extremely strong evidence for a protective effect for the ADH1B R48H variant (OR=0.54, 0.46–0.65, p=10^-12), and the ADH7 A92G variant (OR=0.68, 0.60–0.77, p=10^-9).

The incidence and mortality rates of laryngeal cancer in Poland and notably high and have been increasing for 25 years. Zatonski et al. [26] report a study among persons under the age of 65 in Lower Silesia in southwest Poland, based on 249 newly-diagnosed cases and 965 controls. For smoking more than 2 cigarettes per day, the relative risks compared to non-smokers was 59.7 (95% CI 13–274) and 30.5 for alcohol consumption. The results provided further quantitative evidence of the importance of type of cigarette smoking in particular had an OR of 16.8, 10.4 (95% CI 4–27.2) for low/medium (≥22mg, low to medium tar; <22mg, high tar); (ii) they may have been incomparable exposures at the south, whereas exposures and protective agents may have been different in the north. Taking account of known risk factors, the high level of smoking in males appears to be generally in regions where there is a prevalent habit in the population of drinking strong alcoholic beverages.

Larynx Cancer

It is estimated that between 25% and 30% of all cancers in developed countries are tobacco-related. For both sexes combined the proportion of cancers arising in the oropharynx, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43% and 60%. Although the greatest hazard is caused by cigarette smoking, cigar use causes similar hazards if their smoke is inhaled and both cigar and pipe smoke cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx, and oropharynx.

Smoking has long been recognised as a major cause of cancer of the larynx and especially of the endolarynx [21,22]. Gandini et al. [23] conducted a systematic meta-analysis of observational studies on tobacco smoking and cancer from 1961 to 2003. The aim was to quantify the risk for 13 cancer sites recognized to be related to tobacco smoking by the International Agency for Research on Cancer, and to analyse the risk variation for each site in a systematic manner. Data were extracted from the 254 reports (177 case-control studies, 75 cohort and 2 nested case-control studies) published in this period and included in the 2004 IARC Monograph on tobacco smoke and involuntary smoking [22]. The analyses were carried out on 216 studies with reported estimates for ‘current’ and/or ‘former’ smokers. Sensitivity analysis was performed, and the authors looked for publication and other types of bias. Lang [ER 896, 95% CI 6.73–12.11], laryngeal [ER 6.88, 95% CI 3.14–15.52] and pharyngeal [ER 6.76, 95% CI 2.86–15.98] cancers presented the highest relative risks for current smokers, followed by upper digestive tract (ER 3.57, 95% CI 2.60–4.84) and oral (ER 3.43, 95% CI 2.37–4.94) cancers. As expected, pooled relative risks for respiratory cancers were generally greater than the pooled estimates for other sites. The analysis of heterogeneity showed that study type, gender and adjustment for confounding factors significantly affects the risk estimates and the reliability of the studies. Tyto et al. [24] published results regarding tobacco and alcohol consumption from a large, multistate, case-control study comprising 11,476 male cases (cancer of the larynx and hypopharynx) and 3057 male controls. The relative risk associated with cigarette smoking was approximately 10 for all considered subsites of the larynx and hypopharynx. The risks for alcohol drinking varied by site, however, being higher for larynx and hypopharynx. (OR ≤ 4.3 for 80g/day or more) but lower at the same dose for endolarynx (OR = 2.1). Risk decreased within 10 years of quitting cigarette smoking, and smokers of black tobacco were found to have about half the risk of smokers of black tobacco. The authors also reported that the risks associated with joint exposure to tobacco and alcohol were consistent with a multiplicative relative risk model [23].

The relationship between type of cigarettes smoked and the risk of cancer of the oral cavity and pharynx (excluding salivary gland and mucoepidermoid) was examined in a hospital-based case-control study involving 291 cases and 1036 male controls from Pordenone Province and Greater Milan in Northern Italy (this is the same study base as above) [25]. As a basis for classification, the authors used tax-yield and the brand smoked for the longest time (>22mg, low to medium tar; ≤22mg, high tar). After adjustment for other risk factors, relative to non-smokers the risk among ever-smokers for oral and pharyngeal cancers was 8.5 (95% CI 3.7–17.9) for low/medium and 16.4 (71.3–38.2) for high-tar cigarettes.

For larynx cancer, the corresponding results were 4.8 (2.3–9.8) and 21.3 (21.2–12.6) relative to non-smokers. The authors concluded that these data provided further quantitative evidence of the importance of type of cigarette smoked on the risk of oral cancers as well as of cancers of the upper digestive and respiratory tract [25].

From a case-control study conducted in Liaoning Province (China) in 1991 and 1992, smoking was the most important risk factor for laryngeal cancer accounting for 86% of the male and 54% of the female cases. The adjusted (for age and educational level) OR was 8.7 (95% CI 3.8–19.6) for ever versus never smoking. The risk increased with both the quantity and duration of smoking, with a 25-fold increase in the highest consumption categories; it declined following cessation [31].

The analyses were carried out on 216 studies with reported estimates for ‘current’ and/or ‘former’ smokers. Sensitivity analysis was performed, and the authors looked for publication and other types of bias. Lang [ER 896, 95% CI 6.73–12.11], laryngeal [ER 6.88, 95% CI 3.14–15.52] and pharyngeal [ER 6.76, 95% CI 2.86–15.98] cancers presented the highest relative risks for current smokers, followed by upper digestive tract (ER 3.57, 95% CI 2.60–4.84) and oral (ER 3.43, 95% CI 2.37–4.94) cancers. As expected, pooled relative risks for respiratory cancers were generally greater than the pooled estimates for other sites. The analysis of heterogeneity showed that study type, gender and adjustment for confounding factors significantly affects the risk estimates and the reliability of the studies. Tyto et al. [24] published results regarding tobacco and alcohol consumption from a large, multistate, case-control study compris- Connection between alcohol and cancer. Reduction of this, together with avoidance of cigarette smoking, would lead to a large reduction in risk [1].

The geographical distribution of areas of high cancer risk for oral cancer demonstrates that while the higher mortality rates in France end abruptly at the border with Belgium–the risk being around one half in Belgium (5.9 per 100 000) of that in south-east France and in the north of Italy, in southwest France and northern Spain being at much the same levels. This suggests that there were likely to have been differences in genetic susceptibility studies for aerodigestive cancers have focused primarily on genes related to alcohol metabolism. A pooled analysis of 6 studies on the alcohol dehydrogenase 1C polymorphism comprising over 1000 cases and 1700 controls tested whether the ADH1C variant genotype was associated with the risk of cancer at each site. The analysis detected distinct (i) one has very large sample sizes, (ii) one has excellent lifestyle and environmental data, and (ii) one has identified genetic factors that have a real effect.
The analysis of data from a case-control study conducted in Northern Italy between 1985 and 1987 showed an OR of 14 (95% CI 6–29) for drinkers of 21 or more drinks per week and an OR of 12 (95% CI 4–32) for drinkers of 7 or more drinks per day compared to teetotallers or moderate drinkers. Estimates of attributable risk implied that 77% of laryngeal cancers in men were due to smoking [28].

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Several studies have suggested that alcohol may increase the risk of laryngeal cancer. A large population-based case-control study [34,35] found that reducing only alcohol consumption would result in a 10-year reduction in the number of cases of laryngeal cancer by 30%.

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The separate effects of alcohol and tobacco on laryngeal cancer are quite different. The risk of extrinsic laryngeal cancer is 2.5 times greater in heavy drinkers/non-smokers and over 9 times greater in those who are both smokers and drinkers. Although alcohol drinking increases the risk of upper digestive tract neoplasms, the role of smoking in alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor independently multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the risk increased between 10- and 100-fold in people who drank and smoked heavily. While there were no consistent patterns across studies of the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would be extremely low.

Dietary factors and larynx cancer

Intake of fruit and vegetables may reduce risk of head and neck cancer, although few prospective studies have examined this association. In the USA, 490,000 participants of the NIH-AARP Diet and Health cohort were followed for up to 1973. persons were lost to follow-up from 1995–2000 [44]. Of these, 8,725 participants were diagnosed with head and neck cancer. An inverse association was found between total fruit and vegetable intake, particularly the intake of citrus fruit (third vs. fifth decile: 0.65, 0.50–0.85) than for fruits (fifth vs. first decile: 0.50, 0.40–0.68). When further subs- grouped into botanical groups, those in the highest tertile of leguminous (peas, beans, legumes, and pulses, 0.60, 0.49–0.79), soybeans (peas and peas, 0.69, 0.59–0.9) had a lower risk of head and neck cancer. There was some debate on the nature of the biological and statistical interaction between alcohol consumption and smoking, which is a major risk factor for laryngeal cancer [34,35], although most investigations have con- cluded that the combined risk is multiplicative [26], so that greater than double the risk for smokers. It appears that cigarette smoking alone accounted for an estimated 25% of laryngeal cancer in high-risk areas [34].

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message is that, regardless of family history of HNCC, avoidance of tobacco and alcohol exposure may be the best way to avoid HNCC [46].

In 2002 the IARC initiated the Alcohol-Related Cancers and Genetic susceptibility in Europe (ARCAGE) project, with the participation of 15 centres in 11 European countries. Information and biological data from a total of 2304 cases and 2227 controls have been collected and will be used in a series of analyses. A total of 168 single nucleotide polymorphisms of 76 genes are being studied for genetic associations with UADT cancers. About 80% of cases were males, and fewer than 20% of cases occurred before the age of 50 years [47]. Overall, the most common subsite was larynx, followed by oral cavity, oropharynx, esophagus and hypopharynx. Close to 90% of UADT cancers were squamous-cell carcinomas. A clear preponderance of smokers and alcohol drinkers was observed among UADT cancer compared with controls [47].

Hoshide et al. [48] investigated alcohol dehydrogenase (ADH) genetic variants in over 3800 aerodigestive cancer cases and 3200 controls from three individual studies. Cevi variants n12:99894 (ADH1B) and n15:73496 (ADH4P) were significantly protective against aerodigestive cancer in each individual study and overall (P<0.0001 in each case). These effects become more apparent with increasing alcohol consumption (P trend<0.0002 and 0.005, respectively). Both gene effects were independent of each other, implying that multiple ADH genes may be involved in upper aerodigestive cancer etiology. Using epidemiologic data and biological samples previously collected in three case-control studies from US and Chinese populations, Park et al. selected and genotyped one SNP from each of these three previously determined regions within the BRCA1 locus [44:2409 (region 1), n16:009179 (region 2), and n9:581326 (region 3)], and examined their association with smoking-related cancers including cancer of the larynx [49]. A noteworthy association was observed between n9:581326 and upper aerodigestive tract cancers (adjusted OR 1.95; 95% CI 1.28–2.24), particularly in the oral cavity and oropharynx (adjusted OR 2.84; 95% CI 1.73–4.67). International Agency for Research in Cancer.


Cancer of the esophagus affects more than 450,000 people globally each year, and is the sixth most common cancer among men and ninth among women. Survival is uniformly low, with 5-year survival rates usually less than 10%. In regions with established cancer registries that are included in the IARC Cancer Incidence in Five Continents series, populations with a high incidence are found among US black populations, as well as in South America, Asia, France and Africa (Table 5.2.1). Most notable are the extremely high rates that have been reported in Cixian, China (Group 2A), although confounding from other lifestyle factors could not be excluded. Although SEER data from the same period indicate that among Caucasian Americans, who have an age-standardised incidence for esophageal cancer of 4.7/100,000 among men and 1.2/100,000 among women, 55% of cases are coded as adenocarcinoma as opposed to 45% squamous-cell carcinoma.

The main risk factors for squamous-cell esophageal cancer in Western countries are alcohol and tobacco consumption, which in individual studies have been found to account for 75–90% of the disease [4]. The risk of esophageal cancer increases rapidly with the amount of both tobacco and alcohol consumption, with no evidence of any threshold effect for either. Most studies show a dose-response relation with tobacco consumption, and decreases in risk are found after quitting smoking. Similarly, a dose-response relation is observed with increasing alcohol consumption.

Although alcohol and tobacco consumption are the primary lifestyle risk factors for esophageal cancer in Western populations, dietary factors are also likely to be important. Fresh fruit and vegetable intake appears to have a strong protective effect [5], and although the relationship for particular types of fruits and vegetables is unclear, citrus fruits and green leafy vegetables appear to possess greater chemopreventative effects than other families of fruits and vegetables. Conversely, there is some evidence that frequent dietary consumption of salted meat and fish, as well as pickled vegetables may represent a risk factor.

Regarding the intake of hot beverages, consumption of hot tea, a habitual infusion consumed in parts of Southern Brazil, Argentina and Uruguay, appears to be strongly associated with development of esophageal cancer. Three case-control studies from Uruguay and Brazil have reported an increased risk among drinkers of mate, including a dose-response relationship [2,6,7]. An IARC monograph evaluation of mate consumption concluded that hot mate is traditionally drunk very hot, any information on the temperature of mate consumption has been self-reported, and it is not possible to separate out a possible carcinogenic effect due to the temperature or the composition of the beverage.

Hot tea consumption has also been suggested as a risk factor for esophageal cancer in Western populations. In a UK population-based case-control study on squamous cell cancer of the esophagus comprising 159 female case-control pairs, quantity of tea was identified as a risk factor for esophageal cancer along with a significant positive trend with temperature at which the tea was consumed (p < 0.01) [8]. The increased risk for drinking tea at very hot temperatures was over twofold and, as the authors suggested, when coupled with smoking is likely to explain much of the increased incidence of esophageal cancer among UK women when compared to other European populations.

Other potential risk factors for squamous cell esophageal cancer include contamination of food products by fungus mycotoxins, which has been reported in studies from high-risk areas in China and Italy [9,10]. In the only prospective study of fungus exposure and esophageal cancer, which used sphingolipids as a biomarker of fungus exposure in a high-risk population in Linxian, China, no relation was observed between fumonisin and esophageal cancer was observed [11]. Poor oral hygiene and tooth loss have also been reported to be associated with an increased risk of esophageal cancer, possibly related to alteration in and bacterial flora and subsequent increases in the in vivo production of carcinogens such as nitrosamines [12].

Regarding genetic susceptibility, esophageal cancer does not exhibit any strong familial component, and genetic studies of esophageal cancer have instead focused on genes such as cytochrome P 450 [13]. A genetic variant of the major forms of aldehyde dehydrogenase (ADH) 1C that metabolises suspected tobacco- and alcohol-derived carcinogens, nicotine and tobacco smoking, which in individuals with this genetic variant may have a significant role in the development of esophageal cancer association with smoking is likely to explain much of the increased incidence of esophageal cancer among UK women when compared to other European populations. In a population-based case-control study on squamous cell cancer of the esophagus comprising 159 female case-control pairs, quantity of tea was identified as a risk factor for esophageal cancer along with a significant positive trend with temperature at which the tea was consumed (p < 0.01) [8]. The increased risk for drinking tea at very hot temperatures was over twofold and, as the authors suggested, when coupled with smoking is likely to explain much of the increased incidence of esophageal cancer among UK women when compared to other European populations.

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High rates of esophageal cancer among women were also apparent in the United Kingdom and Ireland. There was a belt of slightly above-average rates across northern France, Belgium, The Netherlands and Denmark, but no evidence of the excess risk in northeast Italy, Slovenia, Slovakia and Hungary that was seen in males [1].

The geographical pattern observed in men can be related directly to the patterns of smoking and alcohol intake (in terms of ethanol) throughout Europe. It is much more difficult to ascribe the pattern of esophageal cancer observed in females to either these or other known risk factors. The similarity of the pattern in the ratios between the rates in men and women in each country with the corresponding pattern for oral cancer confirms that the risks arise from common etiological and/or cultural factors.

Fig. 5.2.4 Age-standardised incidence rates /100 000 of esophageal cancer according to the data of the Caspian Littoral Cancer Registry, 1970 in Mazandaran province, on the eastern coast of the Caspian Littoral. This was subsequently extended to the western province of Gilan and the neighboring city of Ardabil in the southeast of the Caspian Sea in 1970 (Figure 5.2.4).

Initial results from this cancer registry emphasized the very high incidence of esophageal cancer in the eastern portion of Mazandaran province close to Turkmenistan (the Gonbad and Gorgan districts, now Golestan province), and particularly in the semi-desert plain settled mainly by people of Turkoman ethnicity, with incidence rates of 109/100 000 among men and 174/100 000 among women [21,22]. Sharp changes in the incidence of esophageal cancer were evident between regions only a few hundred kilometres apart. The incidence dropped to 17.2/100 000 for men and 5.5/100 000 for women in Gilan, 500 km southwest.

The causes of this increasing trend include obesity, as well as an inverse association with helicobacter pylori [16,17].

Increasing trends of esophageal adenocarcinoma have been reported, particularly in the USA and parts of Europe [14,15]. For example, incidence rates of esophageal adenocarcinoma in white males in the USA surpassed those of squamous cell cancer around 1990. The causes of this increasing trend include obesity, as well as an inverse association with helicobacter pylori [16,17].

Esophageal cancer in very high incidence regions

The geographical distribution of esophageal cancer is characterised by very wide variations within relatively small areas. Although accurate cancer registry information is limited, very high rates (over 50/100 000) have been reported for both genders from northern Iran and the provinces of north-central China, in certain areas of Kazakhstan and also among native Siberians [18,19]. These populations form a “Central Asian Esophageal Cancer Belt” (Figure 5.2.3), although whether these extremely high rates are due to a common risk factor is unclear. One possibility is that very high rates of esophageal cancer are linked to several factors including (i) a severely deficient in fruits and vegetables, (ii) a squamous injury from consumption of very hot beverages and (iii) intense carcinogen exposure from lifestyle factors including smoking or opium consumption. These hypotheses are however untested.

The earliest reports of the high incidence of cancer of the esophagus in northern parts of Iran go back to mid-1960s and early 1970s [20-24]. These reports emphasized the frequency of the disease in many young patients, a predominance of squamous cell cancers and a slightly higher female/male ratio. In order to investigate this finding in more detail, a population based cancer registry was established in 1969 as a joint effort between Tehran University and the IARC, in the city of Babol.

in size. Conversely, a strongly significant protective effect has been observed with ADHIB variants that encode for fast alcohol metabolism [13].

Fig. 5.2.3 Iran and its position in the Central Asian Esophageal Cancer Belt

Fig. 5.2.4 Age-standardised incidence rates /100 000 of esophageal cancer according to the data of the Caspian Littoral Cancer Registry, 1970

Fig. 5.2.5 Highly infiltrative adenocarcinoma in a Barrett oesophagus

Fig. 5.2.5 A highly infiltrative adenocarcinoma in a Barrett oesophagus.
kilometres to the west. Recent reports from the
Andisal cancer registry and from an esophageal
cancer survey carried out in the eastern part of
the Caspian littoral have confirmed these early
findings [25,26].

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Table 5.2.2 Diseases and factors involved in the development of adenocarcinomas from Barrett esophagus.

<table>
<thead>
<tr>
<th>Registries</th>
<th>% by histological type - both sexes</th>
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</thead>
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<td>Africa</td>
<td>Male</td>
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<tr>
<td>Zimbabwe, Harare</td>
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<tr>
<td>Uganda, Kyando</td>
<td>14.1</td>
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<td>America, Central and South</td>
<td>Brazil</td>
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<td>Brazil, Cuiabá</td>
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<td>Africa, North</td>
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</tr>
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<tr>
<td>USA, Georgia: Black</td>
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<td>France, Loire-Atlantique</td>
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<tr>
<td>Scotland</td>
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</table>

Table 5.3.1 Cancer registries with highest esophageal cancer rates, 1993-1997 – CIS Vol IX
5.3 Stomach Cancer

Summary

- In most countries, a steady decline in gastric cancer mortality rates has been observed in the last few decades.
- The bacterium Helicobacter pylori, which establishes long-term infection of the stomach, is a major risk factor for gastric cancer, increasing the incidence rate by a factor of 6. It is estimated to be responsible for 63% of all cases of non-cardia gastric cancer worldwide.
- Genetic variation between strains of Helicobacter pylori may play an important role in gastric cancer risk.
- Epidemiological studies suggest a diet rich in fresh fruits and vegetables is protective against gastric cancer. However, intervention trials that supplement this diet with anti-oxidant vitamins have not been successful in reducing gastric cancer risk.

According to the most recent available estimates, gastric cancer is the fourth most common cancer worldwide, with 934,000 cases per year [2]. Survival from gastric cancer is poor since patients are often diagnosed with advanced disease. In the USA, for example, five-year survival is 24% [3].

Gastric cancer incidence shows wide geographical variation. World Maps 5.3.1 and 5.3.2 show the incidence rates in both sexes in Northern Europe from 1950 to 2005. In 1950, all countries illustrated in Figure 5.3.1 were high-risk countries and Estonia. Even in these countries, mortality rates in both men and women are in decline.

Risk factors for gastric cancer

Epidemiological evidence, mainly from case-control studies, suggests that a diet rich in fresh fruits and non-starchy vegetables is associated with a lower risk of gastric cancer. High salt intake has also been identified as a probable risk factor [8]. The hypothesis that fresh fruits and vegetables have a protective effect through the action of vitamins with anti-oxidant properties (e.g., vitamin C, beta-carotene and vitamin E) led to a number of intervention trials on gastric cancer or its precursor lesions using anti-oxidant vitamin supplementation [9].

Helicobacter pylori (H. pylori) is a spiral gram-negative bacterium that colonizes the stomach. It is one of the most common infections in humans with an estimated prevalence of 50% worldwide and 90% in developing countries. In high-prevalence populations, infection is rapidly acquired in childhood and persists throughout life. Prevalence of H. pylori infection is declining in many developed countries. It is believed that this is mainly a cohort effect, with the prevalence of infection declining in successive birth cohorts. Later acquisition of H. pylori may also contribute to low infection prevalence in children and young adults.

H. pylori was first isolated by Marshall and Warren [10], who demonstrated its causal role in gastritis and peptic ulcer disease, and were awarded the 2005 Nobel prize for Medicine for their discovery. In 1994, an expert working group convened by IARC classified H. pylori as a carcinogenic to humans [10] based on epidemiological evidence for its association with gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Since then, evidence has continued to accumulate for the causal role of H. pylori in gastric cancer.

The strongest epidemiological evidence for the role of H. pylori in gastric cancer comes from a combined analysis of 10 prospective studies in which H. pylori antibodies were measured in stored blood samples, taken years before diagnosis of gastric cancer [11]. In this pooled
of antibody response. Therefore, measurements of H. pylori antibodies in gastric cancer cases are not considered reliable unless taken many years before diagnosis.

Based on the estimated relative risk of 5.9, the proportion of non-cardia gastric cancer attributable to H. pylori has been estimated to be 6.3% [12]. This aggregate measure of risk may conceal the risk factors responsible could help accelerate the decline of this form of cancer which has relatively poor survival (European average 22% in males and 26% in females at five years after diagnosis).

The important role of Helicobacter pylori in the etiology of stomach cancer provides an unusual opportunity for prevention of this common form of cancer. The frequency of Helicobacter pylori infection is very high in many countries, and the infection is strongly implicated with gastric cancer in multiple populations worldwide.

Figure 5.3.2 shows the results of a cross-sectional study on precancerous lesions of the stomach based on detection of H. pylori DNA from gastric biopsies [16]. Subjects in the study who were infected with cagA-positive H. pylori strains were at substantially increased risk of advanced precancerous lesions compared with uninfected subjects. Conversely, infection with cagA-negative H. pylori was not associated with any precursor lesion except chronic gastritis. These findings strongly implicate cagA-positive strains of H. pylori in gastric carcinogenesis.

Genetic susceptibility

The descriptive epidemiology of gastric cancer indicates that the risk is dominated by environmental causes. There may, however, still be a role for genetic factors. Individuals with blood group A have been shown for decades to have an approximately 20% excess of gastric cancer compared with other blood groups. Gastrointestinal mutations in a gene encoding the cell adhesion protein E-cadherin (CDH1) have also been found in familial diffuse gastric cancer [17].

One summary measure of the possible contribution of gastric cancer is the familial relative risk (FRR). The FRR can be estimated from population-based studies that link cancer registries with a genealogical database. Three such studies have been conducted in Utah, USA [18], Sweden [19] and Iceland [20], giving FRR estimates of 2.09 (95% CI 1.35–3.16), 1.31 (0.97–1.70), and 1.90 (1.74–2.05) respectively. Hence there is modest but consistent evidence for an increase in risk among relatives of gastric cancer cases. The impact of this familial aggregation in terms of attributable fraction is small however. In the Swedish study, the population attributable fraction of gastric cancer cases due to familial aggregation was estimated to be 0.045. Moreover, the FRR is not
only a measure of the effect of shared geno-
type, but also includes the effect of shared environmen-
tal risk factors with the family. The
studies in Sweden and Iceland found signifi-
cantly elevated risk among spouses of gastric cancer
patients.

Studies relating individual genes to gastric
cancer risk have focused on candidate genes that
may modulate the host response to infec-
tion with H. pylori. In particular, polymorphisms
in interleukin 1 (IL-1B) and 5-1- receptor
(IL-1RN) genes have been extensively analysed,
but results are not consistent between studies.
Three independent meta-analyses have now
been published, summarising the pooled results of
studies on these polymorphisms, and all three
reach slightly different conclusions [21,23].
This lack of agreement arises from the substantial
heterogeneity between different studies con-
ducted in different populations. A plausible
explanation for this heterogeneity is that gastric
cancer risk and susceptibility are determined by
a combination of host genotype and volatile
H. pylori strain genotype. Both factors must be measured to accurately quantify the risk.

Prevention of gastric cancer

The two major changes that could be made at an organisational level to reduce gastric cancer
incidence are improvement in diet and reduc-
tion in the prevalence of H. pylori. These
changes are already taking place in many
populations, as a consequence of economic
development, and may explain the decline observed in gastric cancer incidence.
Active intervention in a population requires proof
that the intervention is effective, and this can
only come from randomised trials.

Several trials have been conducted using
selected vitamins as an intervention, and with gastric precancerous lesions or gastric cancer as an endpoint.
The aim of vitamin supplementation in these trials
was to simulate improved diet, assuming that the
protective micronutrients in a healthy diet
have been correctly identified. The results of these trials, however, have generally been dis-
appointing, and it is unlikely that anti-oxidant
vitamin supplementation is an effective tool
for gastric cancer control [9]. Nevertheless,
the negative results of randomised trials
cannot be considered to contradict the epi-

demiological evidence for a protective effect
of fresh fruits and vegetables, since the dose,
duration and timing of anti-oxidant vitamin
exposure in such trials are not directly com-
parable with a life-long healthy diet.

Several treatment regimens have been used
to eradicate H. pylori infection, but triple
therapy including bismuth salts, amoxicillin
and clarithromycin is currently the regimen
of choice. Randomised trials of anti-H. pylori

treatment are reviewed by Correa [7], who
concludes that curing H. pylori infection results
in a modest retardation of the precancerous process,
but does not prevent all cancers. The available
trials of anti-H. pylori treatments are limited by the fact that they were conducted
in adults in an advanced state of atrophy or inces-
tinal metaplasia. It is possible that the impact on
gastric cancer prevention may be magni-
died by eliminating H. pylori at an earlier stage of
the precancerous process.

Conclusions

Geographical distribution and time trends
suggest that the risk of gastric cancer is strongly determined by environmental factors.
Epidemiological studies point to infection with
H. pylori and poor diet as the main determinants
of gastric cancer risk. Despite the long-term

dependency of gastric cancer incidence in many
populations, there is considerable opportunity
for active intervention to reduce the burden of
gastric cancer.

References

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On the right: Figure 5.3.4: The Helicobacter pylori Helicobacter pylori structure as revealed by scanning electron microscopy.

Liver Cancer

Summary

- More than 80% of cases of hepatocellular carcinoma occur in Asia and Africa, and irrespective of etiology, the incidence rate is more than twice as high in men as in women.
- In Africa and Asia, hepatocellular carcinoma is most frequently caused by hepatitis B virus infection, concomitant dietary exposure to aflatoxins multiples the risk.
- In Japan, this cancer is predominantly caused by hepatitis C virus infection.
- In Western countries, liver cirrhosis due to chronic alcohol abuse is a major etiological factor. The spread of hepatitis C virus is a major challenge and is responsible for increasing rates of liver cancer in the USA and in parts of Europe.
- Hepatocellular carcinoma is almost always lethal, survival from time of diagnosis often being less than six months, only 5–9% of patients survive five years or more.

Epidemiology

Liver cancer ranks third amongst the organ-specific causes of cancer-related deaths in men worldwide. Liver cancer accounts for approximately 5% of all cancer cases diagnosed worldwide. Liver cancer is the fifth most common cancer among men worldwide, but is the sixth in women [2,3]. Globally, men are about three times as likely as women to be afflicted and the difference is higher in high-incidence than low-incidence areas. Liver cancer is a major health problem in low-resource countries, where more than 80% of the worldwide total occur [1]. In low-income settings, the highest incidence rates are recorded in China (5.5% of the world total), Japan, South East Asia and sub-Saharan Africa. In both high- and low-incidence areas, there is great variability in incidence among ethnic groups [4].

Age-specific rates of incidence show marked geographical variation. In the Oambia, age-specific rates peak in the 45–55 years age range, whereas in Europe and the USA, high-risk is associated with older age.

Trends in liver cancer incidence are difficult to interpret due to changes in classification and variable inclusion of metastatic tumours. However, the incidence of hepatocellular carcinoma in Japan, the UK, Germany and the USA and several Nordic countries has demonstrated a sustained increasing trend over the past several decades and has become progressively associated with younger age groups [5]. Mortality rates have increased in several regions, including France. Some of these increases may be the result of improved detection, but the main causal factors are the widespread hepatitis C virus infection as well as the growing impact of non-alcoholic metabolic diseases.

Etiology

Hepatocellular carcinoma (HCC) arises from hepatocytes and accounts for about 80% of all primary cancers of the liver. Other tumour types include intrahepatic cholangiocarcinoma (involving duct or bile ductules located within the liver), hepatoblastoma (a malignant tumour in children) and angiosarcoma (arising from blood vessels) and are relatively rare compared to HCC. However, in some parts of the world such as eastern Thailand, cholangiocarcinoma occurs at a high rate as the result of infection of biliary ductules by liver flukes (Opisthorchis viverrini) due to the consumption of infected raw fish. The development of flukes in bile ductules induces a chronic inflammatory state that represents a major risk factor for the neoplastic transformation of bile duct epithelial cells.

Aflatoxins are viral oncogens. Globally, the epidemiology of HCC is dominated by the interaction of viral and environmental risk factors. These factors and their overall impact are summarised in Table 5.4.1. The carcinogenic effect of chronic infection with hepatitis viruses B and C is well demonstrated by epidemiological and experimental evidence. Consistent epidemiological data have associated a significant risk of HCC with chronic HBV infection, which accordingly has been classified as causing cancer in the context of IARC Monograph evaluations [6]. Worldwide, the proportion of HCC attributable to chronic hepatitis is about 54% for HBV and 31% for HCV. These figures should be considered as conservative estimates. Persistent chronic HBV infection is usually defined by the release into the bloodstream of the surface antigen HBsAg during at least 6 months post-infection. There is evidence that HBV can also persist in the form of viral DNA. The occult infections may represent the terminal phase in the natural course of HBV persistent infection and they should be taken into account in estimates of the risk of CRC attributable to HBV. Furthermore, co-infections with HBV and HCV may occur, with a cumulative effect on the risk of HCC that varies from additive to multiplicative. Thus, the burden of liver cancer attributable to hepatitis viral infections is likely to be close to 90%.

It should be noted that the impact of hepatitis virus infections shows substantial geographic variation, in both the population prevalence of persistent infection and the specific genetic pattern of predominant infection. In many low-resource tropical countries, chronic HBV carriage is high in the general population [10–13], and it can be estimated that over two thirds of liver cancer cases in low-resource countries are attributable to HBV virus [7]. HBV is particularly implicated in hepatocellular carcinoma in Africa and Asia, and HCV in Japan and the USA. However, the relationship between chronic carrier prevalence and incidence of HCC is a complex one, and striking discrepancies exist in some populations and geographic areas (South America, Greenland and Maoris (New Zealand) have among the highest population rates of HBV carriage in the world but they show relatively modest incidences of HCC. HBV exists in 8 distinct genotypes [defined by groups of viruses that have 8% or more differences in their DNA sequence, Figure 5.4.1], which differ by their infectivity, transmission mechanisms, pathogenicity, rate at which they progress and risk of chronic liver disease and HCC. For example, Genotype F, which is found among the native population of Alaska carries a risk of HCC several fold higher than most other genotypes.

There are an estimated 400 million HBV chronic carriers worldwide. Of these carriers, at least 50% will remain asymptomatic with progressive disappearance of HBsAg. Of the remainder, many will develop chronic liver disease of variable severity, the highest condition is liver cirrhosis. In western countries, about 70–90% of hepatocellular carcinomas develop in patients with cirrhosis. In western Asia and West Africa, the proportion of patients with pre-existing liver cirrhosis at the time of HCC diagnosis appears to be much higher, perhaps in the range of 25–50%. However, there is a lack of detailed prospective studies on precursor liver conditions in these areas. Therefore, cirrhosis is not an obligatory pre-cancer step to HCC.

Significant differences related to the population ratio of chronic carriage and the viral genotypes also exist for HCV. In some countries, for example in Egypt, there is evidence that the estimated chronic carriage is much lower than the prevalence of overt disease, indicating that occult infections may represent the terminal phase in the natural course of HBV persistent infection, which accordingly has been classified as causing cancer in the context of IARC Monograph evaluations [6]. Persistent, chronic HBV infection is usually defined by the release into the bloodstream of the surface antigen HBsAg during at least 6 months post-infection. There is evidence that HBV can also persist in the form of viral DNA. The occult infections may represent the terminal phase in the natural course of HBV persistent infection and they should be taken into account in estimates of the risk of HCC attributable to HBV. Furthermore, co-infections with HBV and HCV may occur, with a cumulative effect on the risk of HCC that varies from additive to multiplicative. Thus, the burden of liver cancer attributable to hepatitis viral infections is likely to be close to 90%.

Dietary and environmental carcinogenesis

In low-resource tropical countries, dietary exposure to aflatoxins, a class of mycotoxins produced by moulds of the genus Aspergillus, is a significant risk factor that operates synergistically with both HBV and HCV chronic infection. Aflatoxins contaminate many traditional crops such as groundnuts (peanuts), grains or
DNA lesions which, if not repaired, lead to base of codon 249 in TP53. Processing of this epoxide that covalently binds on the N7 position of guanine in DNA is catalyzed by a DNA glycosylase. The DNA lesion is opened by the DNA helicase and the resulting abasic site serves as a template for a short-patch direct repair. ATP hydrolysis provides the energy to complete the repair. The product is the 3'-deoxy-2'-desoxynucleoside monophosphate which is subsequently converted to the nucleoside triphosphate by a DNA polymerase and a DNA ligase to complete the repair cycle.

In high-resource countries, the main known risk factors are smoking and, significantly, chronic alcohol abuse [8]. Alcohol is primarily responsible for metabolic liver injury that leads to the development of liver cirrhosis, which is a common sequela of HCC. Iron overload caused by unbalanced haematinic intake or excess exposure to iron in some African populations may provide some patient series a risk of death as much as 45% from hepatocellular carcinoma (HCC). Among patients undergoing bariatric surgery, an AST/ALT ratio greater than 1 may be considered a precursor disease [10].

The toxin is metabolised in the liver to produce aflatoxin B1 and AFMO (produced by Aspergillus flavus) is a significant contaminant of staples such as maize. Aflatoxin B1 can cause DNA adducts to form, which may also result in liver cell necrosis, with or without the development of cirrhosis. Aflatoxin exposure is linked to the development of hepatocellular carcinoma. The malignant transformation induces oxidative stress damage as well as telomerase and microsatellite stress due to accumulation of HBV DNA in the reticulum. These stresses cause widespread cell death and stimulate compensatory cell proliferation, resulting in deregulated, inflammatory context which is one of the hallmarks of cirrhosis. In this modified environment, transformed cells would have several advantages due to their capacity to proliferate and to escape apoptosis, and may thus be selected to form rapidly expanding lesions. Second, HBV may promote the development of hepatocellular carcinoma: a well-differentiated, trabecular carcinoma contains numerous sinusoid-like capillary vessels with HBV DNA integrated into the genome of the host cell and may act as an inserter mutant to act as support or repression of genes in the vicinity of the integration point. There is however no consensus integration region in the genome of hepatocytes. Third, the virus encodes several proteins that have a significant impact on the host cell's signalling pathways. HBV, the protein encoded by the X gene of the viral genome, is a multi-functional protein that acts as a transcriptional regulator, interferes with several signaling pathways, and may thus contribute to the maintenance of several metastatic phenotypes. These biochemical effects may contribute to tumour initiation or to the maintenance of the transformed phenotype.
Invasive hepatic cholangiocarcinoma comprises cells resembling those of bile ducts, which is the site paralyzed by liver flukes [12]. Most intrahepatic cholangiocarcinomas are adenocarcinomas showing tubular and/or papillary structures with a variable fibrous stroma. Mutations of the KRAS and TP53 genes are the most common genetic abnormalities identified.

**Detection**

Screening for HCC in those patients at highest risk is crucial for an effective management strategy. From a diagnostic standpoint, ultrasound and/or computed tomography (CT) (Figure 5.4.3) and a sonography. A definitive diagnosis may depend on histological analysis via fine needle biopsy. Endoscopic retrograde cholangiography, transhepatic or magnetic resonance cholangiography can identify the level of biliary obstruction in the case of intrahepatic cholangiocarcinoma.

**Management**

The treatment of primary and malignant liver tumours depends on the extent of the disease and the underlying liver function [15]. The most frequently used staging system is that in which the patient is evaluated according to the adverse criteria of ascites, serum albumin and bilirubin concentration and tumour size. The TNM system is less useful as it does not take into account underlying liver disease. Liver cancer follows a rapid, progressive course: only about 8% of patients survive at least five years in the USA, and the percentage is much lower in lower-resource countries. In the absence of extrahepatic disease, resection with negative margins is the primary approach in such patients. In Europe and in the USA, the use of this procedure has declined due to a number of factors, including the frequency of extrahepatic disease, resection with negative margins carries a high mortality rate, and the increasing incidence of liver cancer.

**Prevention**

The poor prognosis and lack of effective therapies for hepatic carcinoma indicate that the development of prevention programmes is of critical importance. Since the early 1980s, safe, effective, and affordable HBV vaccines have been available. The World Health Organization has recommended that all newborns receive a HBV vaccine at birth. HBV can lead to liver cirrhosis and liver cancer in young adults, a sharp and significant drop in the incidence of HCC has been observed in areas where HBV vaccination programmes have been implemented. The use of this vaccine has led to a dramatic reduction in the incidence of HCC in the years following the introduction of the vaccine [20]. However, due to the long-term nature of the disease, there is still a need for long-term vaccination programmes. HBV is currently being used in many countries to evaluate the protective efficacy of new HCV vaccines against primary cirrhosis and liver cancer.

**Clinical manifestations**

Common symptoms of hepatic carcinoma are abdominal pain, weight loss, fatigue, abdominal swelling and anemia. Most patients, particularly in sub-Saharan Africa, present with hepatomegaly, other common signs are ascites and jaundice. Hepatocellular carcinoma that infiltrates a cirrhotic liver often presents with jaundice and cholangitis at later stages. The majority of cases can be diagnosed by computed tomography (CT) (Figure 5.4.3) and a sonography. A definitive diagnosis may depend on histological analysis via fine needle biopsy. Endoscopic retrograde cholangiography, transhepatic or magnetic resonance cholangiography can identify the level of biliary obstruction in the case of hepatic cholangiocarcinoma.

**Incidence Data**

Tumour directly invades other organs or structures and/or tumour invades through muscularis propria into subserosa or into non-

**Mortality Data**

Table 5.4.2. TNM classification of cancer of the colon and rectum

<table>
<thead>
<tr>
<th>TNM</th>
<th>Incidence Data</th>
<th>Mortality Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>551 000 cases/year worldwide</td>
<td>54% of the total cases in China</td>
</tr>
<tr>
<td>M0</td>
<td>299 000 deaths/year worldwide</td>
<td>83% of all cases in developing countries</td>
</tr>
<tr>
<td>n0</td>
<td>354 - Section 5 - Cancer Site by Site</td>
<td>8% of total cancer deaths</td>
</tr>
</tbody>
</table>

**Major Etiologic Factors**

| Hepatitis B infection (>50%) | 551 000 cases/year worldwide |
| Hepatitis C infection (>25%) | 54% of the total cases in China |
| Alcohol consumption | 83% of all cases in developing countries |
| Tobacco smoking | 5.4% of the total cases in China |

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Other risk factors are amenable to prevention, such as alcohol drinking, tobacco smoking or exposure to excess environmental iron. One of the biggest challenges in high-resource countries is to develop public health policies that will be effective in curbing the increase in the incidence of NARED.

REFERENCES

Pancreas Cancer

Summary

- Pancreatic cancer is the 13th most common cancer worldwide, with over 232,000 new cases diagnosed each year. In general, the highest incidence rates occur in more developed countries.
- About 20% of pancreatic cancer is attributable to tobacco smoking.
- Familial clustering of pancreatic cancer and pancreatic cancer-related to rare genetic syndromes, including hereditary pancreatitis, occurs in ≤10% of cases of pancreatic cancer.
- No population-based screening or early diagnostic testing procedures are currently available, although there are efforts underway to address these deficiencies.
- The five-year survival rate is 9%, the lowest survival rate of the major cancers.
- Mutations in KRAS, TP53, p16/CDKN2A, and SMAD/DPC4 are implicated in over 50% of pancreatic tumors. Ductal pancreatic adenocarcinomas appear to progress from pancreatic intraepithelial neoplasia (PanIN) to pancreatic adenocarcinoma. Stromal elements and a strong desmoplastic response appear to play a role in the growth and aggressiveness of pancreatic tumors.
- Treatment and management for pancreatic cancer patients have seen few recent improvements. Management for most patients still focuses on palliation.

Pancreatic cancer is one of the most aggressive human tumors. At diagnosis, fewer than 10% of cases present with disease localized to the pancreas. The majority of pancreatic tumors (95%) occur in the exocrine portion of the pancreas, with the remaining 5% occurring in the endocrine portion or arising from the islets of Langerhans. Most pancreatic tumours of the exocrine pancreas are classified as ductal adenocarcinomas. Tumours of the body or tail of the pancreas occur with a 30-40% frequency, while the remainder occur in the head of the pancreas. About 80% of pancreatic tumours occurring in the body or tail are more advanced (stage II), while about 33% of those in the head are diagnosed at stage I. Consequently, survival and prognosis vary by the initial site of the tumour within the pancreas.

Epidemiology

Pancreatic cancer is the 13th most common cancer worldwide, with over 232,000 new cases occurring each year. The overall 5-year survival rate for pancreatic cancer is the lowest of all the major cancers at 3% to 5% (Figure 5.5.1). In the minority of pancreatic cancer patients for whom surgery is an option, the 5-year survival rate is between 10 and 15%. In the USA, pancreatic cancer is now the fourth leading cause of cancer death for men and women, and in the year 2008, it is estimated that there will be 37,380 new cases of pancreatic cancer and 34,290 deaths [2]. Reasons for the poor survival in pancreatic cancer include the typically indolent and aggressive nature of these tumours, late diagnosis, low rates of resection, and lack of effective therapies.

Pancreatic cancer incidence and mortality rates vary around the world. Incidence and mortality are generally higher in the Americas, Europe, Australia and Japan. More specifically, worldwide incidence rates are highest for African American men. New Zealand Māoris (particularly women), Korean Americans, female native Hawaiians, and the male population in Kazakhstan. Worldwide incidence and mortality rates are lowest in India, Africa (although quality data are generally lacking), Southeast Asia, and parts of the Middle East. In Latin America are generally intermediate between the higher rates in North America and the lower rates in India [3].

Etiology

Advancing age is one of the strongest and most consistent predictors of pancreatic cancer risk. Pancreatic cancer is very rare under the age of 30 years, with the majority of cases occurring after the age of 65 years. Incidence rates are about 20–50% higher in men than in women until later in life, when incidence rates become similarly equal. (Figure 5.5.2). These observations, along with data from animal studies, suggest that hormonal factors could play a role in the development of pancreatic cancer. So far, the epidemiological studies that have addressed reproductive factors and hormone use in relation to pancreatic cancer have yielded inconclusive results.

The most important (and avoidable) environmental risk factor for pancreatic cancer is tobacco smoking. Most studies to evaluate smoking and pancreatic cancer report relative risks around two-fold [3]. It is estimated that 20–29% of all pancreatic cancers are attributable to smoking [4,5]. Despite the overwhelming evidence that smoking is a cause of pancreatic cancer, the biological mechanisms underlying the carcinogenicity remains elusive. Quitting smoking can reduce the risk of pancreatic cancer by up to 50% after two years of not smoking, and other about 10 years of not smoking may decrease risks to those seen in never-smokers [4].

Various dietary factors have been associated with increased and decreased risks for pancreatic cancer. Diets high in red meats and fats and high in calories appear to increase the risk of pancreatic cancer, while diets high in fruits and vegetables and fibre appear to decrease risk. Further, the method of cooking, in particular methods that increase heterocyclic amines in cooked meats such as high temperature broiling, grilling and barbecuing, may also increase the risk of pancreatic cancer [6]. Moderate consumption of coffee and alcohol do not appear to increase risk, however, very heavy alcohol drinking and alcohol binging may increase risk. Obesity appears to be related to a higher risk for pancreatic cancer [7]. Higher levels of physical activity, possibly related to higher energy expenditure, appear to be associated with a decreased risk for pancreatic cancer [8].

Long standing diabetes is associated with about a 40% increased risk for pancreatic cancer [9]. Chronic inflammatory pancreatitis, although rare, is associated with a high risk (greater than 10-fold higher) for developing pancreatic cancer. The biological mechanisms underlying the increased risks for pancreatic cancer associated with diabetes and pancreatitis are currently unknown. A recent analysis of pre-diagnostic plasma C-peptide showed a positive association with subsequent risk of pancreatic cancer, suggesting that underlying insulin resistance and hyperinsulinaemia may play a role in pancreatic carcinogenesis [9]. The relation between a history of allergies and pancreatic cancer risk has been evaluated in a number of studies. A
current review and meta-analysis suggested that there is evidence of an association between occupational exposure and risk of pancreas cancer development [11]. There are some indications that occupational exposure may contribute to pancreas cancer risk; however, studies to date have involved too few cases to adequately address this topic. The use of asphiin has been consistently associated with pancreas cancer, with some studies showing inverse associations and others showing no association. To date, the possibility that occupational hazards include occupational exposures in combination with lifestyle and environmental exposures has also been shown to be of interest in defining susceptible subgroups at greater risk for pancreas cancer development [11, 12]. Additional and posited analyses involving thousands of cases may help to define combinations of factors and exposures that increase the risk of developing pancreas cancer. Such information may lead to improved screening and detection as well as treatment and prevention of sporadic forms of pancreas cancer.

Pathology and genetics

There is growing evidence that the molecular pathogenesis of pancreas cancer progresses from early stage neoplasia, or PanIN, to malignancy in pancreatic cancer (Figure 5.5.3). The first stage of neoplasia, flat hyperplasia, involves the columnarisation of the ductal epithelium. This may then advance to papillary hyperplasia, the presence of crowded mucous with a folded structure, which may possess varying degrees of cellular and nuclear abnormalities. True carcinoma of the pancreas is characterised by invasion of the ductal walls of the lumen and a strong desmoplastic inflammatory response. The molecular pathways and genes involved in pancreas cancer progression are being actively pursued by the scientific community [11].

Hereditary conditions. From 5 to 10% of pancreas cancer cases exhibit some degree of familial clustering. There are a number of hereditary syndromes that have been associated with an increased lifetime risk of pancreas cancer (Table 5.5.2). Over 20 genes have been implicated in the molecular pathogenesis of pancreas cancer (Table 5.5.2). Somatic alterations involving four genes have been implicated in over 50% of pancreatic tumors, including KRAS oncogene (>90%) and p16/DMPDK2A (>40%), TP53 (>50%) and DPC4/SMAD4 (>35%) tumor suppressor genes [13] (Table 5.5.2). The genetic progression of pancreas cancer from normal epithelium to invasive carcinoma is generally associated with the accumulation of genetic alterations starting with KRAS mutations and eventually shortening followed by p16/DMPDK2A loss and finally mutations in TP53.

Management

Pancreas cancer is often referred to as a “silent” disease because the tumor can grow for years before there are any noticeable symptoms or signs. Typical symptoms of pancreas cancer include jaundice, generalized itching, pain in the abdomen or back, nausea, loss of appetite, unexplained weight loss, and general weakness. These symptoms are often ignored by many people until they appear, at which point the cancer is usually advanced and not curable.
patients early on and can be mistakenly attrib- 
uted to other general health problems. Tumours
in the head of the pancreas are more likely to
cause jaundice, whereas advanced tumours and
tumours in the body of the pancreas are more
likely to cause pain.

Surgery remains the best chance for a cure,
but only a minority of patients receive any
form of surgery (less than 15% of cases, usu-
ally tumours in the head of the pancreas).

Table 5.5.1 Table of hereditary syndromes with lifetime risk of pancreatic cancer

<table>
<thead>
<tr>
<th>Hereditary condition</th>
<th>Gene (chromosome)</th>
<th>Lifetime risk of pancreatic cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary pancreatitis</td>
<td>p16/CDKN2A (9p21)</td>
<td>2–5%</td>
</tr>
<tr>
<td>Familial atypical multiple mole melanoma (FAMMM)</td>
<td>p16/CDKN2A (9p21)</td>
<td>10–17%</td>
</tr>
<tr>
<td>Familial breast cancer</td>
<td>BRCA2 (13q12)</td>
<td>5%</td>
</tr>
<tr>
<td>BRCA1 (17q21)</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Fanconi anaemia syndrome</td>
<td>(young-age-onset pancreatic cancer)</td>
<td>Unknown</td>
</tr>
<tr>
<td>(young-age-onset pancreatic cancer)</td>
<td>FANCC (9q22)</td>
<td>Unknown</td>
</tr>
<tr>
<td>MSH2 (2p16)</td>
<td></td>
<td>1–3%</td>
</tr>
<tr>
<td>(2p16)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>FANCC (9q22)</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>MSH6 (2p15)</td>
<td></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>(2p15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis (heterozygotes)</td>
<td>BRCA2 (9p22)</td>
<td>Unknown, rare</td>
</tr>
<tr>
<td>Familial pancreatic cancer (D or more first-degree relatives with pancreatic cancer)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Hereditary non-polyposis colorectal cancer (HNPCC)</td>
<td>MSH2 (2p15)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>(D or more first-degree relatives with pancreatic cancer)</td>
<td>MSH6 (2p16)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Cystic fibrosis (heterozygotes)</td>
<td>BRCA2 (9p22)</td>
<td>Unknown, rare</td>
</tr>
<tr>
<td>Familial pancreatic cancer (D or more first-degree relatives with pancreatic cancer)</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.5.2 Genes involved in pancreatic cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Mechanism of alteration</th>
<th>% of cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRA52</td>
<td>19p</td>
<td>Point mutation</td>
<td>&gt;90</td>
</tr>
<tr>
<td>CMYC</td>
<td>8p</td>
<td>Amplification</td>
<td>20–30</td>
</tr>
<tr>
<td>MYB, AKT2, AIB1, EGR1</td>
<td>6q, 19q, 20q, 7p</td>
<td>Amplification</td>
<td>10–20</td>
</tr>
<tr>
<td>ERBB2</td>
<td>18q/20q21</td>
<td>Chromophosphorylation</td>
<td>70</td>
</tr>
<tr>
<td>BRAF</td>
<td>7q</td>
<td>Point mutation</td>
<td>Rare</td>
</tr>
<tr>
<td>TGFa</td>
<td>1q</td>
<td>Tumour suppressor genes</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>17p</td>
<td>Homologous deletion</td>
<td></td>
</tr>
<tr>
<td>DPC4/SMAD4</td>
<td>18q</td>
<td>Loss of heterozygosity and intragenic mutation</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>13q</td>
<td>Promoter hypermethylation</td>
<td></td>
</tr>
<tr>
<td>LE3/STK11</td>
<td>19p</td>
<td>Loss of heterozygosity and intragenic mutation</td>
<td></td>
</tr>
<tr>
<td>ACVR1B</td>
<td>12q</td>
<td>Loss of heterozygosity and intragenic mutation</td>
<td></td>
</tr>
<tr>
<td>TGFB1R1, TGFB1R2</td>
<td>9q, 3p</td>
<td>Loss of heterozygosity</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>17q</td>
<td>Loss of heterozygosity</td>
<td></td>
</tr>
<tr>
<td>MSH2, MSH6</td>
<td>2p, 3p</td>
<td>Inherited mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>MSH2, MSH6</td>
<td>2p, 3p</td>
<td>Inherited mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>Methylation?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Cancer Institute Profile:
Oncology Institute of Southern Switzerland (IOSI)

The Oncology Institute of Southern Switzerland (IOSI) is a multiple oncology institute that comprises all the facilities related to cancer treatment at different public hospitals. Among them, the Ospedale San Giovanni in Bellinzona has the most important assets: the radiotherapy centre, the PET-scan, the haematology division and for aggressive chemotherapy treatment, including autologous bone marrow transplantation.

The institute sees 2500 new patients a year, representing a comprehensive care centre that also includes a cancer register, a central library and facilities for clinical and translational research. Three of Europe’s major cancer research structures have their operational offices at IOSI: ECOG (International Eastern Oncology Study Group), IBCSG (International Breast Cancer Study Group), and SENDO-SAKK (coordinating office at IOSI: IELSG (International Extranodal Lymphoma Study Group), IACT, RTOG, BRIC, and Extranational offices at IOSI: IELSG (International Extranodal Lymphoma Study Group), IACT, RTOG, BRIC, and SENDO-SAKK).

Cancer Institute Profile:
National Colorectal Cancer Roundtable

The USA National Colorectal Cancer Roundtable, cofounded by the American Cancer Society and the US Centers for Disease Control and Prevention, is an interorganizational coalition of public, private and voluntary organizations, and invited individual experts dedicated to reducing the incidence of colorectal cancer through coordinated leadership, strategic planning and advocacy. The Roundtable is a catalyst to stimulate key member organizations to act earlier, act more effectively, and act collaboratively in the area of colorectal cancer.

The Roundtable taps into the expertise of its members to create tools, conduct studies, develop consensus and support projects that can advance the community’s overall work in this area. Many of these projects, such as the creation of the Blue Star symbol, the development of a colorectal cancer Clinician’s Guide and Toolbox, and the development of a study to measure how increasing screening rates impacts downstream costs, fill a key need among collaborating partners. Such initiatives create a multiplier effect in the community’s work against this disease.

For more information, visit the website: www.nccrt.org.
The biliary tract consists of an interconnected system of intra- and extrahepatic ducts that transport bile secreted from the liver to the digestive system of intra- and extrahepatic ducts that transport bile secreted from the liver to the digestive system. The bile ducts take bile from the liver to the gallbladder. The gallbladder is a small organ located beneath the liver. It stores and concentrates bile, which is then released into the small intestine through the common bile duct. Bile is produced by the liver and contains bile acids, bile salts, cholesterol, and pigments. Bile plays a crucial role in the digestion of fats, as it contains bile acids and bile salts that help emulsify fats in the small intestine, making them more susceptible to digestion by digestive enzymes. The gallbladder cancer (GC) is a relatively rare neoplasm, and the most common type of cancer of the biliary tract. GC occurs when cells in the gallbladder lining grow uncontrollably, forming tumors that can spread to other parts of the body. The growth and spread of cancer cells can lead to pain, swelling, and other symptoms. The exact cause of gallbladder cancer is not fully understood, but researchers believe that it may be related to factors such as inflammation, genetics, and the presence of bile duct stones.

### Summary

- **Gallbladder cancer incidence is higher in women than in men in most areas of the world.** The highest incidence areas are China, India and some other countries of Latin America, Asia and central Europe.

- **Incidence and mortality have been declining in most areas of the world over the last few decades, mainly due to the increasing frequency of cholecystectomy.**

- **Gallbladder anomalies and cholelithiasis are the major risk factor for GC.**

- **Other risk factors are obesity and selected aspects of diet, linked to gallstones.**

- **Risk factors:**
  - **Gallbladder cancer incidence is higher in women than in men in most areas of the world.** The highest incidence areas are China, India and some other countries of Latin America, Asia and central Europe.
  - **Incidence and mortality have been declining in most areas of the world over the last few decades, mainly due to the increasing frequency of cholecystectomy.**
  - **Gallbladder anomalies and cholelithiasis are the major risk factor for GC.**
  - **Other risk factors are obesity and selected aspects of diet, linked to gallstones.**

- **Risk factors for GC:**
  - **Gallbladder cancer incidence is higher in women than in men in most areas of the world.** The highest incidence areas are China, India and some other countries of Latin America, Asia and central Europe.
  - **Incidence and mortality have been declining in most areas of the world over the last few decades, mainly due to the increasing frequency of cholecystectomy.**
  - **Gallbladder anomalies and cholelithiasis are the major risk factor for GC.**
  - **Other risk factors are obesity and selected aspects of diet, linked to gallstones.**

- **Descriptive epidemiology:**
  - **Gallbladder cancer incidence is characterised by worldwide variation (Figure 5.6.1).**
  - **Incidence rates recorded by cancer registries in the mid-1990s, the highest incidence rate worldwide occurred in women from India, India (13.7/100 000), followed by South Korea, Pakistan [13.8/100 000] and Quito, Ecuador (12.9/100 000). Cancer registries reporting high GC incidence rates were in East Asia (Korea and Japan), Eastern Europe (including Slovenia, Poland, the Czech Republic) and South America (Colombia). In Western Europe, elevated incidence rates were shown in Granada, Spain. Although systematically lower in women, high incidence rates among men (ranging between 4.4 and 8.0/100 000) were found in some areas of Asia and Eastern Europe.**
  - **Most registries from Northern Europe indicate low incidence rates (below 3/100 000 women and 1.5/100 000 men), with the partial exception of Sweden.**
  - **The female to male (F/M) incidence ratio of GC incidence rates varied greatly, it was >5 in several high-risk areas (e.g. Pakistan, Israel, Colombia and Spain) as well as in a few selected low-risk areas (e.g. Denmark), and was typically between 2 and 3 in the majority of countries. F/M ratio was close to 1 in Korea, Japan and some parts of China (9).**
  - **Incidence rates of GC in various ethnic groups from selected cancer registries in the USA confirmed the worldwide pattern.** (Figure 5.6.2). GC incidence was 3.8/100 000 women and 0.7/100 000 men in the USA, 3.3/100 000 women and 0.9/100 000 men in Puerto Rico, and 0.9/100 000 women and 0.3/100 000 men in South Korea. The incidence rate was highest among black non-Hispanic women, followed by white non-Hispanic women, followed by white non-Hispanic men, followed by black non-Hispanic men.
  - **Incidence rates of GC in various ethnic groups from selected cancer registries in the USA confirmed the worldwide pattern.** (Figure 5.6.2). GC incidence was 3.8/100 000 women and 0.7/100 000 men in the USA, 3.3/100 000 women and 0.9/100 000 men in Puerto Rico, and 0.9/100 000 women and 0.3/100 000 men in South Korea. The incidence rate was highest among black non-Hispanic women, followed by white non-Hispanic women, followed by white non-Hispanic men, followed by black non-Hispanic men.

- **Obesity and overweight are major risk factors for gallbladder disease, and large cohort studies show that the relative risk is one of the strongest seen for any cancer site (Table 5.6.2).** The relative risk of GC among those who were overweight was 1.2 (95% CI 1.0–1.3) and for those who were obese the OR was 1.7 (95% CI 1.5–1.9). The influence of obesity, however, like the influence of belonging to certain ethnic groups, seemed to be at least in part mediated by an increased predisposition to develop gallstones.

- **The overall increased frequency of GC in women suggests a possible role for hormonal factors, especially in the formation of cholesterol gallstones.** High parity and high number of pregnancies, again recognised risk factors for gallstones, have been related to increased GC risk. Among younger women, older age at first birth or pregnancy has been associated with reduced risk of GC. Oral contraceptive use was not materially related to GC risk; neither was duration of use and time since first and last use. Inconsistent results were obtained for the association of GC risk with menopausal status and HRT use. Thus, the precise role of female hormones remains unresolved, but it is unlikely that they play a major role (47).

- **Chronic infection of the gallbladder may contribute to the onset of GC, per se or via gallstone formation.** Most available evidence implicates S. typhi and paratyphi and Helicobacter species (5). Eleven epidemiological studies concerning the relation between Salmonella (S.) typhi and paratyphi and GC have been published. The summary RR for typhoid infection was 4.8 (95% CI 1.4–17.3), and rose to 10.2 (95% CI 2.0–50.9) after exclusion of studies based on self-reported diagnosis of infection. The summary RR for control studies was 2.6 (95% CI 1.0–6.1), which rose to 3.2 (95% CI 1.2–8.7) after exclusion of studies based on self-reported diagnosis of infection (44).
carrier status and GC risk. Also, Helicobacter bilis and pylori have been identified in bile specimens and associated with risk of biliary tract cancer (RR 4.3; 95% CI 2.1–8.8) [4].

Most studies of infection and GC to date have limited power (no more than 15 exposed cases), have lacked well-verified controls (with or without gallstones), and have been hampered by a lack of standardized and normative methods for the detection of these infectious agents.

With respect to dietary factors, in the multinational collaborative study from the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) Programme of the International Agency for Research on Cancer (IARC), which included 169 cases and 1515 controls [9], the strongest direct associations with GC risk were for total carbohydrate intake (RR 11.3 for the highest quartile versus the lowest quartile) and total energy intake (RR 2.5), with inverse associations for dietary intake of fibre, vitamin B6, E and C (RRs ranging from 0.4–0.5). However, apart from obesity, there are no nutritional or dietary factor consistently related to GC risk.

Conclusions and perspectives

It has been proposed that there are two main pathways to GC [2]. The predominant pathway involves gallstones and resultant cholecystitis, and affects women to a greater extent than men. The other pathway involves an anomalous pancreatobiliary duct junction (APBDJ), a congenital malformation of the biliary tract that is more prevalent in Japan, Korea, and possibly China than in Western countries. With APBDJ, the pancreatic and common bile ducts join together before reaching the duodenal wall, allowing reflux of secretions of the exocrine pancreas into the gallbladder. APBDJ appears to be associated with papillary carcinoma of the gallbladder, which is less invasive and fatal than other carcinomas of the gallbladder [2].

Table 5.6.1

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>RR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort studies*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malmgren, 1987</td>
<td>2.8 (0.9–6.0)</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Maringhi, 2004</td>
<td>3.6 (2.4–6.9)</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Case-control studies*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None reported</td>
<td>1.1 (0.4–2.9)</td>
<td>Age</td>
</tr>
</tbody>
</table>

* Adjusted for smoking, alcohol, sex, age, residence and education.

Case-control studies*:

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>RR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato, 1989 (Japan)</td>
<td>7.0 (3.9–12.0)</td>
<td>Age, sex, hospital</td>
</tr>
<tr>
<td>Strom, 1995 (Bolivia, Mexico)</td>
<td>3.9 (3.1–5.0)</td>
<td>Age, sex, region and socioeconomic status</td>
</tr>
</tbody>
</table>

* Adjusted for smoking, alcohol, sex, age, residence and education.

Fig. 5.6.1	Age-standardised incidence rates* per 100 000 (world population) and female/male ratio for gallbladder cancer in 40 selected areas

Table 5.6.1

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>RR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort studies*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malmgren, 1987</td>
<td>2.8 (0.9–6.0)</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Maringhi, 2004</td>
<td>3.6 (2.4–6.9)</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Case-control studies*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None reported</td>
<td>1.1 (0.4–2.9)</td>
<td>Age</td>
</tr>
</tbody>
</table>

* Adjusted for smoking, alcohol, sex, age, residence and education.

Case-control studies*:

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>RR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato, 1989 (Japan)</td>
<td>7.0 (3.9–12.0)</td>
<td>Age, sex, hospital</td>
</tr>
<tr>
<td>Strom, 1995 (Bolivia, Mexico)</td>
<td>3.9 (3.1–5.0)</td>
<td>Age, sex, region and socioeconomic status</td>
</tr>
</tbody>
</table>

* Adjusted for smoking, alcohol, sex, age, residence and education.
Gallbladder cancer is a highly lethal and aggressive disease with a poor prognosis, but radical surgery can be curative when appropriate clinical assessments are performed preoperatively. Behavioural interventions meant to prevent overweight and obesity are difficult to implement, but have the added benefit of preventing diabetes mellitus, cardiovascular diseases and some cancers in addition to GC. If the etiologic roles of S. typhi and paratyphi, Helicobacter species or other agents were better demonstrated, the benefits of prevention and treatment of these infections could be substantial. Diagnosis of gallstones and removal of the gallbladder represent the keystone to GC prevention in the majority of the populations at high risk.

Table 5.6.2 Relative risks (RR) with corresponding 95% confidence intervals (CI) of gallbladder cancer for highest vs lowest category of body mass index (BMI)

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>Reference category</th>
<th>Highest category</th>
<th>RR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moller, 1994</td>
<td>Non obese</td>
<td>Obese</td>
<td>Man 0.5 (0.1-1.8)</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 1.4 (0.9-2.1)</td>
<td>None reported</td>
</tr>
<tr>
<td>Walk et al, 2001</td>
<td>Non obese</td>
<td>Obese</td>
<td>Man 0.9 (0.3-1.4)</td>
<td>Age and calendar year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 1.7 (1.1-2.5)</td>
<td>Age and calendar year</td>
</tr>
<tr>
<td>Calle et al, 2003</td>
<td>18.5-24.9</td>
<td>30.0-34.9</td>
<td>Man 1.8 (1.5-2.9)</td>
<td>Age, race, education and many (10) lifestyle variables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 2.1 (1.6-2.9)</td>
<td>Age, race, education and many (10) lifestyle variables</td>
</tr>
<tr>
<td>Samani et al, 2004</td>
<td>Non obese</td>
<td>White man</td>
<td>Man 1.7 (1.1-2.6)</td>
<td>Age and calendar year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 1.7 (0.7-2.7)</td>
<td>Age and calendar year</td>
</tr>
<tr>
<td>Kuriyama et al, 2005</td>
<td>18.5-24.9</td>
<td>25.0-27.4</td>
<td>Man 0.5 (0.1-1.3)</td>
<td>Age and many (11) lifestyle and reproductive variables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 4.5 (1.6-14.2)</td>
<td>Age and many (11) lifestyle and reproductive variables</td>
</tr>
<tr>
<td>Kuriyama et al, 2005</td>
<td>18.5-24.9</td>
<td>&gt;30</td>
<td>Man 1.4 (1.0-1.9)</td>
<td>Age and birth cohort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 1.9 (1.6-2.2)</td>
<td>Age and birth cohort</td>
</tr>
<tr>
<td>Samani et al, 2006</td>
<td>18.5-24.9</td>
<td>&gt;30</td>
<td>Man 1.4 (0.7-2.7)</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minow, 1994</td>
<td>&lt;27</td>
<td>&gt;27</td>
<td>Woman 1.4 (0.7-2.4)*</td>
<td>Subjects frequently matched for age and sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strom, 1995</td>
<td>&lt;24</td>
<td>&gt;28</td>
<td>BMI average 1.6 (0.4-6.1)</td>
<td>Age and sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zatorski, 1997</td>
<td>&lt;25</td>
<td>&gt;29</td>
<td>BMI maximum 2.6 (0.5-18.6)</td>
<td>Age and sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serra, 2002 (Chile)</td>
<td>0.9</td>
<td>&gt; 30</td>
<td>Man 1.0 (0.3-2.8)</td>
<td>Age, centre, alcohol, smoking and response status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman 2.1 (1.2-3.8)</td>
<td>Age, centre, alcohol, smoking and response status</td>
</tr>
</tbody>
</table>

*Estimated from available data: Australia, Canada, Netherlands, Poland
†Updated from Randi et al, 2006

Fig. 5.6.3 Gallbladder carcinoma with a white, irregular cut surface next to a large gall stone

Fig. 5.6.4 Carcinosarcoma of gallbladder. The tumour shows mucinous glandular elements and a sarcomatous component with osteoid formation

Fig. 5.6.2 Age-standardised incidence rates* per 100 000 (world standard population) and female-to-male (F/M) ratio for gallbladder cancer in selected ethnic groups of the USA

*Truncated for individuals aged 35–74
REFERENCES


CANCER INSTITUTE PROFILE:
The University of Texas M. D. Anderson Cancer Center

The University of Texas M. D. Anderson Cancer Center was created by the Texas Legislature in 1941 and named one of the first three Comprehensive cancer centers by the National Cancer Act of 1971. It was ranked in 2007 by U.S. News & World Report as the top American hospital for cancer care. M. D. Anderson, which receives more research grants from the US National Cancer Institute than any other institution, spent in excess of US $465 million on research last year. Almost 84 000 patients were served in Houston-based facilities that include 512 inpatient beds and ambulatory units where more than 922 000 outpatient visits and treatments were provided. A record 12 000 patients participated in therapeutic clinical trials in 2007. M. D. Anderson awards bachelor’s degrees in seven allied health disciplines and jointly confers master’s and Ph.D. degrees in biomedical sciences. It also operates a two-unit Science Park in central Texas; has affiliations with caregivers as far away as Madrid, Spain, and has sister institution agreements in Asia, Europe, and Central and South America.

Website: www.mdanderson.org
Incidence of colorectal cancer ranks fourth in men (after lung, prostate and stomach) and third in women, after breast and cervix uteri, with high incidence rates in developed countries (accounting for 65% of all new cases)

Colorectal cancer incidence shows wide geographical variation, with higher rates observed in New Zealand, Australia, North America, Europe and more recently, Japan, and lower rates reported in Asia and Africa Overall, similar patterns are observed in the two sexes, although colon and rectal cancer rates are 20% and up to 50% higher, respectively, in men than women. Incidence rates of colorectal cancer are increasing in countries where overall risk was formerly low (especially in Japan, but also slowly rising in Asia), while in high-risk countries, rates are either gradually increasing, stabilising (Northern and Western Europe) or declining with time (North America). Five-year survival estimates (in men) have been reported to be 65% in North America and 54% in Western Europe, 34% in Eastern Europe, and 20% in India. Globally, mortality is approximately one half that of incidence (~529 000 deaths in 2002 in men and women combined). In terms of prevalence, colorectal cancer is the second most common cancer worldwide next to breast cancer (Figure 5.7.1). The majority of cancers occur-
disease. Cigarette smoking is another major modifiable lifestyle factor that recent studies suggest is involved in the colorectal carcinogenesis process [22], although an induction period of four decades has been suggested [23]. Evidence from observational studies indicates that long term use of non-steroidal anti-inflammatory drugs (NSAIDS), particularly aspirin, may reduce the risk of colorectal cancer [24-27]. Although randomised controlled trials on the risk of colorectal adenoma indicate that these medications may have anti-cancer effects [28-32], results from trials actually focusing on colorectal cancer risk have been inconsistent. Trials providing lower-dose aspirin failed to show a protective effect [33-35], while those providing higher doses show a protection against colorectal cancer after at least 5 years of treatment, with a latency period of about 10 years [24]. Nevertheless, recommendations to general populations on NSAID or aspirin use for cancer prevention are premature given that use of these medications is accompanied by many side effects and may increase the risk of other serious medical conditions, necessitating close medical supervision. The most important lifestyle changes for disease prevention appear to be weight reduction, physical activity and smoking cessation. The weight of the current literature suggests that a diet low in alcohol, red/processed meats, and refined carbohydrates, and higher in fruits, vegetables, whole grains and dietary fibre may assist in colorectal cancer prevention. Although NSAIDS and HRT have been shown to decrease colorectal cancer risk, their association with increased risk of other disease states makes their use as chemopreventive agents impractical, except in those at very high risk. Future research should focus on elucidating the role of complex gene-diet interactions, and identifying protective dietary and lifestyle patterns.

Conclusions

The worldwide variations in colorectal cancer risk suggest a large contribution of dietary and lifestyle factors to the etiology of the disease. Most colorectal cancers are sporadic adenocarcinomas arising via a multistep process that involves identifiable pre-cancerous lesions. Although it is understood that regular screening and removal of adenomatous polyps are effective prevention strategies, they are expensive and necessitate close medical supervision. The most important lifestyle changes for disease prevention appear to be weight reduction, physical activity and smoking cessation. The weight of the current literature suggests that a diet low in alcohol, red/processed meats, and refined carbohydrates, and higher in fruits, vegetables, whole grains and dietary fibre may assist in colorectal cancer prevention. Although NSAIDS and HRT have been shown to decrease colorectal cancer risk, their association with increased risk of other disease states makes their use as chemopreventive agents impractical, except in those at very high risk. Future research should focus on elucidating the role of complex gene-diet interactions, and identifying protective dietary and lifestyle patterns.
Nasopharyngeal Carcinoma

Summary

- Nasopharyngeal carcinoma (NPC) is a significant health problem in southern and eastern Asia.
- Preserved foods and EBV are key exposure factors involved in NPC etiology.
- Genetic susceptibility is certainly a risk factor, but which genes are involved remains unclear.

Etiology

NPC incidence has an extremely heterogeneous geographical and ethnic distribution, which is currently not explained. In high-resource nations, NPC is generally a rare malignancy (incidence 3-4/100,000/year). By contrast, relatively high rates are recorded across Asia where age-standardised incidence rates reach 20/100,000 among men [3-5] (Figure 5.8.1). Regions of Southern China contain the most clearly described high-risk areas, although similar high rates are reported across most of Southeast Asia. Relatively high rates have also been reported in Northern Africa and among natives of the Arctic region [4, 7]. The Malaysian region of Sarawak has one of the highest incidences of NPC where age-standardised rates of NPC were 13.5 and 6.5 among men and women, respectively. Rates among Chinese and Malays in Sarawak were similar to rates observed in these ethnic groups in Singapore. However, the Malaysian Bidayuh ethnic subgroup population appeared to have an exceptionally high incidence, reaching 31.5/100,000 and 11.8/100,000 among men and women respectively. These incidence levels represent the highest reported rates in any population, being approximately 50% higher than in Hong Kong (summarised in Figure 5.8.1), which has the next highest reported incidence rate [6].

The reason for this high risk in this particular ethnic subset is unclear, and other studies from other regions show relatively little difference between ethnic subgroups [8].

NPC risk exposures

Epstein-Barr Virus (EBV). From research dating to the 1960s, EBV has been consistently implicated in NPC susceptibility [9]. Titres of EBV antibodies have been found to be higher in NPC cases compared to control individuals [1-5]. The full-length EBV genome is found in the nuclei of almost all malignant NPC cells. The tight correlation between EBV and NPC has meant that there have been efforts to use EBV, or indicators of EBV-related activation, as early NPC detection tools [8, 10]. The carcinogenic mechanisms underlying EBV infection and NPC susceptibility remain unclear. Infection with EBV is relatively ubiquitous in most populations, yet NPC incidence has an extremely heterogeneous geographical and ethnic distribution. It is therefore unlikely that EBV infection itself is a single cause of NPC. An underlying etiological model may be that some EBV strains may escape immune surveillance, with genetic susceptibility and other environmental factors playing an important role in this process.

Preserved foods. The consumption of foods preserved using high amounts of salt or other preservatives has also been consistently linked with NPC risk [6]. Epidemiological studies have consistently noted that consumption of fish is relatively ubiquitous in most populations, yet NPC incidence has an extremely heterogeneous geographical and ethnic distribution. It is therefore unlikely that EBV infection itself is a single cause of NPC. An underlying etiological model may be that some EBV strains may escape immune surveillance, with genetic susceptibility and other environmental factors playing an important role in this process.

World Map 5.8.1

Incidence of Nasopharyngeal cancer: 0-14 (Male-Female / 100,000 age-standardised rates).

World Map 5.8.2

Incidence of Nasopharyngeal carcinoma: 15-64 (Male-Female / 100,000 age-standardised rates).

Nasopharyngeal carcinoma (NPC) is a malignat tumour arising in the epithelial lining of the nasopharynx. NPC presents most commonly among people of 40-55 years of age, but presentation in adolescence has also been observed. There is a gender bias, NPC being approximately 2-3 times more common in males than females. Treatment of this malignancy usually involves radiotherapy, either alone or in conjunction with chemotherapy, with a 5-year survival rate of approximately 60-65% and a slightly better prognosis in women than men [1]. WHO criteria classifies NPC into general histological subtypes: keratinizing squamous-cell carcinoma (WHO-I) and non-keratinising squamous-cell carcinoma. Non-keratinising squamous-cell carcinoma was previously subdivided into differentiated (WHO-II) and non-differentiated forms (WHO-III) but it has more recently suggested to be merged into a single broader category, to account for overlap between the two [2]. A quite rare form, basaloid squamous-cell carcinoma is also recognized [2]. Keratinizing squamous-cell carcinoma histology tends to be more common in Caucasian (non-endemic) populations [2], while non-keratinising squamous-cell carcinoma tends to be more prominent in Asian (endemic) populations [3].

Fig. 5.8.1 Age-standardised incidence rates of NPC across various populations in number of new cases per 100,000 population per year.

Fig. 5.8.2 A and B: Magnetic resonance imaging of nasopharyngeal carcinoma.
preserved using high levels of salt conferred a 2.3-fold increase in NPC risk. This risk appears to be lower in Western diets in which soups and pickled foods are consumed at early ages [11]. Although the evidence is somewhat less consistent, similar risks have been associated with the intake of processed meat and fish [12,13]. The high-risk regions appear to use such preservation practices, notably in Southern China and South East-Asia (salted fish), and similarly in other at-risk populations such as North Africans (salted rabbit, n’dal, butifarra). Early-age exposure may have particular relevance to these populations as use of such foodstuffs as weaning foods is relatively common in many of the high-risk NPC populations.

The evidence that high-salt preservation techniques are implicated in NPC is also supported by experiments in animal models, with diets high in sodium reducing the latency of NPC in rats [12,13]. The carcinogenic mechanism is thought to be related to the food preservation process not being completely efficient, thus the process not being completely efficient, leading to a partial putrefaction of the food material. This partial putrefaction results in high levels of N-nitrosamines (N-nitrosodimethylamine (NDMA), N-nitromelamine (NNM) and N-nitrosopiperazine (NPIP), which have been postulated to be carcinogenic [14].

Tobacco, alcohol and other exposure. There is some evidence to suggest that tobacco exposure increases risk of NPC [15] with most studies finding a 2.6-fold increase in risk for those exposed. Whether consumption of alcohol is involved in NPC risk is less clear [9], with some studies suggesting an increased risk, but most studies finding no association. Although the involvement of EBV in NPC susceptibility. Familial clustering appears common among NPC patients, with family-based linkage analysis has provided evidence of two or three susceptibility loci. A family study based on 200 multisite families from Guangzhou, southern China has also been conducted, [21] showing IOD scores of up to 3.67 for the region 4p15.4p12, suggesting the potential for a major susceptibility locus in this region. A subsequent study was based on 18 multiple-case families from Hunan Province, southern China, including 88 affected and 96 unaffected individuals, who were genotyped for 5 polymorphic markers in the region 4p15.4p12, as well as for 8 markers on chromosome 3q [22]. In contrast to the initial study by Feng et al. [21], no evidence for linkage was identified for polymorphic markers on chromosome 4. An NPC susceptibility locus was identified on 3p21 with a maximum IOD score of 4.18.

While some NPC susceptibility genes have been suggested under the linkage peaks on chromosomes 3, 4 and 6 [23,25], these have been no conclusion candidates, and considerable effort in this area is clearly needed. Additional candidate genes deduced from the proposed function of some genes (e.g. NAP1L1 or CYST3M) have been examined, but again without conclusive evidence (6).

Conclusions

In the high-prevalence regions such as Southeast Asia and southern China, NPC makes a considerable contribution to the overall burden of cancer morbidity and mortality. Exposure to EBV and consumption of partially putrefied foods appear to play key roles in NPC development, but each of these alone does not appear predominant in causing NPC susceptibility. How these factors interact with other unknown NPC risk factors (in particular genetic factors) remains unclear. Recent technological advances in genetic research, in combination with large, well-designed epidemiological studies, offer the possibility of elucidating the factors that lead to this multifactorial disease.

REFERENCES

3. Conclusions

Cancer Epidemiol Biomarkers Prev

Kaposi sarcoma (KS) is an AIDS-defining malignancy, and it has become one of the commonest cancers in both men and women in Sub-Saharan Africa.

Kaposi sarcoma-associated herpesvirus (KSHV), the eighth human herpesvirus to be identified (also called HHV-8) is the causative agent of Kaposi’s sarcoma.

Different subtypes of KSHV are related to geographical localisation, ethnicity and prevalence of HIV.

The widespread use of combined antiretroviral treatment has led to a marked decrease in the incidence of KS in the developed world whereas it remains extremely common among AIDS patients in Sub-Saharan Africa.

Summary

Kaposi sarcoma is an AIDS-defining malignancy, and it has become one of the commonest cancers in both men and women in Sub-Saharan Africa.

Kaposi’s sarcoma-associated herpesvirus (KSHV), the eighth human herpesvirus to be identified (also called HHV-8) is the causative agent of Kaposi’s sarcoma.

Diagnostic tests to detect infection with Kaposi sarcoma-associated herpesvirus (KSHV)

Polymerase Chain Reaction (PCR) KSHV/DNA can be detected by PCR in tumour tissue samples obtained from the large majority of patients with classic, endemic, iatrogenic or epidemic KS (AIDS-KS). Less frequently, KSHV-DNA can be amplified from blood cells obtained from patients with any type of KS, with successful detection in up to 50% in some cases series [2].

KSHV-DNA detection from blood of general populations is difficult. The virus is more often detected in blood donors using second-round PCR or quantitative real-time PCR, with prevalence of detection ranging between 0% in USA to 20% in Sub-Saharan Africa [2] among blood donors.

Serological diagnosis. As with any other herpesvirus, KSHV genome encodes for viral proteins involved in latent and lytic viral life cycles. Serological assays using KSHV latent and lytic cycle-associated viral antigens have been developed to detect KSHV infection [11]. The viral antigens expressed during the latent phase of infection is termed latency-associated nuclear antigen (LANA). Immune-dominant or fluorescence-based assays (IFA) can identify nuclear LANA or cytoplasmic (IFA/lytic assay) punctuate staining under the fluorescence microscope [12]. Since the identification of a handful of KSHV antigens that are able to initiate antibody response, serological assays have been produced using these antigens, withIFA or enzyme-linked immunosorb-
Molecular epidemiology

KSHV is an ancient virus that probably started spreading 100,000 years through human migrations between continents. Molecular studies based on a genetically variable genomic region of KSHV DNA (namely, ORF K1), have identified 5 main subtypes of KSHV (designated A, B, C, D and E) that are not associated with severity of disease, but have preferential geographical distributions [13]. Thus, subtypes A and C are found in Europe, the USA and Asia, strains B and A5 are found mainly in Africa and French Guyana. Subtype D, that is reported in Taiwan and in some Pacific islands, has also been described in Australia, while the most recently reported variant E has been found among South American Americanindian populations from the Amazon and French Guyana [9]. In addition to clustering by geographical localisation, KSHV strains have also been associated with ethnic background, with KSHV subtypes B and variant A5 being distributed mainly in people of African descent and subtypes A and C, being usually found in Caucasian populations. The rare subtypes D and E have only been described in Americanindians and Indigenous people from the Pacific Islands [9,15].

Management of Kaposi sarcoma

No cure exists for KS and the treatment is mostly palliative. In AIDS patients, the control of HIV replication and the consequent increase in CD4+ T-cell counts lead to marked regression of KS miculocutaneous lesions following initiation of HAART. The use of HAART alone is an option for treatment of KS among HIV-infected patients [16]. The dissemination to internal organs and the obstruction of lymphatic systems are rare in AIDS patients receiving HAART, but the severest clinical pictures are often seen in Sub-Saharan Africa, where HAART is not available and life expectancy following the diagnosis of KS is less than one year.

Cutaneous and pulmonary symptoms warrant endoscopic examination to search for visceral KS lesions. Like AIDS patients, organ-transplanted recipients also experience improvement of their KS lesions after the cessation of the immune suppressive treatment. The clinical presentation of classic KS is less severe, and local treatment can often be employed to treat the characteristic indurated lesions.

The use of systemic cancer chemotherapy is indicated when miculocutaneous lesions are disseminated or visceral organs are affected. Chemotherapy agents used in the management of KS include adriamycin, bleomycin, vinblastine, vincristine, doxorubicin and etoposide. The use of liposomal anthracyclines and taxanes are considered the best option for disseminated KS. Other options include radiotherapy, cryotherapy and intralesional chemotherapy for local treatment of isolated cutaneous lesions for cosmetic and palliative reasons [16].

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Population (N)</th>
<th>KSHV infection (% positive)*</th>
<th>Risk factors associated with KSHV seropositivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latin America</td>
<td></td>
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<tr>
<td>Jamaica</td>
<td>Blood donors (n=1,010)</td>
<td>2.7%</td>
<td>Older age &gt; 26 (Preval=0.001) [17]</td>
</tr>
<tr>
<td>French Guiana</td>
<td>Rural community</td>
<td>13.2%</td>
<td>Age &gt; 39 y (Preval&lt;0.001), KSHV-infected sibling (OR=3.8 [95% CI: 1.6-9.1]) [18]</td>
</tr>
<tr>
<td>Brazil, Sao Paulo</td>
<td>Blood donors (N=400)</td>
<td>4%</td>
<td>Female gender (OR=3.86 [95% CI: 1.1-16.6]) [19]</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (San Francisco)</td>
<td>Blood donors (N=1,122)</td>
<td>0</td>
<td>Not analysed [20]</td>
</tr>
<tr>
<td>USA</td>
<td>General population (n=1,184)</td>
<td>1.8%</td>
<td>Hepatitis B (OR=1.9 [95% CI: 1.6-5.6]) [13]</td>
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<td></td>
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<td></td>
<td>Sexual behaviour for men (OR=2.3 [95% CI: 1.4-3.8]) [13]</td>
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<tr>
<td>Europe</td>
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<td></td>
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<tr>
<td>Italy North</td>
<td>Blood donors (n=199)</td>
<td>13%</td>
<td>Not analysed [21]</td>
</tr>
<tr>
<td>Po-valley</td>
<td>Blood donors (n=263)</td>
<td>13%</td>
<td></td>
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<tr>
<td>Milan &amp; Turin</td>
<td>Blood donors (N=139)</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Italy South</td>
<td>Blood donors (n=68)</td>
<td>4%</td>
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<tr>
<td>Calabria</td>
<td>Bl. donors (N=60)</td>
<td>20%</td>
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<tr>
<td>Sicily</td>
<td>Bl. donors (N=174)</td>
<td>5%</td>
<td>Not analysed [22]</td>
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<tr>
<td>United Kingdom</td>
<td>Blood donors (n=174)</td>
<td>5%</td>
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<tr>
<td>Asia</td>
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<tr>
<td>India</td>
<td>N=108</td>
<td>4.0%</td>
<td>Not analysed [23]</td>
</tr>
<tr>
<td>Thailand</td>
<td>N=75</td>
<td>4.0%</td>
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<tr>
<td>Malaysia</td>
<td>N=159</td>
<td>4.4%</td>
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<tr>
<td>Sri Lanka</td>
<td>N=80</td>
<td>3.8%</td>
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<td>Africa</td>
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<tr>
<td>Tanzania</td>
<td>Blood donors (N=174)</td>
<td>2.9%</td>
<td>Not analysed [24]</td>
</tr>
<tr>
<td>Uganda (Kampala)</td>
<td>HIV-infected cancer patients from a case-control study (n=467)</td>
<td>50%</td>
<td>Older age (Preval=0.001), Ever married (OR=2.1 [95% CI: 1.1-4.1]) [25]</td>
</tr>
<tr>
<td>South Africa</td>
<td>HIV-infected cancer patients (n=219)</td>
<td>39%</td>
<td>Older age among men (OR=2.1 [95% CI: 1.2-3.8]) [26]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older age among women (OR=3.8 [95% CI: 1.6-9.3]) [26]</td>
</tr>
</tbody>
</table>

Table 5.8.1 Worldwide prevalence of KSHV infection in serocross-sectional studies of HIV-infected individuals. N, number of HIV-infected individuals tested for KSHV; OR, odds ratio; CI, confidence interval. *Serological asssays detect anti-KSHV antibodies either to lytic or LANA KSHV antigens.
REFERENCES


Lung cancer was a rare disease until the beginning of the twentieth century. Since then, its occurrence has increased rapidly; this neo-naught lung cancer de-rease in incidence. decrease in consumption is followed by a decrease in the incidence of lung cancer; similarly, an increase in tobacco consumption is paralleled some 20—30 years later by an increase in adenocarcinoma among men in most countries and represents the most important cause of cancer death worldwide. It accounts for 20% of all cancer deaths and 10% of all deaths worldwide. The highest incidence rates in men (>70/100 000) are recorded among blacks from the United States and in some Central and Eastern-European countries [2,3]. Rates are declining among US white men and among men in the United Kingdom and Northern Europe. The lowest incidence rates are reported from Africa and Southern Asia. Rates in women are high in the USA, Canada, Denmark and the UK, and low in countries such as Japan and Spain, in which the prevalence of smoking in women has increased only recently. The lowest rates (<10/100 000) are recorded in some countries like China during 1993–1997 [2], despite a low prevalence of smoking.

The main histological types of lung cancer are squamous-cell carcinoma, small cell carcinoma, and large cell carcinoma. Over the last few decades, the proportion of squamous-cell carcinomas, which used to be the predominant type, has decreased and an increase of adenocarcinomas has taken place in both genders. This is probably due to changes in the composition of tobacco products and in smoking behaviour (e.g. use of filtered cigarettes, lower tar content, reduced inhalation). Despite some minor differences, the main risk factors for lung cancer are associated with all histological types.

A carcinogenic effect of tobacco smoke on the lung was demonstrated in the 1950s and has been recognised by public health and regulatory authorities since the mid-1960s. The risk of lung cancer among smokers relative to the risk among non-smokers is of the order of tenfold or more. This overall risk reflects the contribution of the different aspects of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern, with duration being the dominant factor. As compared to continuous smokers, the excess risk decreases in ex-smokers after quitting, but a small excess risk is likely to persist in long-term quitters throughout life. In the United Kingdom, the cumulative risk of lung cancer of a continuous smoker is 16%, and it is reduced to 10%, 6%, 3% and 2% among those who stopped at age 60, 50, 40 and 30, respectively. Smokers of black (air-cured) tobacco cigarettes are at higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. A causal association with lung cancer has also been shown for consumption of cigars, cigarillos, pipes, bidis, water pipes and other smoking tobacco products [4], but not for use of smokeless tobacco products [5].

An association has been shown in many studies between exposure to involuntary smoking and lung cancer risk in non-smokers. The magnitude of the excess risk among non-smokers exposed to involuntary smoking is of the order of 20% [6].

There is limited evidence that a diet rich in vegetables and fruits exerts a protective effect against lung cancer [7]. In particular, a protective effect has been suggested for intake of cruciferous vegetables, possibly because of their high content in isothiocyanates [8]. Despite the many studies of intake of other foods, such as cereals, pulses, meat, eggs, milk and dairy products, the evidence is inadequate to allow a judgement regarding the evidence of a carcinogenic or a protective effect.

A large number of studies have reported a reduced risk of lung cancer for high intake of beta-carotene [9]. Similar results have been obtained in studies based on measurement of beta-carotene in prospectively collected sera. This evidence of a protective effect has been challenged by the results of intervention trials of beta-carotene supplementation [9] in two of the studies, which included smokers and workers exposed to asbestos, on increase in the incidence of lung cancer was observed in the treated groups [10,11]. In the other studies, no difference was found between the treated and the control groups [12,13]. The differences in the results of observational studies and intervention trials can be explained by a confusing effect due to other dietary components in observational studies, or by a paradoxical effect of beta-carotene, which is associated with very high, non-physiological doses, in particular among smokers.

There is inadequate evidence of an increase in the risk of lung cancer from high alcohol drinking, independent from tobacco smoking [9], and for an association between body size and lung cancer risk [14].

A positive familial history of lung cancer has been found to be a risk factor in several studies. Segregation analyses suggest that inheritance of a major gene, in conjunction with tobacco products, the evidence is inadequate to allow a judgement regarding the evidence of a carcinogenic or a protective effect.
The relative risk of major histological types of cancer by average cigarette consumption

There is conclusive evidence that exposure to ionising radiation increases the risk of lung cancer [19]. Atomic bomb survivors and patients treated with radiotherapy for anthracyclines or breast cancer are at moderately increased risk of lung cancer, while studies of nuclear industry workers exposed to relatively low levels of radiation, however, provided no evidence of an increased risk of lung cancer. Underground miners exposed to radioactive radon and its decay products, which emit alpha-particles, have consistently been found to be at increased risk of lung cancer [20]. The risk increased with estimated cumulative exposure and decreased with attained age and time since cessation of exposure.

The risk of lung cancer is increased among workers employed in several industries and occupations. For several of these high-risk workplaces, the agent(s) responsible for the increased risk have been identified [21]. Of these, asbestos and combustion fumes are the most important. Occupational agents are responsible for an estimated 5–10% of all lung cancers in industrialised countries.

Patients with pulmonary tuberculosis are at increased risk of lung cancer; it is not clear whether the excess risk is due to the chronic inflammatory status of the lung parenchyma or to the specific action of the mycobacterium. Chronic exposure to high levels of fibres and dusts might result in lung fibrosis (e.g. silicosis and asbestosis), a condition that entails an increase in the risk of lung cancer [19]. Chronic bronchitis and emphysema have also been associated with lung cancer risk [22].

Indoor air pollution is thought to be responsible for the elevated risk of lung cancer experienced by non-smoking women living in several regions of China and other Asian countries. The evidence is strongest for coal burning in poorly ventilated houses, but also for burning of wood and other solid fuels, as well as for fumes from high-temperature cooking using unrefined vegetable oils such as rapeseed oil [23]. In some countries (e.g. Sweden), indoor exposure to radon decay particles may entail a sizeable increase of risk [22].

Control of tobacco smoking remains the key strategy for the prevention of lung cancer.

Reduction in exposure to occupational and environmental carcinogens (in particular, indoor pollution and radon), as well as increasing in consumption of fruits and vegetables are additional preventable opportunities. To date, no screening interventions have been demonstrated to be effective at reducing lung cancer mortality.
REFERENCES

22. Boffetta P, Trichopoulos D (2008). Biomarkers in cancer prevention and control. AORTIC will achieve this through the facilitation of research and training as well as the provision of relevant and accurate information on the prevention, early diagnosis, treatment and palliation of cancer. Our organisation is dedicated to providing all Africans with these benefits, as well as to increasing public awareness of cancer and reducing the stigma associated with it.

AORTIC Objectives
AORTIC's key objectives are to further research relating to cancers prevalent in Africa, support the management of training programs in oncology for health-care workers, and to deal with the challenges of creating cancer control and prevention programs, as well as raising public awareness of cancer in Africa. The executive members of AORTIC are high-profile scientists from all over Africa volunteering as knowledge workers for the plight of the cancer patient in Africa. Their main value is their ability to gather and analyse information and make decisions that will benefit the cancer patient. They work collaboratively with other cancer organisations via conferences and the internet, sharing knowledge, learning from each other and disseminating relevant ideas and research to the cancer community.

AORTIC is actively connected to the global community, with a vast electronic database as well as paper and electronic newsletters sent out quarterly in English and French. AORTIC has been represented at numerous cancer conferences around Africa and the world, and looks forward to your upcoming seventh AORTIC conference in Tanzania in November 2009.

website: www.aortic.org

CANCER INSTITUTE PROFILE:

Institut Jules Bordet
Located in the heart of Europe, the Institut Jules Bordet (IJB) was among the first European centres to be fully dedicated to cancer, and is currently the only one in Belgium. IJB belongs to the academic research network of the Université libre de Bruxelles. As a Comprehensive Cancer Centre (CCC) IJB fully integrates these key missions: patient care, education and research.

IJB provides a full range of services, including prevention, screening, diagnostics, therapies and rehabilitation using state-of-the-art technologies and the most up-to-date methods. With a capacity of 154 beds and a 13-bed day-care unit, IJB offers 6000 hospitalisation admittances (together with 2000 new diagnosed and 71 000 outpatient consultations a year).

IJB collaborates closely with the International Agency for Research on Cancer (IARC) and coordinates large pivotal multicentric clinical trials. The top-quality translational and clinical research activities at IJB lead annually to more than 200 scientific articles with a high impact factor (820 in 2006). IJB belongs to the Organisation of European Cancer Institutes (OEICI) and is strongly involved in the European Organisation for Research and Treatment of Cancer (EORTC), which is currently chaired by the (IB) head of Medical Department, Prof Marine Pirson.

IJB is a reference cancer centre for the Organization of European Trade Unions (OETU).

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CANCER INSTITUTE PROFILE:

Institut Jules Bordet
Located in the heart of Europe, the Institut Jules Bordet (IJB) was among the first European centres to be fully dedicated to cancer, and is currently the only one in Belgium. IJB belongs to the academic research network of the Université libre de Bruxelles. As a Comprehensive Cancer Centre (CCC) IJB fully integrates these key missions: patient care, education and research.

IJB provides a full range of services, including prevention, screening, diagnostics, therapies and rehabilitation using state-of-the-art technologies and the most up-to-date methods. With a capacity of 154 beds and a 13-bed day-care unit, IJB offers 6000 hospitalisation admittances (together with 2000 new diagnosed and 71 000 outpatient consultations a year).

IJB collaborates closely with the International Agency for Research on Cancer (IARC) and coordinates large pivotal multicentric clinical trials. The top-quality translational and clinical research activities at IJB lead annually to more than 200 scientific articles with a high impact factor (820 in 2006). IJB belongs to the Organisation of European Cancer Institutes (OEICI) and is strongly involved in the European Organisation for Research and Treatment of Cancer (EORTC), which is currently chaired by the (IB) head of Medical Department, Prof Marine Pirson.

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394 - Section 5 - Cancer Site by Site
Chapter 5.10: Lung Cancer - 396
Mesothelioma

Summary

- Mesothelioma of the pleura and the peritoneum is a rare cancer except in workers exposed to asbestos.
- The clinical course of the disease is in most cases fatal.
- Exposure to all types of asbestos increases the risk of developing mesothelioma, although the potency of amphibole asbestos (e.g., crocidolite, amosite) is greater than that of chrysotile asbestos.
- Other known risk factors are environmental exposure to asbestos and asbestos-like fibres, as well as radiation.
- Avoidance of exposure to asbestos and other fibres is the main approach to prevent mesothelioma.

Mesothelioma is the most important primary tumour of the pleura. It can also originate from the peritoneum and the pericardium. Mesotheliomas were considered very rare tumours until large series of cases were reported in the 1960s among workers employed in asbestos mining and manufacturing. The descriptive epidemiology of pleural tumours, and mesothelioma in particular, is complicated by geographical and temporal differences in diagnostic accuracy. In most high-resource countries, the incidence of pleural mesothelioma is of the order of 1–1.5/100,000 in men and around 0.5–1.0/100,000 in women. Lower rates are reported from low-resource countries, where under-diagnosis might be a particularly serious problem. In areas with a high prevalence of occupational exposure to asbestos such as shipbuilding and mining centres, the rates might be as high as 5–10/100,000 in men and 4/100,000 in women. [1] The incidence of mesothelioma has been linked conclusively to asbestos exposure, in particular to amphiboles such as crocidolite and amosite. Past occupational exposure to asbestos is the main determinant of pleural mesothelioma. High-exposure industries include mining, shipyard working, and especially asbestos, textile and cement manufacture [2]. Despite a reduction or ban of asbestos use in many countries, the incidence of mesothelioma was increasing in the USA until the early 1990s, and in most Western European countries until the late 1990s, which reflects the long latency of the disease [3]. In the absence of occupational exposure to asbestos, incidence rates of the order of 0.1–0.2/100,000 are estimated in both genders. In heavily exposed workers, relative risks of the order of 1000 have been reported. There is evidence of an increased risk of pleural mesothelioma following environmental exposure to asbestos; epidemics of mesothelioma have been reported from areas with environmental contamination by other natural mineral fibres, such as some districts of central Turkey, where erionite, a fibrous substance similar to amphibole asbestos, contaminated the materials used for building construction. In several populations, DNA of simian virus 40 has been reported in a high proportion of mesothelioma cases; however, a causal role of this virus, which contaminated polio vaccines used in the 1950s in many countries, has not been confirmed [4]. Exposure to ionising radiation entails an increased risk of pleural mesothelioma, as it has been shown in cohorts of patients treated with thoracotomy, a radiological contrast medium [2]. Tobacco smoking, alcohol drinking and diet do not appear to be risk factors for pleural mesothelioma.

Peritoneal mesothelioma shares many of the epidemiological and biological features of the pleural form of the disease [5]. In particular, patients treated with thoracotomy frequently developed peritoneal mesotheliomas, probably because of local emission of alpha-particles by the contrast medium.

REFERENCES


Fig. 5.11.1 Diffuse malignant mesothelioma. In this CT scan, the pleura shows marked diffuse thickening by mesothelioma, with resulting encasement of the lung.
Non-Melanoma Skin Cancer

### Summary

- Non-melanoma skin cancer includes squamous and basal cell carcinomas.
- These two forms of skin cancer are the most frequent cancer in light-skinned populations, but are rarely a cause of death.
- Their public health importance resides in the huge economic burden their treatment entails, and the loss of quality of life due to disfiguring scars.

### Epidemiology

Incidence

Non-melanoma skin cancer is a disease of light-skinned (white) populations. Hispanic and Asian populations develop less skin cancer, and it is even less frequent in black populations [3,4]. The Squamous-cell carcinomas occur almost exclusively on chronically sun-exposed skin areas, whereas BCC may also occur on body sites only intermittently sun-exposed [5].

In white populations residing in areas close to the equator (e.g. Queensland in Australia), non-melanoma skin cancer incidence surpasses that of any other cancer site. BCC has the highest incidence rate and is 3 to 4 times more frequent than SCC [Table 5.12.1]. Incidence of BCC and SCC increases with age, mainly for SCC whose incidence rises sharply after 65 years of age [6]. The incidence of SCC is about three times higher in men than in women, and the incidence of BCC is twice as high in men as in women [4].

An important variability in incidence rate exists between Europe, the USA and Australia: incidence rates are about 5 times higher in the US and 20-40 times higher in Australia than in Europe. This can partly be explained by differences in latitude of residence. A correlation between incidence and latitude of residence was initially described in the USA [4]. This observation contributed to the hypothesis related to chronic sun exposure and the risk of non-melanoma skin cancer.

A continuous increase in incidence over time is observed in different parts of the world [3,7,13] with no sign of leveling off in the near future [14]. This observation contributed to the hypothesis that of these cancers become life-threatening, and result in distant metastasis. A small proportion of these cancers become life-threatening, and result in distant metastasis. A small proportion of these cancers become life-threatening, and result in distant metastasis. A small proportion of these cancers become life-threatening, and result in distant metastasis. A small proportion of these cancers become life-threatening, and result in distant metastasis. A small proportion of these cancers become life-threatening, and

### Table 5.12.1 Incidence per 100 000 person-years of BCC and SCC reported in different areas of the world

<table>
<thead>
<tr>
<th>Publication</th>
<th>Geographical area</th>
<th>Years</th>
<th>BCC Male</th>
<th>BCC Female</th>
<th>SCC Male</th>
<th>SCC Female</th>
</tr>
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<tr>
<td>Holme et al 2000</td>
<td>Vaud, Switzerland</td>
<td>1998-2000</td>
<td>117</td>
<td>45</td>
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<td>Marks et al 1993</td>
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<td>1971-1972</td>
<td>123</td>
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<tr>
<td>Giles et al 1990</td>
<td>Male</td>
<td>1971-1972</td>
<td>123</td>
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<td>Gallagher et al 1990</td>
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<td>1990-2000</td>
<td>686</td>
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<tr>
<td>Buetten et al 1998</td>
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<td>2058</td>
<td>1136</td>
<td>575</td>
<td>303</td>
<td>303</td>
</tr>
</tbody>
</table>

### Incidence of BCC and SCC in the United States of America as a function of latitude in the white population from 1971-1972

Registration. In spite of its public health importance in white populations, and the continuous increase in incidence observed in all light-skinned populations, non-melanoma skin cancer remains poorly recorded by cancer registries. The main reason for the absence of registration data is the difficulty of obtaining systematic pathological assessment. Also, simultaneous BCC are often diagnosed, and both SCC and BCC have a high recurrence rate. In Australia, non-melanoma skin cancers are so frequent that about half of the population will develop a skin cancer during their lifetime, with many developing multiple recurrences. A complete registration of BCC and SCC in Australia would use all currently available resources for cancer registration and is therefore not feasible.

### Etiology

Most factor - sun sensitivity. BCC and SCC arise predominantly in sun-sensitive people with light skin, red hair and an history of sunburn [16-18].

### Table 5.12.1 Incidence per 100 000 person-years of BCC and SCC reported in different parts of the world

- **Standardized to the US population of 1970.**
- **High standard incidence rate see the world population.**
Sun exposure. The presence of actinic skin lesions, such as solar keratosis, lentigines, elastosis and telangiectasia, is frequently associated with BCC and SCC and reflects the role of chronic sun exposure in the risk of non-melanoma skin cancer [17]. The risk of SCC is strongly associated with increasing cumulative doses of sun exposure, independent of the pattern of sun exposure [19]. The association between sun exposure and BCC is more complex than that of SCC [16], and BCC seems more associated with intermittent exposure to high doses of solar radiation when compared to similar doses delivered more continuously [20].

Immunodeficiency. Immunosuppressed patients (renal transplant patients) have been repeatedly found to be at higher risk for non-melanoma skin cancer [23,24]. These observations strongly suggest that immune suppression could play a role in BCC and SCC etiology. This hypothesis could help in understanding the dramatic increase in the incidence of BCC and SCC with decreasing latitude, as solar radiation would cause SCC and BCC via two interacting mechanisms: the ultraviolet radiation-induced DNA damage of keratinocytes, and a decrease in immune control of carcinogenic events in the skin.

Skin infection with the Human papilloma virus. Non-melanoma skin cancer in immunocompromised subjects (e.g. organ transplant patients) was found to be associated with Human papilloma virus (HPV) infection of skin keratinocytes [25]. Persistent infections of the skin with high-risk genital HPV types (also known to be significant risk factors for cervical cancer) have also been found to represent a risk factor for non-melanoma skin cancers in non-immunosuppressed subjects [26]. HPV infection of skin keratinocytes seems to be essentially associated with increased risk of SCC but not BCC [27]. This association with HPV remains confined to SCC arising on chronically sun-exposed areas of the skin.

Genetics. Mutations of the TP53 gene are frequently observed in human SCC, and are associated with a history of sunburn [28]. In BCC, cell cycle regulatory factors other than TP53 are affected, such as mutations in the hedgehog signaling pathway genes [29].
REFERENCES


Cutaneous Melanoma

Summary

- The risk of developing malignant melanoma varies markedly according to racial background, skin pigmentation, and geography.
- Melanoma incidence is highest in white-skinned populations.
- Male age (0-85+), (Rate per 100,000)

Etiology

Melanoma risk factors include phenotypic pigmentation traits, naevi and sun exposure.[5-7]

It is estimated that 90% of melanomas are caused by ultraviolet damage,[8] to sensitive skin, i.e., skin that burns easily, fair or reddish skin, multiple freckles, skin that does not tan and develops naevi in response to early sunlight exposure.

Prevention of melanoma is based on limitation of exposure to ultraviolet radiation, particularly in the first 20 years of life.

Ultraviolet radiation is particularly hazardous when it involves sporadic intense exposure and sunburn.

Most damage caused by sunlight occurs in childhood and adolescence, making this the most important target group for prevention programmes. Other established risk factors include congenital naevi, immunosuppression and use of tansalas.[9]
While melanoma may occur anywhere on the skin, the majority of melanomas in men is on the back, while in women the majority is on the leg. This difference in site incidence is not completely explained by differential exposure to ultraviolet light.

There is evidence from epidemiological studies that cutaneous melanomas arise through different causal pathways. Patterns of age-specific incidence of melanoma at different anatomical sites in a skin-damaged population show that melanomas arising on intermittently exposed body sites are significantly more common among younger and middle-aged adults, whereas melanomas of the head and neck are most common among older people. In younger patients the incidence of melanoma is higher on intermittently exposed skin areas than on continuously exposed areas.

In both men and women under age 50, the highest melanoma density is on the back, while at ages over 50, the greatest density occurs on fully exposed sites, such as the face. Thus, intermittent sun exposure may have a greater potential for producing melanoma than continuous exposure at ages below about 50, though at older ages melanoma is more common on body sites with continuous sun exposure [10]. It was further shown that melanomas at different body sites arise through different pathways that have different associations with melanocytic nevi and solar keratoses. Patients who develop melanoma of the head and neck tend to have fewer nevi, greater lifetime exposure to sunlight and more evidence of chronic solar damage than those who develop melanomas of the trunk. Patients with lentigo maligna melanomas are also less likely than patients with truncal melanomas to have numerous nevi and tend toward more solar keratoses. Cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation and the other with chronic exposure to sunlight [11]. Most recently, molecular epidemiological studies have brought support to these views.

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spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and lentigo maligna melanoma. This classification has been superseded by a system based on the histopathological parameters of the excised lesion. Melanoma is now classified essentially on the vertical diameter of the lesion from the granular cell layer of the epidermis to the deepest detectable melanoma cell (tumor thickness). In recent years, one additional criterion, ulceration, has been shown to be important in progression and is included in the AJCC/UICC classification system (Table 5.13.1).

While it is clear that the genetic make-up of the melanoma-prone population is very important, a significant proportion of melanomas are associated with specific genetic defects in these populations. Loss-of-function mutations in the human melanocor- tin-1 receptor (MC1R) have been associated with red hair, fair skin, freckles, and decreased ability to tan [14], all physical characteristics that affect susceptibility to skin cancer. While 10% of melanoma patients have a first-degree relative affected, less than 3% of melanomas in Australia [where the incidence of melanoma is high] can be attributed to an inherited gene defect. Familial melanoma is even rarer in low-incidence countries.

The familial melanoma syndromes are associated with germline mutations in highly penetrant genes [15]. About 20% of melanoma-prone families possess germline mutations in the CDKN2A gene, which encodes p15INK4A and p16ARF. Mutations in the p53 binding domain of the gene encoding CDK4 have been identified in melanoma families without mutation of CDKN2A but are extremely rare [16]. The penetrance of the CDKN2A melanoma predisposition allele varies with melanoma population incidence rates and is largely influenced by ultraviolet exposure across geographic latitude [17].

However, melanoma susceptibility genes identified in melanoma-prone families are only rarely mutated in sporadic melanomas. Contrary to other skin cancers, no hereditary predisposition [greater than 20%] of melanomas harbour mutations in the p53 gene. Nocturnal melanomas may display amplification of the MYC oncogene. Inactivation of p16INK4A is associated with a poorer prognosis. Different oncogenes and tumor suppressor genes may be involved in melanoma occurrence. Genes identified as having a role in sporadic melanoma development include CDKN2A, PTF1A, and BRAF, while cytogenetic studies have observed that genes located on chromosomes 1p, 6q, 7p, 9p, and 11q are involved in the pathogenesis of melanoma. A high frequency of mutations of the BRAF gene, which resides on chromosome 7q, has been reported in primary melanoma [18].

The function of BRAF mutation in melanoma occurrence and development is currently being actively investigated. BRAF mutations are more common in melanomas arising on intermittently sun-exposed skin, but do not have the standard UVB signature [19]. It has recently been shown that genes involved in cellular signalling pathways may be inactivated in primary melanomas not only by mutation but also by deletion or epigenetic events [20]. Current data support a model in which genesis of melanoma requires changes that initiate clonal expansion, overcome cell senescence and reduce apoptosis. The interaction of one critical pathway in the response to UV irradiation (such as p53 activation) may increase susceptibility to melanoma.

Catalytic melanoma develops in a spatial/temporal sequence. Changes in expression of numerous melanoma-associated genes can trace steps of melanoma progression from the benign melanocytic lesions, to dysplastic naevi, to primary melanoma with radial (RGP) or vertical (VGP) growth pattern, to the acquisition of metastatic capacities. However, this sequence is currently challenged by the recent identification of melanoma stem cell [21]. One of the major barriers in cancer biology during the last decades has been the identification of cells within tumours with stem cell-like properties. Such cancer stem cells were first identified in haematological malignancies [22].

The greater the number of nodes involved by metastatic melanoma, the higher the risk of systemic spread and survival outcomes are thus related specifically to the tumor thickness measurement. (Fig. 5.13.10) Metastatic melanoma will not only involve the local lymphatic system and the regional lymph nodes, but also there is a systemic circulation. Approximately 50% of melanomas metastasise first to the lymph nodes, thus making the management of lymph node metastases an important part of the treatment. Effective lymph node dissection (i.e. prophylactic removal of lymph nodes) is now rarely practiced in the management of primary melanoma. The standard management for lymph nodes in patients with melanoma is based on surgical guidelines, with therapeutic node dissection if lymph nodes become involved. However, selective lymphadenectomy [25] is used in clinical trials to the present time. This technique enables mapping of the lymphatics in the skin by lymphoscintigraphy or radio- or radio-isotope labelling at the site of the primary and its flow through the skin to the sentinel lymph node (the first lymph node linked to the primary tumor). The sentinel node is then removed for histopathological examination, only patients with positive lymph nodes are subjected to full lymph node dissection. An international trial has shown that the staging of intermediate-risk melanomas (1–2.5 mm) primary melanoma according to the results of sentinel node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy [26].

The greater the number of nodes involved by metastatic melanoma, the higher the risk of systemic metastases and poor prognosis. As the thickness of the melanoma increases and as the number of lymph nodes involved rises, the risk of systemic metastases becomes greater. Melanoma metastases widely, with the lungs, liver and brain being the most common sites. Melanin (a skin condition characterised by failure to form melanin) is a favourable prognostic sign in metastatic melanoma. At the present time, only a small proportion of people (0.5%) live more than two years since systemic metastases become evident. The management for the treatment of systemic metastases is chemotherapy. However, since the original introduction of dacarbazine 40 years ago, clinical trials conducted to date have failed to demonstrate a meaningful impact on survival. No highly effective systemic agent or combination has yet been developed, and metastatic melanoma is characterised by drug resistance [27]. Spontaneous regression of primary or metastatic melanoma, possibly as a result of natural and induced immune rejection, is rare but not uncommon (0.2–0.4% of cases), and this has led to increasing interest in immunotherapy. At the present time this modality remains experimental, although response rates of 15–20% to cytokines, such as interferon-α and interleukin-2, have been reported, and clinical trials of vaccines containing whole cells, lysates, dendritic cells or melanoma-associated antigens, such as MAGE, TRP and MART, are underway [28].

Recent progress in the understanding of melanoma biology has resulted in the identification of genetic lesions and intracellular signalling pathways that could serve as targets for novel therapy. An increasing number of new agents that have been shown to interfere with signalling pathways in melanoma, or to decrease proliferation, survival, migration or invasion, or to interfere with stromal components of melanoma such as angiogenesis and components of the immune system, are currently under evaluation [29].

Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Melanoma thickness</th>
<th>Surgical margins requirements</th>
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<tbody>
<tr>
<td>T1</td>
<td>&gt; 1 mm to 2 mm</td>
<td>Local excision is sufficient</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 2 mm</td>
<td>Incisional biopsy is performed</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 4 mm</td>
<td>Full excision is performed</td>
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<tr>
<td>T4</td>
<td></td>
<td>Full excision with sentinel node biopsy</td>
</tr>
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</table>

Table 5.13.1 Classification of melanoma (American Joint Committee on Cancer/International Union Against Cancer) and corresponding recommended excision margin

Fig. 5.13.10 Time from primary survival for melanoma, according to stage

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REFERENCES


CANCER INSTITUTE PROFILE: European Institute of Oncology (IEO)

The European Institute of Oncology (IEO) in Milan, Italy is the fastest-growing comprehensive cancer centre in Europe. The brainchild of Professor Umberto Veronesi, it opened in 1994, and the hospital has grown such that in 2007 over 11000 new cancer patients were treated, 3000 of whom were suffering from breast cancer. A new Day Hospital and Hotel will be completed within eighteen months, adding 30% to our clinical capacity.

The science base has grown in parallel such that the total number of full-time scientists including the ICOMIEO science campus is now over 380. In 2007 IEO staff published 322 peer-reviewed articles with a total impact factor of 1670.

Last year the hospital staff succeeded in entering around half of its patients in clinical trials ranging from prevention, imaging, staging and therapy to pain control and supportive care. The personnel at the hospital were the first to carry out a random trial of breast cancer tamoxifen, the first to show the value of sentinel node imaging and biopsy, and the first to complete a random trial of all intra-operative radiotherapy (IORT) in breast cancer.

A key focus in the science labs is the molecular biology of normal tissue stem cells and their cancerous counterparts.

In addition, IEO has recently launched the first new online Open Access cancer journal, www.eancancermedsci.com.
Breast Cancer

Summary

- Breast cancer is the most common cancer among women worldwide. Mortality from breast cancer has been declining in developed countries over the last few decades due to improved diagnosis (mammography) and (mainly) improved treatment.

- Breast cancer risk is related to nulliparity and late first birth, early menarche and late menopause, it is reduced by breastfeeding.

- Current use of oral contraceptives and of combined HRT is associated with increased breast cancer risk, which reduces to that of non-users 5 to 10 years after stopping use.

- Family history of breast cancer and high mammographic density are among the best recognised breast cancer risk factors, which assist in identifying high-risk women for screening purposes.

Breast cancer is the most common cancer among women worldwide. It was estimated that 630,000 incident cases occur in developed countries and 514,000 in developing countries during 2002 [2]. Breast cancer is also the most important cause of neoplastic deaths among women worldwide, and breast cancer mortality rates have remained fairly constant in developing countries, and slowly in developed countries. Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas, and then showed appreciable declines, which have reached 25-30% in northern Europe [3]. The incidence increases linearly with age up to menopause, after which a further increase is less marked, or almost absent in developing countries.

Over 80% of the neoplasms of the breast originate from the ductal epithelium, while a minority originates from the lobular epithelium. However, the proportion of ductal carcinomas has been increasing over recent calendar periods. Survival from breast cancer has slowly increased in developed countries, where it now achieves 85%, following improvements in screening practices and treatments. On the other hand, survival in developing countries remains around 50-60%.

The risk of breast cancer increases with cumulative number of ovarian cycles. The risk decreases by about 15% for each year of delay in age at first birth and number of sisters. (Data from Lancet (2001) 358, 1389-99)

Pregnancy increases in the short term the risk of breast cancer, probably because of increase in the level of free oestrogen during the first trimester. In the long run, however, pregnancy has a beneficial effect, since parous women have a higher level of progesteron and a lower level of sex hormone-binding globulin than nulliparous women. These two effects result in a protective role of estradiol and a small residual protective effect of other pregnancies. An additional protective effect of lactation has been shown in several populations, probably attributable to the suppression of the ovulatory function caused by nursing. In a collaborative reanalysis of all 47 studies, the breast cancer risk decreased by 4.3% for each year of lactation (data from the Canadian Biometry and Epidemiology Group). All authors agreed that the data from 53 epidemiological studies providing information on history of spontaneous or induced abortions, and found no association with breast cancer [6].

With reference to exogenous hormones, the risk of breast cancer is 15-25% higher in current and recent users of oral contraceptives (OC) as compared to never-users (Figure 5.14.2) [7]. Further, 10 or more years after stopping OC use the risk levels off to approach that of never-users (Figure 5.14.2) [7]. The risk of breast cancer increases with cumulative number of ovarian cycles. The risk decreases by about 15% for each year of delay in age at first birth and number of sisters. (Data from Lancet (2001) 358, 1389-99)

First-degree relatives affected with breast cancer

<table>
<thead>
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<td>603</td>
<td>404</td>
<td>2.93 (2.73-3.13)</td>
</tr>
<tr>
<td>3 or more</td>
<td>233</td>
<td>136</td>
<td>8.15 (5.37-12.76)</td>
</tr>
</tbody>
</table>

Table 5.14.1 Risk rates of breast cancer and 99% FCI (9-df) in relation to family history of breast cancer in first-degree relatives. Risk is stratified by study, age, menopausal status, parity, age at menopause and number of cases. (Data from Cancer (2001) 518, 1389-99)

Breast cancer risk depends on duration of HRT use and is reduced after cessation of use, levelling all after 5 or more years since quitting HRT. The Women’s Health Initiative, a randomised controlled trial comparing hormone replacement therapy (HRT) with placebo in post-menopausal women, provided comprehensive information on the risk of breast cancer in users of conjugated estrogen alone or in combination with progesterin. In the estrogen-alone trial, after about 7 years of follow-up, there was no significant difference in breast cancer incidence comparing conjugated estrogen use to the placebo group (Hazard ratio, HR=1.00) [10]. On the other hand, a high incidence of invasive breast cancer was observed in the estrogen plus progesterin group as compared to women receiving placebo. Furthermore, breast cancers were diagnosed at a more advanced stage in the estrogen plus progestin group [11].

Besides exogenous hormones, the combined evidence from reproductive factors points towards a role of endogenous hormones in breast carcinogenesis. A direct assessment of the role of estrogen and testosterone is also available from recent prospective studies collecting epidemiological data and biological samples. Estriol concentrations in the blood have been directly associated with breast cancer risk in postmenopausal women, particularly with estrogen and progesterone receptor positive tumours. Similarly, testosterone and androstenedione concentrations are associated with breast cancer risk, but the data are inconsistent for all endogenous hormones across major cohort studies [12].

Phenotypical data from breast cancer, the most common breast diseases, are associated with a 2.3-fold higher breast cancer risk. Likely, these lesions are not pre-neoplastic conditions, but pre-neoplastic proliferation, linked to hormonal alterations, is a feature they share with breast cancer.

Family history of breast cancer is associated with a 2.5-fold higher risk of the same disease, and risk increases with the number of affected first-degree relatives (Table 5.14.1) [13]. This family history is likely to result from low-penetration genes associated with hormonal metabolism and regulation, DNA damage and repair. There is some evidence of an increased risk of breast cancer associated with polymorphisms of genes involved in the biosynthesis of estriol, particularly the CYP19 gene. Several other low-penetration genes have been analysed, but studies have generally reported null or inconsistent findings. In addition, breast cancer risk is greatly increased in carriers of mutations of several high-penetration genes, in particular BRCA1, BRCA2 and p53. Although the cumulative lifetime risk in carriers of these genes might be over 50%, they are rare in most populations and explain only a small fraction (25%) of total cases.

Although a role of nutrition in breast cancer risk is strongly suggested by international comparisons, the combined evidence from epidemiological studies is inconclusive for most aspects of diet [14]. Several studies have been conducted to investigate whether intake of fruit, vegetables and related micronutrients, dietary fibre, total and saturated fats, dairy products, glycaemic index and food, and intake of phytoestrogens have an influence on breast cancer risk. No association emerged consistently from prospective studies, although there is some evidence of a protective role played by soy intake [15] and folate [16]. Although a role of nutrition in breast cancer risk is strongly suggested by international comparisons, the combined evidence from epidemiological studies is inconclusive for most aspects of diet [14]. Several studies have been conducted to investigate whether intake of fruit, vegetables and related micronutrients, dietary fibre, total and saturated fats, dairy products, glycaemic index and food, and intake of phytoestrogens have an influence on breast cancer risk. No association emerged consistently from prospective studies, although there is some evidence of a protective role played by soy intake [15] and folate [16].
Control of weight gain and of overweight and obesity in postmenopausal women would have favourable implications in breast cancer risk. Tamoxifen, an anti-oestrogen drug used in chemotherapy, has shown a chemopreventive action against breast cancer, although the magnitude of the protection is uncertain [22]. Aspirin and other nonsteroidal anti-inflammatory drugs might also have a chemopreventive effect on breast cancer risk, although results from epidemiological studies are heterogeneous [23].

Secondary prevention through mammography is the most suitable approach for breast cancer control. The effectiveness of screening by mammography in women older than 50 years was shown in the Netherlands [1].

There are several notable features of the geographic distribution of breast cancer mortality in women in Europe. There is an aggregation of high rates that covers Denmark and westwards through northern Germany, The Netherlands and Belgium and then across to the United Kingdom and Ireland; mortality was also slightly above average in parts of Slovenia and Hungary. Rates were low in the Nordic Countries (apart from Denmark), Portugal, Spain, France, southern Italy and Greece. There is nothing known about the etiology of breast cancer that can explain the geographic pattern demonstrated on the map. The pattern will change in the future as national breast screening programmes make their effects in reducing breast cancer mortality [1].

Further, in post-menopausal women, there is consistent evidence of a modifying effect of HRT use, as the increase in risk of breast cancer related to a high body weight and/or weight gain is stronger or limited to non-users of HRT.

Male breast cancer is a rare disease. Less than 1% of all breast cancer patients are men [20]. Incidence rates in developed countries provide limited evidence of geographical and intercultural variations, except for Jewish men who have higher than average rates. There is no clear correlation between incidence rates in men and women. Conditions involving high oestrogen level, such as gonadal dysfunction and liver damage, alcohol abuse and obesity, are risk factors for breast cancer in men. BRCA2 mutations are more frequent than BRCA1 in male familial breast cancers [21].

Primary prevention of breast cancer has been attempted via nutritional intervention, involving reduction of energy intake, reduction of proportion of calories from fat, and increase in fruit and vegetable consumption. No evidence of efficacy has been produced so far. However, alcohol drinking is an established aetiological factor for breast cancer. Alcoholism is a high body weight and/or weight gain is stronger or limited to non-users of HRT.

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years has been demonstrated, and education programmes have been established in various countries. The effectiveness in women younger than 50 is not yet demonstrated, though there is some evidence for a reduction in risk of dying from breast cancer in women aged 40–49 who undergo annual mammography. MRI has also been valuable in the screening of high-risk (BRCA-positive) young women [24].

REFERENCES

10. Beral V, Bull D, Doll R, et al. (2004). Breast cancer and 100,239 women without breast cancer from 54 countries. The effectiveness in women younger than 50 is not yet demonstrated, though there is some evidence for a reduction in risk of dying from breast cancer in women aged 40–49 who undergo annual mammography. MRI has also been valuable in the screening of high-risk (BRCA-positive) young women [24].
Cervical cancer is the second most common cancer among women world-wide, more than 80% of the global burden of cervical cancer is found in developing countries.

Cervical cancer is caused by persistent infection with one or more of the 15 oncogenic types of human papillomaviruses (HPV).

Invasive cervical cancer is preceded by well-defined precancerous lesions that can be detected early by screening tests.

Population-based screening, leading to early detection of cervical precancerous lesions and their treatment, has led to greatly reduced cervical cancer incidence and mortality in developed countries.

HPV vaccination offers a promising option for cervical cancer prevention.

Cervical cancers arise in the epithelium covering the uterine cervix, particularly at the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix, a site of continuous metaplasia between the columnar epithelium of the uterine cervix, particularly at the junction between the endocervix and the squamous epithelium of the uterine cervix. In most women HPV infection resolves spontaneously, but it may persist in some. If the infection persists, integration of viral genome into the host genome may lead to the development of precancerous lesions thereon.

The cervical columnar epithelium is replaced by metaplastic squamous epithelium over several years after first pregnancy. The area of the cervical columnar epithelium where this squamous metaplasia occurs is the ectocervix, and it is here where cervical neoplasia occur. The peak of HPV infection occurs soon after the onset of sexual activity, but the risk of HPV infection is highest for women who are sexually active and have multiple sexual partners.

Natural history

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The high incidence rates in developing countries are mainly due to the lack of or ineffective control measures in many high-risk countries. It is a major cause of mortality and premature death among women in their most productive years in low- and medium-resource countries in Asia, Africa and Latin America, despite the fact that it is an extremely preventable cancer.

There is a more than twofold difference between the highest and lowest incidence rates of cervical cancer worldwide (Figure 5.15.1). In sub-Saharan Africa, Central and South America, South Asia and South-East Asia, age-standardized incidence rates of cervical cancer exceed 25/100 000 in many countries. Rates lower than 7/100 000 women are observed in West Asian countries and in urban China, while there are countries where the rate is lower than 10/100 000 women in most developed countries. The highest risk is observed in sub-Saharan Africa, Malawi, South Africa, Korea and the Caribbean and South-East Asia (World map 5.15.1). The incidence of cervical cancer begins to rise at ages 30–39 and then increases rapidly to reach a peak in the fifth or sixth decade of life. The high incidence rates in developing countries are mainly due to the lack of or ineffective control measures in many high-risk countries. It is a major cause of mortality and premature death among women in their most productive years in low- and medium-resource countries in Asia, Africa and Latin America, despite the fact that it is an extremely preventable cancer.

Pathology

Persistent infection with one or more of the oncogenic types of HPV, as well as genetic, biological and other factors, result in dysplasia, which is sufficient evidence in humans for the carcinogenicity of HPV 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 66, 73. HPV DNA has been detected in virtually all cervical cancer specimens [15,16]. The association of HPV with cervical cancer is equally strong for the two main histological types: squamous-cell carcinoma and adenocarcinoma.

However, since most cervical abnormalities caused by HPV infection are unlikely to progress to high-grade CIN or cervical cancer, as most of them regress by themselves, other exogenous or endogenous factors acting in conjunction with HPV may be necessary for progression of the disease. Epidemiological studies have identified a number of other risk factors that contribute to the development of cervical cancer precursors and cervical cancer. These include sexual intercourse at an early age, multiple sexual partners, long-term oral contraceptive use, tobacco smoking, low socio-economic status, infection with Chlamydia trachomatis, and immunodeficiency in vegetarians and fruitlets (fruit, 12,13,17). It is now clear that the well-established risk factors associated with sexual behaviour, such as multiplicity of sexual partners and early age at initiation of sexual activity, simply reflect the probability of being infected with HPV. The assessment of the risk of HPV infection is complex and may involve the co-factors that require the central and strong evidence that their effective prevention may significantly reduce the burden of cervical cancer. The high mortality in developing countries has resulted in the failure of studies fulfilling this requirement to have high, population- and long-term survival and oral contraceptives are co-factors that increase the risk of cervical cancer [18]. Additional co-factors such as herpes simplex virus type 2 (HSV-2), Chlamydia trachomatis infection, HIV and immunosuppression, certain micronutrient deficiencies and genetic susceptibility, are implicated in cervical carcinogenesis [19,20].
over a six-month period. Monovalent (HPV 16), bivalent (HPV 16 and 18) and quadrivalent (HPV 6, 11, 16 and 18) virus-like particle (VLP) vaccines have been evaluated in randomised Phase II and III trials. Recent studies indicate that HPV vaccines are safe, highly immunogenic inducing high levels of serum antibodies in virtually all vaccinated women, and confer a high degree of protection (~99%) against HPV 16/18 infection and related CIN in fully vaccinated women [24,25]. The current information is based on a maximum of 5-year follow-up after vaccination and long-term immunogenicity and efficacy in preventing cervical neoplasia, cross-protection against HPV types not targeted by the vaccine antigens, the need for boosters and the efficacy of different, more logistically feasible dose regimens in inducing and maintaining immunogenicity, remain to be established.

Prevention by screening

Early changes in the cervix, specifically CIN, can be detected years before invasive cancer develops by screening tests such as conventional cytology (Pap smear), liquid-based cytology, HPV testing and visual screening with acetic acid or Lugol’s iodine [26]. An affordable, fast and simple new HPV test (careHPV) developed to detect 14 high-risk types of HPV is a promising test to screen women in developing countries [27]. Women with abnormal screening results are further investigated with colposcopy (a 4–20X magnified inspection of the cervix with a binocular endoscope), directed biopsies from abnormal areas identified on colposcopy [28]. For women whose TZ is not or only partially visible, a tissue specimen may be obtained using endocervical curettage (ECC) or by excising the cervical tissue by the loop electrosurgical excision procedure (LEEP) and subjecting these for histological examination.

The treatment of CIN has evolved from inpatient procedures like hysterectomy and cold knife conisation towards more conservative, safer, simpler and more effective approaches. CIN may be treated by destructive therapy such as cryotherapy, electrocoagulation, cold coagulation or laser vaporisation or by local excision methods such as the LEEP, large loop excision of the transformation zone (LLETZ), or laser excision. The basic principle of treatment of CIN is that the entire TZ of the cervix including the extension into the crypts (average depth 5mm) should be destroyed or removed [28]. Currently, cold knife conisation under local or general anaesthesia is reserved only for the treatment of micro-invasive cancer where evaluation of the margin is of prime importance. Hysterectomy should be reserved only for a
Early, asymptomatic preclinical invasive cervical cancers may be detected during colposcopic assessment of screen-positive women. As invasion progresses, symptoms manifest with characteristic clinical features, depending on the clinical stage of the disease. Women with invasive cervical cancer often present with one or more of the following symptoms: intermittent bleeding, postcoital bleeding, hemoptysis, menorrhagia, excessive vaginal discharge, dysuria, dyspareunia, abnormal weight loss, or symptoms of kidney failure (due to ureteral obstruction), mass effect on pelvic structures, and extranodal extension. Awareness of symptoms and signs of invasive cancer should prompt visual inspection of the cervix to rule out cancer. Clinical suspicion and symptomatology are important in the early detection of invasive cancer. Once a diagnosis of invasive cancer is made, it is mandatory to stage the clinical extent of disease, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, to guide treatment and prognosis (Table 5.15.1).

A diagnosis of invasive squamous-cell carcinoma or adenocarcinoma requires prompt referral for definitive treatment with surgery or radiotherapy, with or without chemotherapy. Clinical stage of disease at presentation is the single most important predictor of long-term survival. Survival rates also decline with advancing clinical stage IA disease.

The 5-year survival in stage IA disease ranges from 90-95%, 80-85% in stage IB, 50-65% for stage IIIA, 25–35% for stage IIIB and <10% for stage IV disease (Table 5.15.1).

### Stage Description of the stage of disease 5-year survival %

**IA**
- Invasive cancer identified microscopically: invasion is limited to stratum basale with maximum depth of 5 mm and no wider than 7 mm.
- Stage IA1: Measured invasion of the stratum 3 mm or less in depth and 7 mm or less in diameter.
- Stage IA2: Measured invasion of stratum more than 3 mm but less than 5 mm and 7 mm or less in diameter.
- Stage IA3: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA1.

**IB**
- Clinical lesions more than 7 mm wide.
- Stage IB1: Clinical lesions more than 7 mm in diameter.

**II**
- Carcinoma that extends beyond the cervix but has not penetrated the pelvic wall. The carcinoma involves the vagina but not as far as the lower third section.
- Stage II A: No clinical parametrial spread.
- Stage II B: Obvious parametrial involvement.
- Stage II C: Carcinoma that extends to the pelvic sidewall and/or has penetrated the pelvic wall.

**III**
- Carcinoma that has extended to the pelvic sidewall and/or for the lower third of the vagina.
- Stage III A: No clinical parametrical spread.
- Stage III B: Extension onto the pelvic sidewall or hydronephrosis or obstructive kidney.
- Stage III C: Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
- Stage III D: Spread of the tumor onto adjacent pelvic organs such as bladder or rectum.

**IV**
- Carcinoma involving the vagina but not as far as the lower third section.
- Stage IV A: Carcinoma involves the vagina but not as far as the lower third section.
- Stage IV B: Spread of the tumor onto adjacent pelvic organs such as bladder or rectum.
- Stage IV C: Carcinoma involving the vagina but not as far as the lower third section.
- Stage IV D: Spread of the tumor onto adjacent pelvic organs such as bladder or rectum.

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Most malignant neoplasms of the ovary originate from the coelomic epithelium, less frequent are the carcinosarcomas and endometrioid adenocarcinomas. In 2002 the estimated number of new cases worldwide was 204,000 (granulosa cell tumors). In 2002 the estimated number of new cases worldwide was 204,000 (granulosa cell tumors).

The protection afforded by combined oral contraceptives (OC) is the other established, and most important from a public health perspective, feature of epithelial ovarian cancer. The overall estimated protection is approximately 40% in ever OC users and increases with duration of use to about 60% for users for 10 years or longer. The favourable effect of OC against ovarian cancer risk seems to persist for at least 15–20 years after OC use has ceased, and it is not confined to any particular type of OC formulation (4).

The implication of reproductive factors in the etiology of ovarian cancer suggests a major role of endogenous hormones in the disease. Several hypotheses have been postulated, as suggested by the data of the Nurses’ Health Study (6) (Fig. 5.16.1). These studies however have somewhat equivocal results in the association of exogenous sex steroids and ovarian cancer risk, with discordant results. Conversely, two case-control studies nested within large cohorts have shown an increased risk of ovarian cancer with increasing circulating maternal growth hormone concentrations in blood in young women (pre- or perimenopausal age) (7).

Nulliparity and low parity have been consistently related to ovarian cancer. Most studies have shown a decline in risk associated with number of full-term pregnancies beyond the first one, thus suggesting that the inverse association is not due to infertility per se, but to some other factor(s) that may be linked to parity. Additional risk reduction is conferred by events accompanying each pregnancy (3).

The prevention of ovarian cancer is hampered by the lack of availability of early diagnostic techniques and the absence of a proven screening test.
While there are certain similarities with breast cancer in the geographic distribution of mortality from cancer of the ovary, there are also some potentially interesting differences [1].


REFERENCES

CANCER INSTITUTE PROFILE: Karolinska Comprehensive Cancer Centre

Recently there was a merger of the two university hospitals in Stockholm, Sweden into the Karolinska University Hospital. The aim was to integrate research and education at the Karolinska Institute with the health care system in Stockholm and build a structure for translational medicine. The hospital and the campus of the Karolinska Institute together form an organisation with more than 18,000 employees. This decision has been made to develop a more visible and functional comprehensive cancer centre within this structure in order to form an environment for improved translational cancer research. With about 120 research groups involved in cancer research, there is a strong platform for basic, translational and epidemiological research. There is also important infrastructure for translational research, with experimental cancer research laboratories linked to oncological health care (Cancer Center Karolinska, a translational research structure), patient data registers containing population-based data, a clinical trial unit, a structure for biobanking and a platform for biomics. A particularly strong area of interest is proteomics, evidenced by the collaboration with the human proteome resource at the Royal School of Technology. The Centre provides oncological service for the 2 million inhabitants in the Stockholm area. About 700 to 800 scientific reports in the area of cancer are published each year, as well as around 80 PhD theses.
Endometrial Cancer

Summary

- The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) is the most widely accepted hypothesis on the etiology of endometrial cancer.
- Obesity is the most important risk factor for endometrial cancer worldwide, and has been estimated to account for up to 40% of endometrial cancer incidences.
- The use of oral contraceptives is associated with a long-lasting decrease in endometrial cancer risk.
- Much of the effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake, expenditure and body weight.

Endometrial cancer is the seventh most common cancer in women worldwide, and the fourth in developed countries, after breast, lung and colorectal cancers. This cancer appears more important in terms of number of new cases than in terms of mortality, representing 3% of all new cancer cases in women compared to 1.7% cancer deaths (2). The highest incidences are in North America and in Western Europe, where it is about 10 times higher than in Asia or in rural Africa (2). In these areas, endometrial cancer is the most common cancer of the female genital tract. The wide differences in incidence of endometrial cancer between rural and urban areas, as well as results of studies on migration from low to high-risk areas, strongly suggest strong environmental rather than genetic risk factors.

The overall incidence of endometrial cancer is rising as life expectancy increases. This cancer mostly arises in post-menopausal women: more than 90% of cases occur in women who are older than 50, with the highest incidence reached after 65 years of age (2). Survival is rather good and parallels that of breast cancer (65% according to the SEER registries, and 79% in European registries) (2).

There are two major types of endometrial cancers: About 80% of endometrial type, are well to moderately differentiated, and are generally associated with endometrial hyperplasia (type I). They have favourable prognosis, and are strongly related to hormonal imbalances (3). About 10% of endometrial cancers are type II (high-grade or poorly differentiated). Type II tumors are more common in young, nulliparous, acyclic, obesity or cell clear cell carcinomas, and seem to be unrelated to estrogens (3). Women with type 2 tumors are at high risk of relapse and of metastatic disease. Type I carcinomas are associated with mutations in the ras oncogene and PTEN tumor suppressor gene, as well as with microsatellite instability, while the majority of type-2 tumors are associated with p53 mutations.

Since endometrium is a tissue that is very responsive to hormone stimulation, hormones seem to play an important role in the etiology and in the development of this cancer. Endometrial cell mitotic rate is sensitive to estrogens, especially to estrogens that are unopposed by progesterone: the proliferation rate of endometrial cells seems to reach its maximum during the first 18 days of the menstrual cycle (follicular and early luteal phases), phases in which progesterone levels are particularly low. The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) (4) is the most widely accepted hypothesis on the etiology of endometrial cancer and can explain most of the risk factors already identified: early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. An early age at menarche and a late age at menopause increase the exposure of a woman to estrogens. Indeed, in personal experience, many pregnancies mainly increase her exposure to progesterogens (through placental products). Obesity is the most important risk factor for endometrial cancer worldwide, and it has been estimated to account for about 40% of endometrial cancer incidence. In pre-menopausal women, obesity is associated with anovulatory cycles during which the endometrial tissue receives continuous stimulation. In post-menopausal women, increased body fat mass increases the concentration of endogenous estrogens, because in this population estrogens are not produced by the ovary anymore, but are mainly produced by the aromatisation of androgens in the adipose tissues. Excess weight is associated with insulin resistance and chronically elevated insulin concentrations in blood, and with increasing concentrations of bioavailable sex steroids (5), factors that are associated with increased endometrial cancer risk (Figure 5.17.1). Type-2 and type-1 diabetes are strongly associated with an increase in endometrial cancer risk, as well as with hypertension. Hyperglycaemia has also been associated with an increase in endometrial cancer risk, especially in overweight women.

The use of HRT is associated with a long-lasting decrease in endometrial cancer incidence (3). Also, only when the contraceptives used contain progesterone, in addition to estrogens (6) (Figure 5.17.2). Since in these drugs the concentrations of progestagens are dominant compared to estrogens concentrations, the proliferation of endometrial cells happens only during the few days of the menstrual cycle when OIC are not taken. Based on this assumption, the use of HRT has been estimated to account for about 10% of endometrial cancer worldwide, and has been calculated to be about 10% per year of OIC use. Ovulation-containing pills only, conversely, increase the risk of endometrial cancer. The use of HRT in post-menopausal women increases about twofold the risk of developing endometrial cancer (7) (Figure 5.17.3), and the risk increases with duration of use and with increasing estrogen concentrations in the medium. Adding progesterone daily to estrogen therapy seems to lower the risk of endometrial cancer similar (or lower) to that of non-estrogen users (6). A recent publication suggests that the relative higher estrogen concentrations in blood are associated with an increase in endometrial cancer risk mainly in postmenopausal women, while higher endogenous androgen concentrations are associated with an increase in endometrial cancer risk in both pre- and postmenopausal women (5).

Polyovulatory ovary syndrome (PCOS) is a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes) has been repeatedly associated with an increase in endometrial cancer risk (5).
In respect to dietary factors, phytoestrogens, antioxidant and vegetable consumptions have been linked to the decrease in risk of endometrial cancer (8,9). Conversely, recent publications have suggested an increase in endometrial cancer risk with high consumption of meat.

Women who develop breast cancer are at increased risk of developing endometrial cancer, and are more likely to develop type2 rather than type1 endometrial carcinoma. This increase in risk could be partly explained by common risk factors between breast and endometrial malignancies (i.e. multiparity or late age at menopause), but the use of tamoxifen for the treatment of breast cancer has also been questioned. Women under tamoxifen therapy had more than a twofold increase in endometrial cancer risk compared to non-users. Physical activity has shown to decrease the risk of developing the disease, and an additional study is needed to finally assess its influence on the disease. Epidemiological evidence suggest that smoking may be protective against endometrial cancer in post-menopausal women, but it seems to be associated with an increase in endometrial cancer risk in pre-menopausal women. Mush F not all, of the reported effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake and expenditure, and body weight. The same may be true for the apparent lower risk among smoking women, as they tend to be leaner than non-smoking women.

As stated previously, genetic causes of endometrial cancer are uncommon, although having a first-degree relative with endometrial cancer has been associated with the double risk of developing the disease, and an association with hereditary non-polyposis colon cancer (HNPCC) syndrome has been observed (3).

Screening for endometrial cancer does not seem to improve survival or reduce mortality from endometrial cancer, since most of the cancers detected with screening would be most likely low-risk cancers (3,10). Post-menopausal bleeding is the most common symptom of endometrial cancer, which is present in 75% of women with the disease. Women should therefore be aware of the importance of detecting post-menopausal bleeding or spots. Conversely, no tests have so far been validated or are recommended for endometrial cancer screening (10).

In the WHO African Region, a few countries including Guinea, Senegal, South Africa and Tanzania have national cancer control policies and programmes. Data on the magnitude of cancer are scanty or nonexistent. Cervical cancer prevention programmes have been implemented in many countries including Guinea, Uganda, South Africa, Zimbabwe and Tanzania; these initiatives must be scaled up. Well-equipped infrastructure and facilities for early cancer detection or management requiring surgery, chemotherapy and radiotherapy are very lacking in most countries. While there is an acute shortage of cancer specialists such as pathologists for diagnoses, oncologists for treatment and radiation therapists for care, some national universities, especially in South Africa, Nigeria, Kenya and Senegal, have started training programmes for health personnel specialists in various cancer domains. There is increasing political will to address cancer-related issues and challenges.

The WHO Regional Office for Africa (AFRO) is committed to public health actions designed to reduce cancer incidence and mortality and to improve quality of life of patients through the systematic implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment and palliative care. The WHO-AFRO Regional Director has made cancer prevention and control a priority for the Region, and the Regional office with resources to tackle the problem. There have been:

- actions of advocate to increase commit-
ment, such as a roundtable held on August 2007 during the AFRO Regional commit-
tee to underline the best approaches to increase awareness and put cancer high on the national agendas;
- statements of commitment facilitated among member states including the adopt-
ion of resolutions, and, a regional strategy for cancer control to be submitted to next regional committee in September 2008 for adoption by Member States;
- normative guidance and technical sup-
port for national programme development and imple-
mentation, such as a tool for key interventions in cancer prevention and control to be published soon and an inte-
grated approach for non-communicable diseases that incorporates comprehensive health promotion components.
During the last several decades, epidemiological studies conducted in various parts of the world have demonstrated a rapid increase in the incidence of germ-cell testicular cancer, predominantly in young men. While considerable efforts have been made in studying the etiology of testicular cancer, little is known about the etiology and the cause(s) of the observed increase in incidence of the disease. Nevertheless, the following descriptive epidemiological features of germ-cell testicular cancer as summarised by Zhang et al. [2] offer important clues for searching for the risk factors of germ-cell testicular cancer:

1. Different populations or different birth cohorts of the same population have very similar age-incidence patterns. Testicular cancer has a very small peak in the postnatal period (participation in sports, games, and socialisation), followed by a rapid increase after puberty, and a peak at around age 25 for non-seminomas and age 35 for seminomas. The youngest age at diagnosis of the cases of germ-cell testicular cancer are diagnosed between age 15–14. The early onset of the disease, the rapid increase in rate after puberty and the peak at young age suggests that social environment and life exposure and male sex hormones are related to the occurrence and/or progression of germ-cell testicular cancer.

2. Few studies so far have investigated the relationship between genetic susceptibility and gender at the same time when developing the disease. The following summarises the major suspected risk factors for germ-cell testicular cancer:

   a. High levels of androgenic hormones during early pregnancy or adolescence: Henderson et al. [5] and Depue et al. [6] hypothesised that the major risk factor for testicular cancer is the male sex hormones or environmental exposures, as well as adult male sex hormones are abnormal, this would suggest early sex hormone induction or difference during early pregnancy, even before the gestational period. Several studies of early life-exposure to elevated levels of circulating maternal hormones have suggested that early androgen exposure has been consistent with the increase of testicular cancer. In particular, the ratio of sex hormones (estrogens/androgens) is higher in the offspring of those with a high androgen exposure during pregnancy. Therefore, the results linking major suspected risk factors (such as androgenic hormones and environmental hormone disruptors) to testicular cancer risk have been inconsistent, possibly due to small sample sizes in the majority of the studies. Studies so far have investigated the relationship between genetic susceptibility and gender at the same time when developing the disease. The following summarises the major suspected risk factors for germ-cell testicular cancer:

   b. The observed relationship between these prenatal exposure surrogates and testicular cancer risk has generally been considered to be due to a raised maternal level of available estrogen during the first trimester. For example, the cause of severe nausea in pregnancy is considered to be due to the rapid rise of estrogen levels in the mother in the first 2 months of pregnancy. Higher risk of testicular cancer for early birth order was found in the world. Danish estrogen concentrations are higher during the first pregnancy. Cryptorchidism is related to an excess of available maternal estrogen during early pregnancy. Thus, rather than as a cause of testicular cancer, cryptorchidism may simply share common risk factor(s) with testicular cancer [7]. Neonatal jaundice is also related to high estrogen levels among infants. Abnormally high birth weights are associated with testicular cancer risk since fetal growth was reported to be positively correlated with pregnancy testosterone levels. Thus, prenatal exposure to excess estrogens (while subnormal or androgenic exposure has also been proposed as a risk factor) may play a major role in the development of the CIS, while adolescent exposure to excess male sex hormones may play a major role in the progression of the CIS to invasive testicular cancer.

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Based on recent laboratory studies in animal systems, investigators have suggested that environmental hormone disruptors may be risk factors for testicular cancer, and several epidemiological studies have examined exposure to estrogenic or other hormonally active (e.g., antiandrogenic) compounds may be at least in part responsible for the observed increasing trend in the disease [9,10]. Specifically, there is concern over the relationship between environmental exposure to organochlorines (e.g. polychlorinated biphenyls, organochlorine insecticides such as DDT and its analogues, and others), polycyclic aromatic hydrocarbons (PAHs) and the risk of testicular cancer.

While there has been considerable interest in the relationship between environmental endocrine disruptors and increased risk of testicular cancer risk is mainly based on the following observations:

1. Experimental studies show that exposure to both endogenous and exogenous hormonally active compounds produces testicular cancer and other male reproductive disorders.

2. Results from a pilot study suggest a potential relationship between environmental hormone disruptors and testicular cancer risk. In this small study, Hessel et al. [11] reported that the mothers of testicular cancer patients had higher serum levels of PCBs, hexachlorobenzene (HCB), transnonachloridane (TNC), hexachlorodibenzo-p-dioxin (PCDD), and the sum of chlorobenzenes than did the mothers of noncancerous controls. When using the median concentration for the controls as 0.01 μg/L, the OR was 4.3 (95% CI 1.4–14) for PCBs, 4.4 (1.7–12) for HCB, 4.1 (1.5–11) for TNC, 3.1 (2.7–8) for PCDD and 1.9 (0.7–5.0) for sum of chlorobenzenes.

3. Men exposed in utero to dieldrin/hexachloroethane (DES) showed an increased risk of testicular cancer in some studies, and the combined estrogenic effects of environmental estrogens may exceed those of DES.

4. Pesticide applicators were reported to have an increased risk of testicular cancer, though the results are inconsistent.

5. While testicular cancer is increasing, other male reproductive disorders, such as cryptorchidism, hypospadias, reduced sperm count and quality, and infertility, are also increasing. These disorders are now collectively called testicular dysgenesis syndrome (TDS). TDS and testicular cancer may share a common risk factor—environmental hormones.

6. The hormone properties, carcinogenicity, tumour promotion activity and enzyme induction ability of these chemicals strongly support that exposure to environmental hormone disruptors may increase the risk of testicular cancer.

In summary, the hypothesis that environmental hormone disruptors are risk factors for testicular cancer is plausible based on animal data and limited human data. Organochlorines, for example, possess estrogenic and antiandrogenic activity, are known animal carcinogens and suspected human carcinogens, and have tumour promotion activity. Due to these properties, along with the continued widespread exposure to environmentally persistent organochlorine compounds and PCBs among the general population, there exists a need to determine whether these compounds are risk factors for testicular cancer.

Family history and genetic susceptibility. It is estimated that about 25% of the cases of testicular cancer are familial. The association has been noted by the family history of testicular cancer. While few studies have investigated the relationship between testicular cancer risk and genetic polymorphisms, there is evidence that certain genetic factors might influence risk of testicular cancer.

Studies of genetic polymorphisms and testicular cancer risk have been inconsistent. Some studies have suggested that certain genetic polymorphisms may influence the risk of testicular cancer. For example, the variant-B allele of the hormone receptor gene (nuclear hormone receptor) may be associated with an increased risk of testicular cancer.

In a study of estrogen receptor polymorphisms and risk of testicular cancer for example, Hsieh et al. [12] found that the variant-B allele was somewhat more frequent in cancer patients than did controls, although this was not statistically significant. They also noted that the variant-B allele tended to increase in incidence in the past few decades. If these trends continue, it is possible that the variant-B allele will be found to be a risk factor for testicular cancer.

Similarly, a variant of the androgen receptor (AR) is also associated with an increased risk of testicular cancer. The hormone properties, carcinogenicity, tumour promotion activity and enzyme induction ability of these chemicals strongly support that exposure to environmental hormone disruptors may exceed those of DES.

The enhanced CYP1A1 activity from exposure to environmental hormone disruptors increases the risk of testicular cancer. The enhanced activity of enzymes involved in steroid hormone metabolism may also increase the risk of testicular cancer.

In summary, the hypothesis that environmental factors may play a major role in the occurrence and/or progression of testicular cancer, thus a large proportion of the disease is potentially preventable. However, since so little is known about the etiology of testicular cancer, it is not possible at this stage to develop effective preventive measures to reduce the disease. Greater efforts must be made to better understand the etiology of testicular cancer and to better understand the underlying causes for the observed increase in the disease during the past few decades. If indeed hormone exposure to environmental hormone disruptors increases the risk of development and progression of testicular cancer, greater effort needs to be made to reduce human exposure to these man-made environmental pollutants. While it is difficult to develop effective preventive measures to reduce disease incidence, testicular cancer could almost be eliminated as a cause of death worldwide if the political will, adequate finance, and the necessary training and logistics to deliver appropriate treatment were implemented [22].

Prevention

The descriptive epidemiological features of testicular cancer as summarised previously suggest that environmental factors may play a major role in the occurrence and/or progression of testicular cancer, thus a large proportion of the disease is potentially preventable. However, since so little is known about the etiology of testicular cancer, it is not possible at this stage to develop effective preventive measures to reduce the disease. Greater efforts must be made to better understand the etiology of testicular cancer and to better understand the underlying causes for the observed increase in the disease during the past few decades. If indeed hormone exposure to environmental hormone disruptors increases the risk of development and progression of testicular cancer, greater effort needs to be made to reduce human exposure to these man-made environmental pollutants. While it is difficult to develop effective preventive measures to reduce disease incidence, testicular cancer could almost be eliminated as a cause of death worldwide if the political will, adequate finance, and the necessary training and logistics to deliver appropriate treatment were implemented [22].

Conclusion

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In summary, much of the etiology of testicular cancer remains unexplained, and hitherto unidentified risk factors remain to be identified. The question that must be answered is to what extent are endogenous hormones, environmental hormone disruptors, and genetic polymorphisms not only responsible for the observed age-incidence pattern, but also for the observed secular-incidence trend of testicular cancer. Unless major risk factors of testicular cancer are identified, no effective preventive measures can be developed to reduce the disease.

REFERENCES


BRIEF REPORT FROM THE WHO REGIONAL OFFICE FOR EUROPE (WHO EURO)

Cancer in the WHO European Region

Cancer was estimated to cause 19% of deaths and 11% of the disease burden (as measured by DALYs) in the WHO European Region in 2004. The WHO Regional Office for Europe has been tracking approximately 2.8 million deaths from cancer in the Region in 2003, leading causes of cancer death in the WHO European Region in 2003 were: lung, breast, colorectal, stomach and testicular cancer and prostate.

Disease patterns cannot simply be generalised—overall cancer incidence and mortality rates vary at least two-fold between European countries, and differences are often greater for specific cancers. Across WHO European Region as a whole, death rates from cancer have been decreasing since late 1980s, however the picture is more complex and according to age, sex, type of cancer, and country. Cancer incidence is rising for the Region as a whole—mainly largely reflect changes in the age structure of the population and its risk factor profile, which is in turn related to the success of primary and secondary prevention programmes. In view of changes in risk, the demographic changes alone are projected to substantially increase cancer incidence in next few decades.

There are marked disparities within countries and between countries in cancer survival, which partly reflects success of the health system in early detection and effective care. There are some indications that this survival gap is narrowing, suggesting improvements in care in countries with previously poor survival.

Steps being taken by WHO Regional Office for Europe

WHO EURO promotes a comprehensive approach to cancer prevention; early detection; diagnosis and treatment; palliative care. All countries, no matter what their resource level, can mount an effective response to cancer; only their prioritisation will differ. During 2008-09 WHO EURO is working in-depth with 8 countries in development of national Cancer Control Programmes, and at least another 10 countries on strategies for the prevention and control of Noncommunicable diseases (NCDs) including cancer.

Primary prevention, particularly tobacco control, is key. Cancer shares common risk factors with other NCDs such as heart disease and stroke. EURO promotes an integrated approach to prevention across such diseases through the European Strategy on Prevention and Control of Noncommunicable Diseases. As well as through WHO strategies, frameworks and action plans for individual risk factors such as tobacco control, food and nutrition, alcohol, counteracting obesity, physical activity, environment and climate.

Cancer incidence is working in-depth with 8 countries in development and the European Strategy on Prevention and Control of Noncommunicable Diseases. As well as through WHO strategies, frameworks and action plans for individual risk factors such as tobacco control, food and nutrition, alcohol, counteracting obesity, physical activity, environment and climate.

There are now 41 Member States of the WHO European Region that are parties to the Framework Convention on Tobacco Control (WHO FCTC), and a further 5 that have signed. Regarding infectious agents, WHO EURO works with countries and partners to prevent spread of tobacco control, food and nutrition, alcohol, counteracting obesity, physical activity, environment and climate.

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Good palliative care and access to morphine could significantly improve the lives of many. Working closely with its WHO Collaborating Centres and other partners, WHO EURO is promoting a public health approach to palliative care and the rational use of drugs for cancer treatment. A meeting of countries is planned for autumn 2008.

hepatitis B in their national immunisation programmes. In May 2007, WHO EURO held a meeting with policymakers from more than 40 countries to discuss cervical cancer prevention in Europe, and is following up during 2008-09 with support to a number of countries in developing and strengthening cervical cancer prevention programmes. This work is underpinned by the broader work of the office to strengthen health systems in particular to improve quality assurance systems.

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website: www.euro.who.int
Czech Republic (21.1/100 000 in men and 10.2/100 000 in women). In men, other regions with high incidence rates included Estonia (17.3/100 000), Lithuania (14.7/100 000), Hungary (14.7/100 000), Slovakia (13.7/100 000) and Poland (13.5/100 000). Among females, the intermediate high incidence rates were found in Lithuania (8.4/100 000), Estonia (7.1/100 000), Austria (6.8/100 000), Slovakia (6.6/100 000) and Hungary (6.6/100 000). In both sexes, the lowest rates were found in Africa and Asia.

A sharp increase in the incidence of kidney cancer was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.

Regarding time trends for kidney cancer and using data reported in two volumes of the CI5 series from various cancer registries for the calendar periods 1983–1987 and 1993–1997, a sharp increase in incidence was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.

These increasing trends are unlikely to be explained by increasing detection of presymptomatic tumours, and are instead likely to reflect real increases in the numbers of new cases.

Risk factors for kidney cancer

Cigarette smoking. Cigarette smoking has consistently been observed to be a risk factor for kidney cancer, with increased risks compared to never smokers in the order of 50%.[10,11] A number of studies have also demonstrated a dose-response relationship with increasing consumption, with risks of developing kidney cancer for heavier smokers ranging from 2.7 to 4.0 times that of people who have never smoked. The risk appears to decline with increasing years of smoking cessation. Population-attributable risk estimates indicate that cigarette smoking, both past and present, is responsible for approximately 20% of kidney cancer cases among men and 10% of cases.
among women.[12,13] Approximately half of this attributable risk is due to current smoking. The mechanism by which cigarette smoking increases the risk of kidney cancer has not been elucidated, although this clearly represents a major opportunity for prevention.

Obesity. A recent overview of the relationship between obesity and kidney cancer concluded that there was sufficient evidence to conclude that weight gain led to an increased risk of developing renal cancer.[14] The review was based on consistent evidence from four cohort and fifteen case-control studies that reported a steadily increasing risk with increasing weight gain, and indicated that the effects among men and women were similar. Approximately 25% of kidney cancer cases among both men and women are likely to be due to being overweight and obese.[15,16] The mechanism by which obesity causes kidney cancer is unclear, although hormonal changes such as increased levels of endogenous oestrogens might be responsible. Other correlates of obesity, such as hypertension and lack of physical exercise, have not been found to explain this relationship.

Medical conditions and treatment. A history of hypertension has also been consistently linked to kidney cancer.[17]22] The increase in risk appears to occur in a dose-response manner, with even moderately increased blood pressure resulting in an increased risk of kidney cancer. Several studies have tried to separate the effect of hypertension and a possible effect from diuretic and non-diuretic antihypertensive medications. Given the strong correlation between hypertension and the use of these drugs, this has been very difficult. However, evidence that reductions in blood pressure over time may lead to a decrease in kidney cancer risk would appear to indicate that the primary effect is with hypertension and not treatment related.[17] It is also likely to account for a substantial proportion of cases. The attributable risk of reported hypertension or treatment with antihypertensive drugs has been estimated to be 21% overall, and 39% among women.[23] There is also strong evidence for a role of diabetes mellitus in the etiology of kidney cancer. Two large nationwide cohort studies in Sweden and Denmark both identified an increased risk of kidney cancer among patients with diabetes, in the order of 40% among men and 70% among women.[24,25] The risk appeared to be constant with follow-up and was restricted to type II diabetes.

Acquired cystic kidney disease, which occurs in end-stage renal disease, is associated with the development of kidney cancer, as are both kidney stones and kidney infections.[26] Dietary factors. A recent IARC evaluation on the potential cancer preventative effect of diets high in fruits and vegetables reported that higher intake of both fruits and vegetables possibly reduce the risk of kidney cancer.[27] The amount of evidence from prospective cohort studies was, however, sparse, with only two studies reporting on fruit consumption and one on vegetable consumption. A more recent report from the European Prospective Investigation into Cancer and Nutrition (EPIC) reported no overall protective effect for high consumption of fruits and vegetables, although an increased risk at low levels of consumption could not be ruled out.[28]

High protein consumption from meat and dairy products has been associated with chronic renal conditions that may predispose to kidney cancer, although the evidence is inconsistent.[29] The role of coffee and alcohol have also been studied extensively for kidney cancer, although no increase in risk with increased consumption of coffee or alcohol appears to exist.[30] Occupational risk factors. Consistent and strong increases in risk with occupational exposures have not been detected for kidney cancer. Suggestive increases in risk have been observed for a variety of occupations with exposure to polycyclic aromatic hydrocarbons such as coke and coal oven workers, five-lighters, painters, and tar workers.[31] Excess risks have also been reported for occupations with exposure to gasoline and other petroleum products such as refinery workers and gas station attendants, as well as with exposure to asbestos.[32] Exposure to organic solvents, in particular to toluene, has been associated with a specific mutation pattern in the von Hippel-Lindau (VHL) tumour suppressor gene, with the potential for familial cancer within the family. However, evidence for evidence of familial cancer in the VHL is not conclusive.[33] The contribution of these two factors might be greater between siblings as compared with that between parent and child, indicating the possible existence of recessive genetic effects. The largest twin study to date has not been informative.

Fig. 5.19.3 Surgical specimen of a bisected kidney showing a trabecular pattern of abundant clear, lipid-containing cytoplasm, arranged in a haphazard manner. Many areas in the kidneys were replaced by tumour tissue composed of large renal cell carcinoma. Much of the kidney has been destroyed.

Fig. 5.19.4 Clear cell carcinoma of the kidney showing a microscopically uniform proliferation of polygonal tumour cells, with abundant clear, lipid-containing cytoplasm, arranged in a haphazard pattern.
tive due to the lack of consistent trends with kidney cancer [36].

One of the important genetic alterations identified in familial RCC is the aforementioned VHL syndrome, a rare autosomal dominant condition caused by the presence of somatic VHL gene inactivation. Several genes predisposing to non-clear cell RCC have also been characterized, including mutations in the VHL oncogene and hereditary type 1 papillary RCC, and mutations in the BHD gene causing several hereditary subtypes of RCC. Identifying rare genetic variants that result in a high risk of renal cancer is important for understanding the etiology of cancer and potentially identifying high-risk groups among family members; however, such genes explain very little of the familial risk of renal cancer. It is likely that most of the genetic contribution will be due to multiple low- or moderate-risk variants that act in combination with each other or with environmental risk factors. Such genetic variants will not be detected in studies based on multiple cases in individual families, but instead will require large series of cases and controls and genotyping for hundreds of thousands of genetic variants across the genome. These studies are currently in progress.

Avoiding risks

The main known avoidable causes of kidney cancer include cigarette smoking, excess body weight and hypertension, which together are likely to account for up to 60% of all cases of renal tumors. Primary prevention by reducing cigarette smoking, obesity and hypertension are, therefore, the clearest strategies for reducing the incidence of the disease. A substantial proportion of cases is also likely to be related to diabetes, although further information on whether this is an independent risk factor is required. It seems unlikely that these exposures can explain the very large disparities in incidence that occur between different populations, but further important causes of renal cancer are likely to exist. Ongoing studies into the genetic epidemiology of kidney cancer might provide new hypotheses for such exposures, and may also help lead to the identification of high-risk subgroups.

REFERENCES

Bladder Cancer

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Summary
>
> Populations with a high incidence of bladder cancer include those of Mediterranean Europe and Egypt
>
> Survival improves with early age of onset
>
> Tobacco smoking is the most important risk factor for bladder cancer. Occupational exposure to aromatic amines and infection with Schistosoma haematobium are also recognized risk factors
>
> Gene variants of GSTM1 and NAT2 are involved in bladder cancer risk, interacting with smoking status for NAT2

Histological types

The most common type of bladder cancer is urothelial carcinoma, also called transitional cell epithelium [2], although the proportion of this histological type among all cases of bladder cancer varies between countries. For example, 92-99% of bladder cancer cases with available histology in North America, Europe and Australia are urothelial carcinoma, whereas the proportion is 70-80% in Southeast Asia and substantially less than 50% in parts of Africa [3-7]. In general, urothelial carcinoma constitutes a slightly higher proportion of bladder cancer cases in males than in females. Other types of bladder carcinoma include squamous-cell carcinoma and adenocarcinoma. In Africa, squamous-cell carcinoma is the most common type of bladder cancer, resulting from schistosomiasis haematobium infection. Non-invasive urothelial tumours are often considered as bladder cancer in cancer registries. Non-invasive papillary carcinoma has a tendency to recur and to develop into invasive bladder carcinoma [2]. The variable degrees to which such tumours are reported might substantially influence available descriptive data [8].

Stage of diagnosis

Comprehensive data on stage of diagnosis include the US National Cancer Database (NCDB) and the Eindhoven cancer registry. In 2003, 47% of bladder cancer cases diagnosed in the USA were at stage 0, 22% at stage 1, 11% at stage 2, 5% at stage 3, and 6% at stage 4; for 8% the stage was not reported [9]. Bladder cancer data from the Eindhoven cancer registry showed a considerable shift towards lower stage at diagnosis between 1975 and 1989, mainly in favor of stage 0 [10]. This trend was less evident when invasive tumours were considered separately.

Relative survival rates compare the observed survival over a period of time to the expected survival based on background mortality rates. Figure 5.20.1 shows 5-year relative survival rates for patients with bladder cancer diagnosed in 1990-1994, in selected countries, by age at diagnosis (source: Eurocare-3 study). Relative survival rates were based on 104 000 bladder cancer cases diagnosed in Europe in 1990-1994. The prognosis of patients with bladder cancer depends on many factors, including age, stage at diagnosis, and smoking status. The 5-year survival rate for patients diagnosed at age 15-24 years was 61% for patients diagnosed at 75 years or older. In average, Austria showed the highest survival rates, whereas Czech Republic had the lowest rates, with little difference between countries. However, survival rates improved with lower age at diagnosis.

Relative survival rates at 5 years after bladder cancer diagnosis by age at diagnosis

Fig. 5.20.1: 5-year relative survival rates (%) for bladder cancer cases diagnosed in 1990-1994, in selected countries, by age at diagnosis (source: Eurocare-3 study). Relative survival rates were based on 104 000 bladder cancer cases diagnosed in Europe in 1990-1994. The prognosis of patients with bladder cancer depends on many factors, including age, stage at diagnosis, and smoking status. The 5-year survival rate for patients diagnosed at age 15-24 years was 61% for patients diagnosed at 75 years or older. In average, Austria showed the highest survival rates, whereas Czech Republic had the lowest rates, with little difference between countries. However, survival rates improved with lower age at diagnosis.

Relative survival rates at 5 years after bladder cancer diagnosis by age at diagnosis

Fig. 5.20.2: Observed survival rates (%) for bladder cancer cases diagnosed in 1998 in the USA (source: National Cancer Database). Important differences were found between the survival rates for different stages at diagnosis.

Relative survival rates at 5 years after bladder cancer diagnosis by age at diagnosis

Fig. 5.19.3: Risk of bladder cancer among men who smoke relative to never-smokers, according to daily cigarette consumption.
Austria showed the highest survival rates, whereas Wales had the lowest survival rates for bladder cancer.

In men, the highest rates of bladder cancer were found in Spain (33.0/100 000), the Netherlands (32.6/100 000), and Italy (29.8/100 000). In women, the pattern is different: The highest rates were found in Egypt (37.1/100 000), Spain (33.0/100 000), and Italy (29.8/100 000). In men, the highest rates of bladder cancer were reported among workers in industries that involve exposure to aromatic amines, in particular 2-naphthylamine, 4-aminobiphenyl and benzidine, including the rubber and dyestuff industries. Working in aluminium production, azo dye manufacture, coal gasification and magenta manufacture also significantly increases the risk of developing bladder cancer. Other occupations that might increase the risk of bladder cancer include leather workers, painters, hairdressers and barbers, coke production workers, and petroleum refining workers, possibly because of exposure to a variety of chemicals including polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde and solvents. The uncertainty surrounding these occupations is partly due to the difficulty of measuring past exposure to specific chemical agents.

Risk factors for bladder cancer

Tobacco use. The most important risk factor for bladder cancer is cigarette smoking, which is thought to account for approximately 60% of new cases in men and 30% of cases in women in industrialized populations [12,13]. Irrespective of the study design, most of the epidemiological studies found relative risks of 1.5–3.0 in smokers compared to non-smokers, as well as dose-response relationships considering both number of cigarettes smoked and duration of cigarette smoking [12,13]. Cigarette smoking seems to have the same effect in males and females, and in different races/ethnicities. A pooled analysis which combined nontransitional cell bladder cancer data from a number of studies found the same associations as for transitional cell carcinomas [14]. It is likely that smokers of black (tar-cured) tobacco are at a higher risk than smokers of blond (flue-cured) tobacco [12,13], and this likely explains much of the higher incidence rates observed in Spain, Italy and Uruguay, where smoking of black tobacco was common in the past. An immediate decrease in risk (around 40%) of bladder cancer is observed among both men and women who give up smoking, implying a late stage effect in the carcinogenic process, and the decrease in risk continues with time since cessation.

Most of the risk associated with smoking is likely to be due to aromatic amines present in cigarette smoke, including benzidine, 4-aminobiphenyl, naphthylamine and 4-chloroacetanilide.

Occupational risks. A high risk of bladder cancer has been reported among workers in industries that involve exposure to aromatic amines, in particular 2-naphthylamine, 4-aminobiphenyl and benzidine, including the rubber and dyestuff industries [15]. Working in aluminium production, azo dye manufacture, coal gasification and magenta manufacture also significantly increases the risk of developing bladder cancer. Other occupations that might increase the risk of bladder cancer include leather workers, painters, hairdressers and barbers, coke production workers, and petroleum refining workers, possibly because of exposure to a variety of chemicals including polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde and solvents. The uncertainty surrounding these occupations is partly due to the difficulty of measuring past exposure to specific chemical agents.

Dietary factors. Investigations into dietary factors have provided evidence of decreased risks associated with consumption of fruits but not with vegetables [16]. No consistent association has emerged between intake of related micronutrients and reduced risk of bladder cancer [17]. An increased risk with coffee consumption has been reported in some studies [19]. Tobacco use is an important risk factor. Risk assessments based on dietary habits, as the risk is elevated fivefold in smoking women compared to nonsmokers [20]. This relative risk is likely to interact with smoking habits, as the risk is elevated fivefold in smoking probands compared with non-smokers [20]. The enzyme N-acetyltransferase 2 (NAT2) is involved in the detoxification of various bladder carcinogens including acrylamides. The gene encoding NAT2 includes a dominant mutation.
that results in slow metabolism of arylamines and is associated with an increased risk of bladder cancer of around 40% [21]. This increased risk of developing bladder cancer appeared to be stronger in cigarette smokers (particularly black tobacco smokers) than nonsmokers, and a joint effect between NAT2 slow acetylators and heavy smokers was observed, translating to a much higher risk of developing bladder cancer than exists in nonsmokers who do not possess the NA202 mutation. The GSTM1 null genotype also increases the risk of bladder cancer, although it has no interaction with smoking status [21].

Pharmacological-related risk factors

A consistent relationship has been observed between use of phenacetin-containing drugs and bladder cancer, with relative risks varying from 2.4-fold to over 6-fold [22]. Cyclophosphamide, an alkylating agent which has been used to treat both malignant and non-malignant diseases, has also been linked to bladder cancer. Studies based on cohorts of heavily exposed subjects.

Infection

Infection with Schistosoma haematobium is prevalent throughout Africa and is associated with an increased risk of bladder cancer of approximately 2- to 6-fold [23,24]. Infection occurs via contact with water contaminated by cercariae. Under optimal conditions, infection with Schistosoma infection through avoidance of contaminated water is important in endemic areas. No effective screening approach is available for bladder cancer.

Bladder cancers associated with Schistosoma infection are mainly of the squamous cell type. The infection is responsible for an estimated 50% of bladder cancer cases in some parts of Africa, and about 3% of cases overall [25].

Avoiding risks

Regarding prevention, past changes in industrial processes have undoubtedly led to a decrease in some occupational exposures. Regarding prevention, past changes in industrial processes have undoubtedly led to a decrease in some occupational exposures.

REFERENCES

5.21 Prostate Cancer

Summary

- Prostate cancer is a very common, and while the incident rate is rising quickly, in many countries the mortality rate has started to fall.
- While aggressive testing with Prostate specific antigen (PSA) has contributed to this decline in mortality, it does not explain all of the effect.
- The etiology of prostate cancer remains obscure. Tobacco smoking and alcohol consumption are not associated with prostate cancer risk. There is weak evidence of an association with certain dietary practices although the attributable fraction is small.
- Chemoprevention studies have been conducted using finasteride, and a major randomized trial of Selenium and Vitamin E is on-going.
- Despite many large prostate cancer families, with cases spreading over many generations, there has not been a major gene found for this disease.

Geographical variation

- The Nordic countries (Denmark, Finland, Sweden and Norway) provide some important clues to explain this situation. Incidence rates were increasing and similar in the Nordic countries during the 1980s. Around 1990, a more rapid incidence increase began in all Nordic countries except Denmark, where an increase was seen 5 years later. In 2001, incidence rates in Denmark were half of those seen in the other Nordic countries, but mortality rates varied only marginally among countries. Mean annual declines in prostate cancer mortality of 19% and 14% were observed from 1996 to 2004 in Finland and Norway, respectively. During the same period, mortality rates levelled off in Iceland and Sweden but continued to increase in Denmark.

Comparisons between trends in incidence and mortality in countries where both are available demonstrate a tendency for large increases in incidence accompanied by little change, and perhaps subsequent declines in mortality rates (Figure 5.21.4).

- The rapid increase in incidence during the early 1990s coincided with the introduction of the prostate specific antigen (PSA) test and conveys little information about the occurrence of potentially lethal disease. Mortality rates, however, have recently stabilised or declined in countries where PSA testing and curative treatment have been commonly practised since the late 1980s. Although other explanatory factors may be in operation, these trends are consistent with a moderate effect of increased curative treatment of early diagnosed prostate cancer and improved treatment of more advanced disease.

In order to quantify the plausible contribution of PSA screening to the nearly 20% decline in the United States prostate cancer mortality rate observed during the 1990s, two mathematic modelling teams independently projected disease mortality in the absence and presence of PSA screening using the same data source, the Surveillance, Epidemiology and End Results (SEER) registry [5]. The teams projected similar mortality increases in the absence of screening and decreases in the presence of screening after 1985. By 2000, the models projected that 43% (Fred Hutchinson Cancer Research Center) to 70% (University of Michigan) of the decline in prostate cancer mortality could be plausibly attributed to the stage shift induced by screening. While PSA screening may account for much, but not all, of the observed drop in prostate cancer mortality, other factors, such as changing treatment practices, may also have played a role in improving prostate cancer outcomes.

Etiology and genetics

- The etiology of prostate cancer remains shrouded in mystery [6]. An IARC Monograph Working Group found no association with Tobacco Smoking [7], and this was confirmed subsequently [8]. Another IARC Monograph Working Group found no association with Alcohol Consumption [9], and this too was confirmed subsequently [10].

There appears to be little association with macronutrient intake and prostate cancer risk. Dietary fat and meat as potential risk factors for prostate cancer have been the focus of many
epidemiologic investigations, and findings from recent studies in particular have been inconsist-
tent. Analysis of the information in the Multiethnic Cohort Study found that intake of different types of fat (total, saturated, mono-unsaturated or polyunsaturated), n-6 fatty acid, cholesterol, various meats and fats from meat showed no association with overall prostate cancer risk or with non-localised or high-grade prostate cancer. There was little evidence of any relation of n-6 fatty acid intake with prostate cancer risk within any of the 4 racial/ethnic groups (African Americans, Japanese Americans, Latinos and whites). The overall findings from this large cohort study of ethnically diverse populations gives no indication that intake of n-6 fat and meat substantially affects prostate cancer risk [11].

Omega-3 fatty acids are purported to reduce the risk of cancer although studies have reported mixed results. A meta-analysis of 28 articles from prospective epidemiological studies investigated the risk of cancer with intake of omega-3 fatty acids. For prostate cancer, there was no evidence of association. Dietary supple-
mentation with omega-3 fatty acids is unlikely to prevent cancer [12].

There are some potential relationships which still need to be clarified. Inverse associations with prostate cancer have been observed for allium vegetables and weak inverse assos-
ciation with omega-3 fatty acids is unlikely to reduce the risk of cancer [11].

Calcium and dairy foods in relation to prostate cancer were examined in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study [14].

During up to 6 years of follow-up (n=301 804), the authors identified 10 180 total prostate cancer cases (87 584 non-advanced, 14 426 advanced and 1 780 fatal cases). Total and sup-
plemental calcium were unrelated to total and non-advanced prostate cancer. These findings do not provide consistent support for the hypoth-

e that calcium and dairy foods increase pros-
tate cancer risk.

Several studies have reported an inverse asso-
ciation between tomato and/or lycopene intake and the risk of some types of cancer, prompting two petitions to the US Food and Drug Administration (FDA) for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer, notably prostate cancer. The FDA review found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colo-rectal, gastric, breast, ovarian, endometrial or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of prostate, lung, colorectal, breast, ovarian, and pancreatic cancers [15].

Statins are commonly used cholesterol-lowering drugs that have prognostic and anti-metastatic activities that could affect cancer risk or progression. Results from previous epidemiologic studies of the association between statin use and cancer have been inconsistent. Platz and co-workers (2008) investigated the association of statin use with total and advanced prostate cancer, the latter being the most important endpoint to prevent in an ongoing prospective cohort study of 34 989 US male health professionals. Use of statin drugs was not associated with risk of pros-
tate cancer overall but was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer [16].

Some recent epidemiologic studies have failed to confirm positive associations between insu-

dulin-like growth factor-I (IGF-I) and the risk of prostate cancer observed in earlier studies, but have reported suggestive evidence for a posi-
tive association between IGF-1-binding protein-3 (IGFBP-3) and prostate cancer risk, a result contradicting the earlier assumption that high levels of IGFBP-3 would be protective against prostate cancer. The association between IGFBP-3 and IGFBP-3 and prostate cancer risk was determined by measuring the two peptides in plasma samples collected at baseline in a prospective cohort study of 17 049 men. The risk of prostate cancer was not associated with baseline levels of IGFBP-3 or the molar ratios (IGFBP-3/ IGFBP-3) (all odds ratios 0.82–1.08; Phrend 0.20), whereas the risk increased with baseline levels of IGFBP-3 (Phrend = 0.008), the hazard ratio (HR) associated with a doubling of the concentration of IGFBP-3 being 1.70 (95% CI 1.15–2.52). The HR for quartile 4 rela-
tive to quartile 1 of IGFBP-3 was 1.49 (95% CI 1.17–2.09). The HR did not differ by tumor aggressiveness or age at onset [all Ps < 0.04] (95 levels of IGFBP-3 and IGFBP-3 were associated with an increased risk of prostate cancer [17].

Attention has recently focused on the metabolic syndrome, characterised by insulin insensitivity, central obesity, dyslipidaemia and hypertension, on the risk of prostate cancer. It is recognised as a risk factor for cardiovascular disease in men. By the time metabolic syndrome is diagnosed, however, most men already have entrench ed cardiovascular disease [18]. One third of men with type 2 diabetes mellitus and cardiovascular disease are treated as testosterone deficient. Emerging evi-
dence suggests that testosterone therapy may be able to reverse some aspects of metabolic syndrome [18], although the impact of such a strategy on prostate cancer risk remains an open question.

Endogenous androgens have long been suspected as being involved in the etiology of prostate cancer; although epidemiologic studies have failed to support the hypothesis that circulating androgens are positively asso-
ciated with prostate cancer risk. Some recent studies have even suggested that high testo-


crine levels might be protective particularly against aggressive cancer. In a large Australian study, high levels of testosterone and adrenal androgens have been associated with reduced risk of aggressive prostate cancer but not with non-aggressive disease [19].
Despite the large number of families with prostate cancer in brothers and across multiple generations, there is no gene which has been identified for prostate cancer with similar significance to those genes (BRCA1 and BRCA2) discovered some years ago for breast cancer. However, the search goes on and there have been some very interesting developments reported recently [20-22].

**Prevention of prostate cancer**

The dramatic international variation in prostate cancer incidence and mortality rates suggests that changeable environmental factors exert an influence [23]. This has prompted a search for ways to prevent the disease. Epidemiologic studies have reported variations in the strength and consistency of the evidence that dietary factors such as the carotenoid lycopene, selenium, vitamin E and high intake of fat have roles in prostate cancer risk. Impediment of androgen suppression lowers the risk of prostate cancer [24]. 5-alpha-reductase inhibitors have been shown to decrease prostate size by decreasing androgenic stimulation to the prostate. However, less developed interventions include vitamin D supplements and modification of diet. Any manipulation to decrease one’s risk of prostate cancer will by necessity have to be given to a large population to decrease one’s risk of prostate cancer [24].

Prevention of prostate cancer would have a major impact on disease-associated cost, morbidity and mortality for a large segment of the population. A major advance in prevention of prostate cancer came in 2003 with the publication of the Prostate Cancer Prevention Trial [25] which demonstrated that use of finasteride is associated with a 23% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years with normal digital rectal exam and initial prostate specific antigen <3.0 ng/ml. Use of finasteride was associated with a slightly higher risk of Gleason sum 7-10 tumours, some sexual side effects, and fewer urinary symptoms.

A substantial body of new molecular evidence supports the existing body of clinical and epidemiologic data leading to testing of vitamin E and selenium as preventive agents in men at risk for prostate cancer [25]. A large chemoprevention trial has been organised. SELECT is a randomised, prospective study designed to determine if selenium and vitamin E can reduce the risk of prostate cancer among healthy men. Preliminary epiregional and Phase II data suggest that both selenium and vitamin E have potential efficacy in prostate cancer prevention [26]. The experience of the Prostate Cancer Prevention Trial and the rapid accrual of SELECT during its first year demonstrate the interest and dedication of healthy men at risk for prostate cancer. A total of 32,400 men are planned to be randomised in SELECT, enrollment began in 2001 with final results anticipated in 2013 [26].

**REFERENCES**

In most areas of the world, the incidence of thyroid cancer among women is in the range 2.5–3/100 000; that in men is 1.2–2.0/100 000. High-risk areas (incidence >5/100 000 in women) include Central America, Japan and the Pacific islands. International comparisons, however, are complicated by possible differences in diagnostic procedures. The most common thyroid neoplasm (50–80% of the total) is papillary carcinoma, followed by follicular carcinoma (10–40%) and medullary carcinoma (5–15%).

Survival from thyroid cancer is very good (over 85% 5-year survival rate in Europe and North America), resulting in low mortality rates in iodine-rich areas (below 1/100 000 in women and 0.6/100 000 in men in most areas of the world).

In most countries, incidence rates have been stable or have been slowly increasing (<1%/year) during the last decades; mortality rates have steadily declined, likely because of improved treatment.

Ionizing radiation is the main established risk factor for thyroid cancer (2). The carcinogenic effect seems greater for exposures before age 5 than subsequently. The pooled analysis of studies of individuals irradiated in childhood for medical conditions and atomic bomb survivors resulted in a summary excess relative risk of 4.4 (95% CI 1.9–10) per 10 000 person-years Gy. Several studies have been published on adults exposed to 131I for medical purposes. Although those studies suggest an increased risk, their interpretation is made complex by the fact that those patients were treated because of thyroid diseases. 131I was the main exposure resulting from the accident of the Chernobyl nuclear reactor in 1986; since then, an increased incidence of thyroid cancer has been reported among children living in the contaminated areas of Belarus and Ukraine. Iodine supplementation in the immediate period following the Chernobyl accident has been shown to protect against thyroid cancer (3). Studies of occupational exposure to low-level ionizing radiation, typically in the nuclear industry, have failed to show an increased in mortality from thyroid cancer.

An association between thyroid cancer and a history of benign thyroid diseases has been observed in most studies, although the strengths of these associations have varied across studies. Because thyroid cancer incidence rates in women are consistently 2–3 times higher than those in men, some studies in various geographic areas have focused on women in an attempt to identify hormonal factors that might explain this excess. However, findings related to menstrual and reproductive factors as well as to exogenous hormone use have been inconsistent, as have findings related to diet and to anthropometric and lifestyle factors.

In a pooled analyses, goiter and benign nodules/adenomas were shown to be the strongest risk factors for thyroid cancer apart from radiation in childhood. In women, the pooled odds ratios (OR) were 5.9 for goiter and 3.8 for benign nodules/adenomas. Elevated risks were observed for men and women and in relation to both major histologic types (papillary/follicular). No significant heterogeneity was seen across geographic areas or across studies. The excess risk was greatest within 2–4 years prior to thyroid cancer diagnosis, but an elevated OR was present 10 years or more before cancer. Prior hyperthyroidism was related to a small, statistically non-significant increase that was reduced after allowance for a history of goiter. A history of hypothyroidism was not associated with cancer risk (4).

Elevated levels of thyroid-stimulating hormones are associated with thyroid growth and possibly thyroid cancer. The evidence of an association between iodine deficiency (and presence of endemic goiter) and thyroid cancer is equivocal. Studies from central and southern Europe support such an association, which was not confirmed in studies from northern Europe and North America. It is possible that iodine deficiency increases the risk of follicular thyroid cancer, while the papillary type is linked to iodine-rich diet.

Among other risk factors considered, pooled analyses have focused only on fish/seafood (5) and cruciferous and other vegetables (6). Fish was not associated with thyroid cancer in all studies combined, but there was a suggestion of reduced risk in endemic goiter areas. It was reassuring to note that high levels of fish consumption did not appreciably increase risk in iodine-rich areas, and fish consumption was inversely related to thyroid cancer risk in endemic goiter areas. Cruciferous vegetables, which contain goitrogenic substances as well as several constituents which can inhibit carcinogenesis, were weakly and non-significantly related to reduced risk of thyroid cancer.

A strong genetic component has been shown for medullary carcinoma: about 20% of these neoplasms are assigned within an autosomal dominant gene, with penetrance close to 100% (7). It can also be associated with other endocrine neoplasms within the multiple endocrine neoplasia syndromes (MEN type 2). These include medullary thyroid carcinoma and hyperparathyroidism (MEN2A), resulting from mutation in the RET/PTC on chromosome 10q11.2; medullary thyroid carcinoma and hyperparathyroidism (MEN2B), resulting from mutation in the RET proto-oncogene, or mucosal neuromas of the lip and gastrointestinal tract (MEN 2B, [2]). Familial factors play a role in papillary carcinoma, too. Among the genes associated with papillary thyroid cancer are the ret and the APC gene.

The prospects for prevention of thyroid cancer are made complex by the limited understanding of its etiology, with the exception of relatively rare high-risk conditions, such as childhood exposure to ionizing radiation and high-risk families.
In females, there was the same pattern of generally higher rates in Austria and adjacent countries, and mostly lower-than-average rates in much of western Europe. However, it must be kept in mind that all these mortality rates were very low in absolute terms [1].

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In males, there appears to be an aggregation of high rates in the centre of Europe, the neighbouring countries of Austria, central and southern Germany, Switzerland and the west of the Czech Republic. There were generally low rates in the United Kingdom, Spain, Portugal, France and Greece [1].
Summary

- Tumours of the nervous system account for less than 2% of all malignancies (about 175,000 cases per year worldwide), the incidence does not vary markedly between regions or populations.
- The incidence of these tumours tended to increase in most cancer registration areas over the last few decades, most probably because of better reporting by cancer registries and improvement in non-invasive imaging technologies.
- The nervous system is frequently involved in inherited tumour syndromes, including neurofibromatosis (NF1/NF2, germline mutations), von Hippel-Lindau disease (VHL, neuroepithelial TSC1/TSC2) and Li-Fraumeni syndrome (p53).
- Neurofibromas are the most common brain tumours and mainly affect adults. These tumours are surgically incurable and largely resistant to radiation and chemotherapy; only 3% of patients survive longer than 3 years.
- Embryonal tumours, including cerebellar medulloblastomas, retinoblastomas and peripheral neuroblastoma, predominantly afflict children, ranking second amongst primary neuronal tumours, including cerebellar medulloblastomas (also called medulloblastomas) and tumours of the spine and the peripheral nerves.

Although not very frequent, brain tumours contribute significantly to morbidity, often affect children and overall have a poor prognosis. Due to marked resistance to radiation and chemotherapy, the prognosis for patients with glioblastoma is very poor. The majority of patients die within 9–12 months, and lesser than 3% survive more than 3 years.

Epidemiology

- Data on the descriptive epidemiology of nervous system tumours are difficult to interpret, because many studies include both benign and malignant tumours.
- The age distribution of brain tumours is bimodal, with a peak incidence in children and a second larger peak in adults aged 45–70. In most developed countries, brain tumours are the 12th most frequent cause of cancer-related mortality in men.

The incidence of brain tumours is slightly higher in men than in women; the male:female ratio is approximately 1:3 for gliomas and 0.6:1 for meningiomas. There is a geographical variability in the incidence of brain neoplasms: rates in men are 6 to 8/100,000 in most countries from the Americas, Europe and Oceania, and in the range of 2 to 3/100,000 in Africa and Asia. In the USA, rates of gliomas are 20–30% higher in Whites than in other ethnic groups, while rates of meningiomas are slightly higher in Blacks.

During the last decades, incidence and mortality from brain tumours have increased in most developed countries, mainly in the older age groups. The increase in the incidence was confirmed in the late 1970s and early 1980s and coincided with the introduction of improved diagnostic methods (3). After 1983 and more recently during the period of increasing prevalence of mobile phone users, the incidence has remained relatively stable for both men and women. Analysis of temporary trends in introduction of medical technologies and improved diagnosis of brain tumours shows that most if not all of the increase is attributable to (i) the introduction of high-resolution neuroimaging (e.g. CT Scan, Magnetic Resonance Imaging, PET Scan) in the last decades, (ii) variations in diagnostic and reporting procedures; and (iii) the brain as a frequent site of metastases, principally from breast and lung cancers, because with more primitive imaging modalities, brain metastases may have been misclassified as primary brain tumours.
Etiology

During the last few decades, incidence and mortality from brain tumours have increased in most developed countries. However, differences in the descriptive epidemiology of brain cancers, including time trends, can be partially due to variations in diagnostic and reporting procedures.

Ionizing radiation is the only established non-genetic risk factor for brain tumours. It causes all three major types of central nervous system tumours, but the association is stronger for meningiomas and acoustic tumours (as in the case of jobs with exposure to loud noise) as a risk factor for acoustic schwannoma. Nitrosamine compounds, in particular nitrosoureas, are potent experimental brain carcinogens, and are part of tobacco smoke. The evidence of an etiological role of tobacco smoking, either active or passive (i.e. childhood exposure to tobacco smoke) in humans is inconclusive. Several other lifestyle, environmental (e.g. occupational exposures, use of pesticides) and medical (e.g. allergy; conditional factors have been suggested to play an etiological role in brain cancer, but the evidence is not sufficient to draw a conclusion.

Some studies have suggested an increased incidence of central nervous system tumours associated with certain occupations, including farming, fire-fighting, metalworking and the rubber and petrochemical industries, and with those who work as anatomists, pathologists and embalmers, but most of these reports have not been confirmed and causative agents have not been identified. Suggestions that radio-frequency radiation generated by mobile phones and microwave telecommunications may play a role in the etiology of malignant gliomas remain to be substantiated.

Pathology and genetics

The WHO classification of tumours of the nervous system contains more than 50 clinicopathological entities with a great variation in morphological features and clinical behaviour. The very limited knowledge about the etiology of tumours of the central nervous system offers scarce resources for an effective preventive strategy.
Chapter 5.23: Tumours of the Nervous System

5.23.1 Tumours of the Nervous System

5.23.2 Familial Tumour Syndromes

5.23.3 Biological Behaviour, Response to Therapy and Clinical Outcome

5.23.4 Cancer of the Eye

Syndrome | Gene | Chromosome | Nervous system | Skin | Other tissues
--- | --- | --- | --- | --- | ---
Neurofibromatosis 1 | NF1 | 17q11 | Neurofibromas, MPNST, optic nerve gliomas, astrocytomas | Café-au-lait spots, axillary freckling | Café-au-lait spots, axillary freckling
Neurofibromatosis 2 | NF2 | 22q12 | Bilateral facial schwannomas, peripheral schwannomas, meningiomas, neurofibromas, spinal ependymomas, astrocytomas, micro-hemangiomas, cerebral calcifications | Facial nerve palsy, retinal haematomas | Facial nerve palsy, retinal haematomas
von Hippel-Lindau | VHL | 3p25 | Haemangioblastomas | - | Haemangioblastomas
Tuberous sclerosis | TSC1 TSC2 | 9q34 16p13 | Subependymal giant cell astrocytoma, cortical tubers | Cataracts, angiofibromas ("adenoma sebaceum") | Cataracts, angiofibromas ("adenoma sebaceum")
Li-Fraumeni | p53 | 17p13 | Astrocytomas, glioblastomas, medulloblastomas | - | Breast carcinoma, bone and soft tissue sarcomas, adrenocortical carcinoma, leukemia
Cowden | PTEN (MMAC1) | 10q23 | Dyplastic gangliocytoma of the cerebellum (Sutton-Duclos), megacystic kidney | Multiple ichthyomas, fibromas | Multiple ichthyomas, fibromas
Trenton | APC | 5q21 | Medulloblastoma | - | Colorectal cancer
Mainzer | NHL1 | 3p21 | Glioblastoma | Café-au-lait spots | Glioblastoma
MPM2 | 7p22 | Medulloblastoma | Multiple basal palmar and plantar pits | Low cysts, ovarian fibromas, skeletal abnormalities | Multiple basal palmar and plantar pits
Naevoid basal cell carcinoma syndrome (Gorlin) | PTCH | 9q31 | Medulloblastoma | Multiple basal palmar and plantar pits | Multiple basal palmar and plantar pits

Table 5.23.2 Major familial tumour syndromes involving the nervous system

Fig. 5.23.3 Pedigree of a family with Li-Fraumeni syndrome, caused by a germline mutation in codon 248 of the p53 tumour suppressor gene. Blood samples of affected family members were examined for mutations. In women, the second allele is usually deleted. The family shows a marked clustering of brain tumours.

Cancer of the eye

Neoplasms of the eye are rare, the incidence is below 1/100,000 in all regions of the world, with the exception of Central and Southern Africa. The main histological types are squamous cell carcinoma arising from the conjunctiva, retinoblastoma, which arises in children and is relatively common in Africa, and uveal melanoma, which is the main adult type outside of Africa. Solar radiation and solar elastosis are causes of conjunctival carcinoma, while the role of sun exposure in uveal melanoma is controversial. For instance, in populations where a sustained increase in cutaneous melanoma incidence is observed, since several decades, the incidence of uveal melanoma remains quite constant. About 50% of cases of retinoblastoma are caused by an inherited mutation in the RB1 gene.
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Lymphoma

Summary

- Hodgkin lymphoma occurs mainly in young adulthood and then at old age. The main known cause of this disease is infection with Epstein-Barr virus.
- Non-Hodgkin lymphomas are a heterogeneous group of neoplasms with different causes and clinical behaviour. Their incidence has risen in recent decades but the increase has stopped since 2000: the causes of this trend are not well known.
- Severe immunodeficiency, such as that occurring in AIDS patients, leads to non-Hodgkin lymphomas. Loss of some of the immune function allows these tumours to develop, but a causal link has not been confirmed.
- Several environmental factors, such as pesticides, have been suspected to cause lymphomas, but a causative link has not been established.

Lymphomas are neoplasms which originate from the lymphopoietic system. Traditionally, lymphomas have been divided between B and T cell lymphocytes, with over 20 different clinicopathological entities. Importantly, this classification incorporates all lymphoproliferative diseases, including multiple myeloma, B-cell acute lymphoblastic leukaemia, Burkitt lymphoma and HL.

Hodgkin lymphoma

The incidence of HL varies from low-incidence populations, with rates lower than 1/100,000, including areas of Eastern and Southern Asia and of Sub-Saharan Africa, to high-incidence populations, with rates in the order of 3/100,000 found in the USA and some European countries, as well as in Jewish Jews [3]. The incidence in men is consistently higher than in women, with a ratio of between 1.5 and 2. The incidence has been relatively stable over time and may even be declining. The age of onset of HL shows a bimodal distribution in high-resource populations, with a first peak between age 15 and 35 and a second peak after the age of 60. In low-resource countries the first peak tends to be observed during childhood. This bimodal distribution suggests that the HL includes at least two different entities.

Viral infections play an important role in the etiology of HL. [4]. Its onset may be related to decreased or delayed exposure to infectious agents during childhood, as indicated by its association with having fewer siblings, living in single-family houses, and early birth order.

Infection with Epstein-Barr virus (EBV) is associated with the majority of HL cases. EBV is ubiquitous throughout the world, with 80–100% of individuals being infected by age 30 [5]. In low-resource countries infection occurs earlier in life, whereas in high-resource countries infection is often delayed until adolescence. The EBV genome is present in about 50% of the lymphoma cells, and another EBV-related condition, infectious mononucleosis, is associated with a moderately elevated risk of development of HL. Serological studies indicate that patients with HL can be distinguished by a characteristic antibody profile to EBV.

The most recent World Health Organisation classification of lymphoma [6] characterises two main groups of lymphomas with different causes and clinical behaviour. Their incidence has risen in recent decades but the increase has stopped since 2000: the causes of this trend are not well known.

- Several environmental factors, such as pesticides, have been suspected to cause lymphomas, but a causative link has not been established.

World Map 5.24.1

Infection with HL occurs at increased familial risk of HL and NHL, and several environmental factors, such as tobacco smoking, alcohol consumption, and exposure to ionizing radiation, have been suggested as risk factors.

- Several environmental factors, such as pesticides, have been suspected to cause lymphomas, but a causative link has not been established.

The causes of NHL have been used to separate different subtypes. Infections with EBV and HCV. Human T-cell lymphotropic virus 1 (HTLV-1) and human herpes virus 8 (HHV-8) are also known to be associated with NHL.

Infectious agents associated with lymphoma include EBV, HCV, HTLV-1, and HHV-8. EBV is associated with NHL in high-resource countries, with rates in the order of 3/100,000, whereas in low-resource countries infection occurs earlier in life. Infection with EBV is particularly prominent in lymphomas of the gastrointestinal tract, including gastric lymphoma.

Non-Hodgkin lymphoma

The incidence of NHL is higher than that of HL. Rates of over 10/100,000 are reported from the USA, Australia, Western Europe, and from Israel and the West Asia, while low rates of less than 5/100,000 are reported in Southern and Eastern Asia and parts of Africa [3]. Men have a 1.5–2 fold higher incidence than women. There is a strong geographical variation for some lymphoma subgroups. For example, Burkitt lymphoma is common among children in eastern Africa, and rates of adult T-cell leukaemia/Lymphoma are higher in southern Japan and parts of Africa. The trend by age of NHL, on the other hand, shows a steady increase with age in most populations. Exceptions are the populations in which a specific type of lymphoma predominates, such as Burkitt lymphoma in children.

An increase in the incidence of NHL was observed in most high-resource countries until the end of the 20th century. The rate of increase was approximately 45% per year in most populations. In the last few years, however, this increase has levelled off. The reasons for the increase in NHL incidence have been widely discussed, and it is likely that improvement in diagnostic procedures during the 1980s and 1990s explains part of it, in particular in the elderly. However, it is accepted that the trend also reflected a real increase in the number of cases, the causes of which are not known.

The current knowledge of potential risk factors for NHL is limited [6]. However, there is strong evidence that altered immunological function, either immunosuppression or immunosuppression, entails an increased risk of NHL. For example, immunosuppressed renal transplant patients have a risk 30 times higher for developing NHL compared to the general population. The incidence of lymphomas that develop in immunosuppressed patients share common characteristics. They are generally high-grade B-cell lymphomas and are more likely to be extracranial and of worse prognosis. Lymphomas have also been reported for a variety of other conditions which are either autoimmune in nature, or require immunosuppressive treatment, including Sjögren syndrome and systemic lupus erythematosus.

EBV is particularly prominent in lymphomas developing in immunosuppressed patients, and also in Burkitt lymphomas. The relationship with other forms of lymphomas is, however, unclear. Regarding NHL, HIV is 60 times more frequent among patients with AIDS than in the general population [7]. Around 3% of patients with AIDS, developed NHL, represents a small contribution to the overall incidence of NHL except in populations with a high HIV prevalence such as regions of Sub-Saharan Africa. AIDS-related lymphomas tend to be high-grade B-cell lymphomas.

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Highly penetrant genetic predisposition to lymphomas is not very common but includes ataxia-telangiectasia, Wiskott-Aldrich syndrome and hypogammaglobulinemia. Approximately 25% of the patients with rare forms of genetic immunodeficiency will develop a lymphoma.

The increasing recreational exposure to ultraviolet radiation in some populations and the decrease in the atmospheric ozone layer have been related to the observed increase in the incidence of NHL, but this hypothesis has not been supported by analytical studies, which, if anything, showed a decreased risk of lymphoma for high UV exposure [8].

Exposure to pesticides has been associated with NHL risk in studies conducted both on manufacturing workers and applicators in agriculture [9]. The results, however, are not very compelling, with the possible exception of phenoxy herbicides and chlorophenols. This effect might be due to contamination with dioxin. Farming as an occupation has also been weakly associated with lymphoma risk. Organic solvents represent another group of chemicals whose association with lymphoma risk has been widely investigated, without conclusive findings.

**Human T-cell lymphotropic virus-1, and possibly human T-cell lymphotropic virus-2, appear to be associated with the rare adult T-cell leukaemia/lymphoma, a disease entity with strong geographical clustering in Japan, the Caribbean and parts of Africa. Transmission of the human T-cell lymphotropic virus is similar to that of HIV, involving vertical (mother-to-child) transmission, sexual contact or blood transfusion.**

A familial aggregation is present for lymphoma: the risk of the disease among first-degree relatives of cases has been reported in the order of 1.5–4. However, the risk seems higher for siblings of the same sex, suggesting a role of shared environmental factors rather than genetic.

**European Map 5.24.1** In men, the highest national mortality rates from Hodgkin lymphoma were in Lithuania (0.4), Poland (0.4), Estonia (0.3), Latvia (0.2), Austria (0.2), the Czech Republic (0.2) and Greece (0.2). The lowest national rates were recorded in Sweden (0.3), Norway (0.3), France (0.3) and Switzerland (0.3). No deaths were recorded from this cause among males in Iceland during the period [1].

**European Map 5.24.2** In females, the highest mortality rates from Hodgkin lymphoma were in the Czech Republic (0.8), Austria (0.8), Lithuania (0.8), Latvia (0.8), Estonia (0.7) and Poland (0.7). Rates in most of the other countries were 0.2 to 0.6 per 100 000 [1].

**European Map 5.24.3** In men, there were high regional mortality rates from Non-Hodgkin lymphoma in the south of Norway, Sweden and Finland, in the United Kingdom and in northern Italy. There were aggregations of low rates in central and southern Europe [1].

**European Map 5.24.4** The broad geographical pattern of the variability in mortality rates from Non-Hodgkin lymphoma was very closely similar to that for men, with high regional rates in parts of Norway, Sweden and Finland, in the United Kingdom, and in southern Italy. There were aggregations of low rates in central and northern Europe [1].
MATURE B-CELL NEOPLASMS – The most important types are:

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- MALT lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK-cell leukaemia
- Systemic EBF-associated T-cell lymphoproliferative disease of childhood
- Burkitt lymphoma
- Anaplastic large cell lymphoma (ALK positive)
- Anaplastic large cell lymphoma, ALK negative

HODGKIN LYMPHOMA

- Nodular sclerosis classical
- Lymphocyte-rich classical
- Mixed cellularity classical
- Lymphocyte-depleted classical

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Leukaemias

Summary

> Recognized risk factors for leukaemias are ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure. However, the etiology of most leukaemias is not known. Familial clustering is seen in 5% of cases of chronic lymphoblastic leukaemia.
> Chronic myeloid leukaemia was one of the first cancers to be linked to an acquired genetic abnormality, translocation (9;22), known as the Philadelphia chromosome.
> Due to differing access to treatment, there is considerable global variation in survival. Among men in the USA and Western Europe, 5-year survival is at 43%, in Eastern Europe 29%, Japan 25%, India 19%, South America 24%, Thailand 15%, and in sub-Saharan Africa 14%.
> In recent decades, there has been considerable progress in the development of treatments for leukaemia. In areas with good access to these treatments, 5-year survival in children has reached 80%.

Leukaemias arise in one of the types of white blood cells. They may arise in lymphoblasts, which are lymphoid cells in the early stage of development, resulting in a rapid onset illness termed acute lymphoblastic leukaemia. Alternatively, when the neoplasm involves mature cells, it is termed chronic lymphocytic leukaemia and is usually more indolent. In the WHO classification, chronic lymphocytic leukaemia is part of NHL [2]. Leukaemias may also be granulocytic in origin, occurring in either young myeloblastic cells resulting in acute myeloid leukaemia, or in the mature granulocytes resulting in chronic myeloid leukaemia.

There also exist several rarer varieties including monocytic and hairy cell leukaemias.

Epidemiology

Acute lymphoblastic leukaemia is the most common childhood cancer, while over 80% of lymphoid leukaemias occurring in adulthood are chronic lymphocytic leukaemia. Incidence rates for chronic lymphocytic leukaemia are difficult to interpret because it is often diagnosed incidentally in the course of evaluating other conditions. Differences in medical care may therefore substantially bias incidence data. Bearing this possible ascertainment bias in mind, the highest rates of lymphoid leukaemias are observed in areas of Canada, the USA, Western Europe and Oceania, and the lowest are in South America, the Caribbean, Asia and Africa. Rates tend to be lower in females although the ratio is usually less than 2. Some increases in leukaemia over time have been reported, although the extent to which these represent real increases in incidence is uncertain. Some increasing incidence trends have been reported for both chronic and acute myeloid leukaemia, although these are not consistent and may simply reflect changes in clinical practice.

Etiology

Although the cause of most leukaemias is not known, there is consistent evidence for three factors, namely ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure [3]. Leukaemia was the first cancer to be linked to ionizing radiation after the atomic bombings in Hiroshima and Nagasaki. Excess incidences have been observed for acute lymphoblastic leukaemia, acute myeloid leukaemia and chronic myeloid leukaemia, but not for chronic lymphocytic leukaemia. Cohorts of patients who have received radiotherapy for both malignant and non-malignant conditions have also been found to have an increased risk of leukaemia, usually myeloid.

Whether there is any increased risk of leukaemia from other sources, including low-level diagnostic radiation, occupational exposure in the nuclear industry for workers and their offspring, or nuclear test explosions, is more controversial. Part of the problem lies in extrapolating from high acute doses experienced in particular circumstances like atomic bombing, to small or chronic exposures in other instances. There is no consistent evidence that exposure to electromagnetic fields is associated with leukaemia risk (see Chapter 2.12).

Some leukaemias are also related to, or induced by therapy for a prior malignancy, most notably Hodgkin lymphoma. Such patients have a 20–40 fold increased risk of leukaemia, most of which are acute myeloid leukaemia. The risk appears to be related to chemotherapy including alkylating agents (the majority being combination therapy with MOPP (mustargen, oncovin (vinristine), procarbazine, prednisone)). The effect is greater when patients are treated with both chemotherapy and radiotherapy; although whether an independent effect exists for radiotherapy is unclear. Other chemotherapy regimens which appear to be associated with acute myeloid leukaemia are those which contain the epipodophyllotoxin drugs teniposide and etoposide.

Occupational benzene exposure is also a recognized cause of leukaemia, in particular for acute myeloid leukaemia. An increased risk of between 3- and 5-fold has been observed in several occupational cohorts of workers following exposure to high levels of benzene, as has occurred in the past in shoe manufacturing, rubber manufacturing and printing. This type of leukaemia is be-
Acute myeloid leukaemia is a heterogeneous disease with regards to chromosome aberrations and clinical features. Broadly, this malignancy can be differentiated into three groups based on cytogenetics: the first group comprising <15% of cases, includes generally younger patients who have more favourable chromosome abnormalities including inv(16), t(8;21), t(15;17) and t(16;16). These individuals respond well to specific chemotherapy regimens. The next group, comprising nearly a third of patients, many of whom are older, have unfavourable cytogenetic profiles including deletions of the long arms of chromosomes 5 and 7 or complex karyotypes. The remaining intermediate prognostic group is comprised of persons with all other aberrations [5].

Chronic lymphocytic leukaemia is characterised by a proliferation of CD5 surface antigen-expressing B cells, and has been associated with a precursor condition, monoclonal B-cell lymphocytosis. Although specific susceptibility genes have yet to be identified for chronic lymphocytic leukaemia, familial aggregation is found among approximately 5% of cases [6]. Chromosomal abnormalities are common in CLL, with the most frequently documented being an interstitial deletion in 13q14 (>50% of cases), which is associated with a more favourable prognosis [7]. Aberrations associated with intermediate survival are trisomy 12 (15-20% of cases), while poorest survival is seen with del(11q), involving ATM (15-30%), and del(17p), involving P53 (10-20%) [7].
The importance of mutations in IgH as a prognostic indicator has been recently recognised, with the presence of unrelated gene signatures being a poorer cytogenetic profile and more advanced disease.[8]

Acute lymphoblastic leukaemia is characterised by clonal expansion of lymphoblasts, either B-cell (B-ALL) or T-cell phenotype. B-cell immunophenotypic subtypes exhibit a variety of genetic abnormalities. Multiple molecular pathways are involved in pathogenesis. Common genetic abnormalities include hyperdiploidy and translocations (BCR-ABL1, E2A-PBX1, TCL1) in B-cell acute lymphoblastic leukaemia patients; half have a normal karyotype, while recurrent translocations are seen in one third of patients.

**Fig. 5.35.3** Immunophenotype in ALL. The green appearance of the clusters is an aid to cell typing and assists in establishing whether a lympho-epithelial pattern is present.

**Fig. 5.35.4** Acute myeloid leukaemia with associated monocytic differentiation. Monocytic monoblastic cells with large basophilic coloured granules are present.

**Management**

In the last 50 years, marked improvements in the management of leukaemia have resulted in increased survival among patients with leukaemia. Advances in treatment have contributed to 5-year survival reaching 80% among children.[10] The treatment process involves a cytoge- netic workup, as this is used to select the therapy or treatment course. Supportive care is often required to manage the sequelae of myelosuppression and severe, life-threatening infections.

For acute leukaemias, treatment strategy should include control of both systemic disease (bone marrow, liver) and central nervous system-directed therapy. Treatment choice and intensity is guided by risk stratification, which is determined by age and specific clinical and biologic markers. Current therapeutic regimens involve induction of remission using specific chemotherapy or biologic agents. Induction of remission using specific chemother- apy regimens, followed by consolidation or intensification of treatment, and with acute lymphoblastic leukaemia, are then followed by maintenance therapy. For ALL, induction therapy includes a glucocorticoid, vincristine, an anthra- cycline and possibly PEG-asparaginase.[11] Postremission therapies consist of chemother- apy and, if indicated, hematopoietic stem cell transplantation.[12] Minimal residual disease burden should be determined after initial treat- ment to assess treatment response.

Treatment of chronic leukaemias ranges from palliative care to a variety of therapies. Chronic lymphocytic leukaemia usually occurs in elderly patients and is not curable, and consequently is frequently treated conservatively. With the exception of patients with p53 mutations, treat- ment is not indicated for early-stage asymptomatic chronic lymphocytic leukaemia, as there is no evidence that treatment improves survival.[13] With advanced chronic lymphocytic leukaemia, the recommended frontline treatment is fludarabine in combination with cyclophospho- mide.[14] At the present time, oblimersen, rituximab and autologous stem cell transplant are among the second-line treatments which appear promising.[15] The tyrosine kinase inhibitor Glivec (imatinib mesylate) is the first- line therapy for chronic myeloid leukaemia. If resistance is seen, clinical strategies may involve imatinib dose escalation, interferon or a second emerging therapies.[16]

Given differing access to treatment due to cost, survival rates vary considerably between developed and developing countries. Survival rates for all leukemias in the USA and Western Europe (43% among men and 45% among women) are the highest, while rates (lag consid- erably) in Eastern Europe (29% among both men and women), Japan (25% men, 29% women), India (19% among both), South America (24% among both), Thailand (15% among both) and sub-Saharan Africa (14% men, 17% women) are among the lowest.[17] Rates differ by condition. In the USA, 5-year survival rates in adults are 60% for acute lymphoblastic leukaemia and 75% for chronic lymphocytic leukaemia; lower survival rates are seen with acute myeloid leukaemia (75%) and chronic myeloid leukaemia (40%).[18]

**WHO Classification of tumours of haematopoietic and lymphoid tissues**

**Fig. 5.25.5** WHO Classification of tumours of haematopoietic and lymphoid tissues.
REFERENCES


13. Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumour
- Indeterminate dendritic cell tumour
- Disseminated juvenile xanthogranuloma

14. Post-transplant lymphoproliferative disorders (PTLD)

- Early lesions
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma type PTLD
- WHO Classification of tumours of haematopoietic and lymphoid tissues

Table 5.25.1 (cont.)
Cancer in Children

The term childhood cancer usually comprises all cancers arising in individuals before the age of 15 years. These tumours are rare, but present specific ethical, psychological and societal concerns. Historically, childhood tumours are very variable and are classified into twelve major groups (Figure 5.26.1), which are divided into 47 diagnostic subgroups. There are some specific ethical, psychological and societal concerns. Historically, childhood tumours are very variable and are classified into twelve major groups (Figure 5.26.1), which are divided into 47 diagnostic subgroups. Some 160 000 new cases and 90 000 deaths of cancer in children under 15 years of age are estimated to occur each year [4].

Occurrence

In childhood populations of Europe, North America and other developed regions of the world, cancer incidence rates are around 100 per million [3]. Cancer incidence in the developing countries is less well known, because there have been too few efficient population-based cancer registries. Overall incidence rates for the most recent period evaluated systematically among the world populations are shown in Figure 5.26.2. In some developing countries, where the children comprise 40–50% of the population, the proportion of childhood cancers represents 3–10% of the total, whereas in the developed countries, it is less than 1%. Mortality patterns also differ. Cancer accounts for some 4–5% of childhood deaths in developed countries, whereas it is the second-leading cause of death among children aged 1–14 years, and less than 1% in developing countries, whereas deaths from infectious diseases are much more prominent. Globally, some 160 000 new cases and 90 000 deaths of cancer in children under 15 years of age are estimated to occur each year [4].

The proportion and rank of various cancers varies between childhood populations around the world, as shown in Figure 5.26.2. The sample of the world populations was selected to illustrate the geographical variability and the pattern is not necessarily the same in the neighbouring countries. Overall, the most common cancer groups are leukemias, lymphomas and central nervous system (CNS) tumours. Acute leukaemia is the most common form of cancer in most countries, especially in early childhood. Only in tropical Africa, lymphomas seem to be more common. In the developed countries, brain tumours generally account for one fifth to one quarter of childhood cancers. Their rapid registration in developing countries is at least partly due to under-diagnosis. Wilms tumour is very rare in Asian children, as is Ewing sarcoma of bone. Retinoblastoma appears to be rather more common in African children than elsewhere, while neuroblastoma appears to be very rare in central Africa. Black children are more prone than others to development of Wilms tumour and osteosarcoma. Generally very rare Burkitt lymphoma is one of the most common registered tumours in some countries of sub-Saharan Africa [3].

Pathology and genetics

Childhood cancers share a number of common characteristics which distinguish them from adult tumours arising later in life. Typical tumours of childhood resemble embryonal tissues arrested at different stages of maturation (retinoblastoma, hepatoblastoma, Wilms tumour). The unique morphologic features of some childhood malignancies (clear cell sarcoma of kidney, malignant rhabdoid tumour, melanotic neuroectodermal tumour) are not generally encountered in those occurring in adults. Cancer in childhood is also typical by the frequent occurrence of the undifferentiated tumours, commonly referred to as “small round cell tumours” such as the Ewing family tumours, Burkitt lymphoma and several acute leukaemia types. Finally, childhood neoplasms are rarely preceded by precursor lesions [5].

Table 5.26.1 summarises selected identified genetic syndromes associated with childhood cancers, according to the review by Stiller in 2004 [6]. However, these genetic syndromes account for only as very small proportion of the childhood cancer cases. Numerical chromosome abnormalities are also associated with childhood cancer. For example, Down syndrome (trisomy 21) appreciably increases the risk of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) [6]. Recently, epigenetic alterations were implicated in the development of childhood neoplasms. An example is the loss of imprinting of IGF2, shown to be involved in the carcinogenesis of Wilms tumour [7].

Etiology

In general, little is known about etiologic factors of childhood cancer, as most studies are limited in statistical power due to its rarity. Because of its onset early in life, exposure to environmental factors either in uterus or after birth may be less determining than for cancers developing in adults. Only if a few exposures, mostly exceptional, have been shown to cause cancer in children. For example, thyroid cancer has increased dramatically in the population of childhood living in the three countries surrounding Chernobyl, due to the radioactive fallout from the accident there [8]. A causal association has been reported between increased incidence of the virus in the female offspring of women who used a medication called diethylstilbestrol during their pregnancies to alleviate morning sickness in the 1970s [9]. In-utero diagnostic radiography was associated with risk of childhood leukaemia [10], but due to the substantially reduced doses used nowadays, the impact on incidence is undetectable.

Fig. 5.26.1 Composition of tumour types across childhood age groups. Based on the 51 395 cases of cancer registered in the European cancer registries in the 1970s–1990s and assembled in the ACCIS study (1), 148, nervous system, CNS, central nervous system

Fig. 5.26.2 Cancer incidence rates in children aged 0–14 years in the countries shown in the 1980s and assembled in the international comparative study (3). ASR, age-standardised incidence rate (world standard). CNS, central nervous system.
Pathogenesis of some childhood cancers involves both genetic changes and exogenous risk factors. For example, the African type Burkitt lymphoma is associated with both the Epstein-Barr virus (EBV) and a chromosomal translocation deregulating expression of the c-myc oncogene [11]. Other co-factors, which must operate to activate the carcinogenic action of such a common infectious agent, as yet unidentified [12,13]. Additional hypotheses, concerning the timing of infections, or the presence of important co-factors, would be required to clarify the causal relationship.

A number of other risk factors have been studied to reveal their part in the causation of various childhood neoplasms, but the evidence is not decisive. The suspected exposures include non-ionising radiation, maternal smoking, alcohol consumption and diet, paternal occupation, exposure to various chemicals such as benzene, nitrosamines, pesticides, hair dyes and some medications; etc. and have been reviewed in several publications [6,14,15].

Detection

Many paediatric malignancies are seen predominantly in pre-school children, while others, such as non-Hodgkin lymphomas, most cases of Hodgkin disease, bone tumours and different epithelial tumours occur in older children and adolescents (Figure 5.20-1). Cancer usually develops over a short time with no pre-cancerous stage, and it is often disseminated at diagnosis. Therefore, there is little room for implementation of screening practices. Screening for neuroblastoma, conducted nationally in Japan, and on population samples in Germany, France and the UK, did not reduce the mortality rate from this neoplasm. The increase in incidence in the screened population was thus due to over-diagnosis of non-symptomatic cases not necessarily requiring a treatment [16].

Being rare, detection of cancer in children often depends on the preparedness of primary health providers. In the poorest countries many cancers may remain undetected in children, due to the lack of training or experience of health professionals and paediatricians who are used to dealing primarily with infectious diseases. Other factors contributing to under-diagnosis may be a preferential choice of a traditional healer and other traditional beliefs. In cancer registration data such prejudices are reflected in a relative lack of registration samples in Germany, France and the UK, did not reduce the mortality rate from this neoplasm. The increase in incidence in the screened population was thus due to over-diagnosis of non-symptomatic cases not necessarily requiring a treatment [16].

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% of boys. Fig. 5.26.2. Survival of childhood cancer patients registered (age 0—14 years) during the periods shown in Western Europe and analysed in the ACCIS study [1]. 95% confidence intervals are represented by the dots around the yearly survival estimates. N: numbers of cases diagnosed in the period shown and followed up for 5, 15 and 5 years, respectively.

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Continued development of non-invasive diagnostic methods, such as computerised tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine scans increase the accessibility, the timeliness and the precision of diagnosis [17]. These advances probably explain at least in part the rapid increase in the incidence of CNS tumors observed in the USA and Europe in recent decades [18,19], as well as their low incidence rates in developing countries [3].

Management

Survival of childhood cancer patients is good, at least in developed countries. Since the 1960s, when most children who were diagnosed with cancer died, the treatment has improved remarkably (Figure 5.26.3), such that nowadays 75% of children survive 5 years from diagnosis or more [1, 20, 21, 22]. The prognosis differs by tumour type, with highest survival in the incidence of CNS tumours observed in the USA and Europe in recent decades [18,19], as well as their low incidence rates in developing countries [3].

Taking into account the differences observed in Europe and in the absence of data on childhood cancer survival in most of the developing world, it is generally assumed that the survival of these children is dismal. The main reasons are late diagnosis, unavailability of treatment, therapy abandonment, prior underestimation, inadequate supportive therapy and unsuccessful follow-up. All these factors relate to lack of financial resources to support efficient health care system for childhood cancer patients [23].

The improvement of survival reported from high-resource countries [1,20,21,22] results from increasing use of intensive chemotherapy, combined with other modalities of treatment, improved generalised supportive management, application of results of clinical trials and centralisation of care permitting each patient to benefit from the best of the multidisciplinary expertise and technologies available for these rare conditions. The current challenge is to optimise treatment to achieve a maximal treatment effect with minimal toxicity. This may be achieved through elucidation of mechanisms of resistance and exploration of the potential of novel therapeutic approaches [17]. The aim is to eliminate or reduce the numerous late effects of treatment and thus improve the quality of life of the growing population of survivors of childhood cancer.

REFERENCES

5.27 Sarcomas are very rare in African Americans. The onset of this process tends to occur a bit earlier, which coincides relatively well with the period of physical, mental, and societal specificities makes the usual classification by tumour site (used to classify cancers in predominantly adult populations) unsatisfactory. International Classification for Childhood Cancer (ICCC) [1], reflecting primarily morphological entities, is therefore often used in descriptive studies. This is similar to the classification adopted specifically for adolescents [2].

### Occurrence

Adolescence is a period characterized by physical, sexual, mental, and societal maturation. The two first aspects influence the spectrum of cancer types occurring in this age group, which is different from that in childhood and in adulthood. In the populations of Caucasian descent, the most common cancers are lymphomas and carcinomas (Figure 5.27.1). Other frequent cancer groups are CNS tumours, germ cell tumours, bone tumours, and sarcomas of bone and soft tissues, with slightly different ranks in males and females (Figure 5.27.1). Worldwide, the rates vary about three-fold in males (90–300 per million) and in females (88–270 per million). In some populations, incidence rates in females are higher than in males, although overall incidence rates for large series was 202.2 per million person-years during 1986–1995 in the USA [4], with an estimated increase to 216 in year 2000 [5]. In Europe, the incidence rate was 186.0 per million person-years in the period 1988–1997 (Table 5.27.1). These variations are illustrated in Figure 5.27.2, which is based on the most recent international data series classified according to tumour site [6].

Adolescence is the age of predominant occurrence of a few specific tumour types. Bone tumours (both osteosarcoma and Ewing tumour) usually present the first age-specific peak in adolescents and overall, and in males (in females the first peak of the two types of bone tumours occurs in the age group 10–14) [7]. This peak is present in all ethnic groups in the US population, although it is worth noting that Ewing sarcomas are very rare in African Americans (Figure 5.27.3). Ovarian germ cell tumours, including dysgerminoma, malignant teratoma and mixed germ cell tumours, are most common in adolescent girls [8]. In the world regions with information, overall incidence rates of the nasopharyngeal carcinoma, the first age peak of this tumour is seen in adolescents [8].

The incidence rates were reported to increase in Europe by 2% per year over the period 1978–1997, mainly due to the increase of incidence of lymphoid leukaemia, Hodgkin lymphoma, astrocytoma, gonadal germ cell tumours, thyroid carcinoma and melanoma [8]. In the USA an overall annual increase of 0.7% was reported for the period 1973–2000 [4]. The highest increase was previously reported for the gonadal germ cell tumours in both sexes, acute lymphocytic leukaemia, non-Hodgkin lymphomas and testiculargerm [4]. Although some of this increase may be related to improvements in diagnosis and reporting, the true rise in incidence of some of these tumour groups cannot be disregarded.

### Pathology and genetics

Together with the particular spectrum, cancers in adolescents present special biological characteristics. Thus, acute lymphocytic leukaemia usually bears poorer prognosis in adolescence than in childhood. Astrocytic and glial tumours of the brain are usually diagnosed with higher grades. Common adult tumour categories occurring in this early period in life may be more often associated with genetic factors that cause these tumours to arise earlier in life. For example, 20% of breast cancers in women aged less than 30 years may be caused by pathogenic alterations in breast susceptibility genes [9]. Some tumours occur as part of familial syndromes, sometimes as second primary malignancies after a childhood cancer. As reviewed by Bird et al. [10], 1953 mutations were shown specifically in adolescents and young adults with anaplastic astrocytoma, glioblastoma and osteosarcoma, while medulloblastoma diagnosed in older children, adolescents and young adults may be more frequently associated with the APC gene. Ewing sarcoma is also conditionally genetically, as suggested by the variation of its incidence across ethnic groups [5.27.3] and various chromosomal aberrations, of which (11;22)(e24;q12) is detectable in a large majority of cases [11]. Chromosomal changes have also been reported for germ cell tumours of testes and ovaries in adolescents with a typical amplification of the 12p chromosome [12]. Melanoma is common in fair-skinned populations, and may occur in a familial form, which indicates genetically underlined etiology [13]. However, inheritance probably explains only a small fraction of cancers in adolescents [5].
Etiology

Apart from genetic susceptibility, a large proportion of cancers in adolescents may probably be attributed to infection. Infectious etiology is a likely explanation for acute lymphocytic leukaemia (ALL) and lymphoma. While the infectious agent for ALL has not been identified as yet, Epstein-Barr virus (EBV) is implicated in several cancers. In Hodgkin lymphoma, its effect is modified by age, sex, geographical residence, ethnicity, and the level of economic development [14]. Non-Hodgkin lymphomas are also linked to EBV, but also to human immunodeficiency virus (HIV) and human T-cell lymphotropic virus type 1 (HTLV-1). EBV is also implicated in nasopharyngeal carcinoma, especially in the areas of the highest incidence (East Asia). Helicobacter pylori may play a role in gastric carcinoma, possibly together with other infectious [15,16]. Most cases of hepatic carcinoma, occurring with highest frequencies in Hong Kong and sub-Saharan African registries, are due to Hepatitis B and C viruses [17]. HIV infection is behind the spectacular rise in the incidence of the previously endemic form of Kaposi’s sarcoma in some African countries (Figure 5.27.2) [17]. Simian-virus (SV40) (the contaminant of the polio vaccine in the 1950s, was suspected to cause some brain tumours and soft-tissue sarcomas in childhood [21]. The single most important issue specific to the detection of a range of cancers occurring in adolescents is probably the delay in diagnosis. Diagnosis may be delayed in the age group more than in others due to a combination of specific circumstances, including the inexcusable attitude, unrealistic, insufficient health insurance coverage, change of primary health care provider or inadequate training of attending practitioners [24]. Some testicular germ cell tumours are thought to arise in response to hormonal stimulation by oestrogens in utero or oestrogen-like substances in the environment. However, sedentary lifestyle may also contribute to the explanation of the continuous increase of testicular germ cell tumours in western populations (Figure 5.27.2) [19]. The age-sex specific incidence rates for bone and bone tumours further suggest that their occurrence is entangled with socio-economic factors [23]. While the infectious agent for ALL has not been confirmed [19].

Detection

The single most important issue specific to the detection of a range of cancers occurring in adolescents is probably the delay in diagnosis. Diagnosis may be delayed in the age group more than in others due to a combination of specific circumstances, including the inexcusable attitude, unrealistic, insufficient health insurance coverage, change of primary health care provider or inadequate training of attending practitioners [24].

Management

Compared to other age groups in the USA, adolescents and young adults (ages 15–45) have shown the smallest improvement in survival over the period 1975–1997 [5]. The reasons for this lag may be multiple: delay in diagnosis, lower participation in clinical trials, poor compliance with treatment and psychosocial issues [24]. The referral pattern for the adolescents with cancer is not clearly defined in most countries, although this group has specific needs that differ from those of children and adults. Adapted specialised cancer units for adolescents were established in the UK, although their number is largely insufficient to cover the totally of demand [25]. These units respect all aspects of the management specific for adolescents, including therapy, psychosocial support, palliative treatment and follow-up. The recent debate about the appropriate care for adolescents with cancer [26–28] will hopefully bring about a greater increase in survival for this group of cancer patients.

Overall survival at five years since diagnosis for adolescents diagnosed in the 1990s in Europe was almost 75% (Table 5.27.2). Having improved over the last two decades of the 20th century (Figure 5.27.4). Should this trend continue, and specialised approach to the management of adolescents with cancer be adopted widely, the patients diagnosed nowadays may expect outcomes that are better still. Five-year survival at the adolescents diagnosed with cancer in the USA by the end of 1990s was 50%, based on SEER data [29]. Leukaemia (especially ALL), bone tumours and soft-tissue sarcomas are the most challenging diagnosis.

Fig. 5.27.1 Incidence rates of cancer in adolescents aged 15–19 years (both sexes), based on 9814 cases registered in SEER registries in the USA during 1973–1993 [26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia.

Fig. 5.27.2 Five-year survival of adolescents aged 15–19 years (both sexes) diagnosed in the calendar periods shown in the European registration areas contributing to the ACCIS study [23]. Line sections represent the 95% confidence intervals of the survival estimates. N, total number of cases included in survival analysis for each tumour group. CNS, central nervous system.
## Table 5.27.1

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>N</th>
<th>OS (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>All cancers</td>
<td>6494</td>
<td>73 (67,76)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>811</td>
<td>44 (40,48)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>450</td>
<td>50 (44,56)</td>
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<tr>
<td>Acute myelogenous</td>
<td>243</td>
<td>35 (29,41)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1597</td>
<td>81 (79,83)</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>1034</td>
<td>85 (84,87)</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphomas</td>
<td>360</td>
<td>64 (59,69)</td>
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<tr>
<td>unspecified</td>
<td>137</td>
<td>70 (65,81)</td>
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<tr>
<td>CNS tumours</td>
<td>864</td>
<td>70 (64,75)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>368</td>
<td>65 (59,75)</td>
</tr>
<tr>
<td>Other primary bone</td>
<td>162</td>
<td>72 (65,79)</td>
</tr>
<tr>
<td>unspecified</td>
<td>141</td>
<td>65 (61,70)</td>
</tr>
<tr>
<td>Bone sarcomas</td>
<td>464</td>
<td>46 (41,51)</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>271</td>
<td>52 (45,59)</td>
</tr>
<tr>
<td>Other sarcomas</td>
<td>164</td>
<td>51 (43,57)</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>430</td>
<td>40 (37,47)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>164</td>
<td>81 (74,88)</td>
</tr>
<tr>
<td>Other specified</td>
<td>123</td>
<td>74 (64,81)</td>
</tr>
<tr>
<td>Gastrointestinal tumours</td>
<td>839</td>
<td>87 (84,89)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>520</td>
<td>90 (87,93)</td>
</tr>
<tr>
<td>Carcinomas and epithelial neoplasms</td>
<td>1248</td>
<td>88 (86,91)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>283</td>
<td>99 (97,95)</td>
</tr>
<tr>
<td>Renal</td>
<td>427</td>
<td>88 (84,91)</td>
</tr>
<tr>
<td>Skin</td>
<td>150</td>
<td>90 (92,100)</td>
</tr>
<tr>
<td>Other</td>
<td>231</td>
<td>26 (23,39)</td>
</tr>
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## Table 5.27.2

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>N</th>
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<tr>
<td>All cancers</td>
<td>6372</td>
<td>4.8</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1006</td>
<td>1.7</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>356</td>
<td>2.0</td>
</tr>
<tr>
<td>Acute non-lymphocytic</td>
<td>512</td>
<td>1.3</td>
</tr>
<tr>
<td>CNS</td>
<td>2009</td>
<td>1.2</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>1311</td>
<td>2.0</td>
</tr>
<tr>
<td>Other specified</td>
<td>423</td>
<td>2.6</td>
</tr>
<tr>
<td>Other specified</td>
<td>1584</td>
<td>2.7</td>
</tr>
<tr>
<td>Bone sarcomas</td>
<td>672</td>
<td>1.9</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>139</td>
<td>1.9</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>185</td>
<td>2.0</td>
</tr>
<tr>
<td>Other unspecified</td>
<td>212</td>
<td>1.2</td>
</tr>
<tr>
<td>Other unspecified</td>
<td>576</td>
<td>1.3</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>131</td>
<td>1.8</td>
</tr>
<tr>
<td>Other specified</td>
<td>373</td>
<td>1.3</td>
</tr>
<tr>
<td>Bone sarcomas</td>
<td>204</td>
<td>2.0</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>410</td>
<td>2.5</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>173</td>
<td>2.5</td>
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<td>Other specified</td>
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<td>5.1</td>
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<tr>
<td>Bone sarcomas</td>
<td>197</td>
<td>3.8</td>
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<tr>
<td>Ewing sarcoma</td>
<td>1640</td>
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<tr>
<td>Soft tissue sarcomas</td>
<td>368</td>
<td>0.3</td>
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<tr>
<td>Other specified</td>
<td>371</td>
<td>0.6</td>
</tr>
<tr>
<td>Bone sarcomas</td>
<td>165</td>
<td>0.8</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>418</td>
<td>0.3</td>
</tr>
</tbody>
</table>

REFERENCES

There is no precise definition of rare cancer, and many cancers may or may not be considered rare, depending on the precision of the criteria employed. For example, a threshold incidence rate of less than 1/50 000 would place breast cancer in the rare category, but that is not so in women [1]. Neuroblastoma is rare, but in infants (below 1 year of age) it is the most common cancer, comprising 49 381 cases in males and 53 466 cases in females [5]. Finally, placental cancer (Figure 5.28.2) is rare, with a rate of less than 1/50 000 per 100 000 births. The cancers shown are those occurring with a frequency of around 1 in 100 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7], except those included under the study of rare cancers in the National Program of Cancer Registries of the USA [6]. The cancers shown are those occurring with a frequency of around 1 in 100 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7], except those included under the study of rare cancers in the National Program of Cancer Registries of the USA [6].

### Occurrence

Table 5.28.1 shows a list of cancers, as defined by the International Classification of Diseases, that may be considered rare because of their low incidence rates. Table 5.28.1 does not include those rare cancers that are described in other chapters of this World Cancer Report, such as gall bladder carcinoma, testicular cancer, thyroid cancer and others.

### Pathology and genetics

Rare cancers comprise a large number of pathologic entities. For example, cancers of the skin, except basal cell carcinoma occurring before the age of 20 years, and melanoma have been shown in Li-Fraumeni syndrome [14]. The Lynch Cancer Family Syndrome, characterized by the frequent occurrence of multiple types of common cancers, may also be associated with rare cancers [13]. Familial clustering of rare tumours has also been shown in LIFRA syndrome [14]. The syndromes associated with some rare cancers may result from both genetic and environmental causes [15] and may be influenced by individual cancer susceptibility [16].

### Etiology

The etiology of many rare cancers is unknown, because recruitment of a sufficient number of cases requires very large studies. In addition, there is little comparability between the studies dealing with rare neoplasms due to the lack of standard definition. On the other hand, clusters of rare cancers detected in specific circumstances may quickly lead to identification of an external cause.

There is no precise definition of rare cancer, and many cancers may or may not be considered rare, depending on the precision of the criteria employed. For example, a threshold incidence rate of less than 1/50 000 would place breast cancer in the rare category, but that is not so in women [1]. Neuroblastoma is rare, but in infants (below 1 year of age) it is the most common cancer, comprising 49 381 cases in males and 53 466 cases in females [5]. Finally, placental cancer (Figure 5.28.2) is rare, with a rate of less than 1/50 000 per 100 000 births. The cancers shown are those occurring with a frequency of around 1 in 50 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7], except those included under the study of rare cancers in the National Program of Cancer Registries of the USA [6]. The cancers shown are those occurring with a frequency of around 1 in 100 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7], except those included under the study of rare cancers in the National Program of Cancer Registries of the USA [6].
noma in the early 1960s [20]. The exogenous hormone diethylstilboestrol, used for therapeu-
tic purposes, has caused vaginal carcinoma in the daughters of women using this drug
during their pregnancy [21]. Dioxin (2,3,7,8-TCDD), a toxic pollutant of pesticides, has been declared a human carcinogen [22], based on studies of both common and rare cancers (including soft
tissue sarcoma) after exposure to dioxin. Viruses (HPV, HIV) may play a role in the origin of anal cancer [23]. A dose-response relationship was detected between alcohol intake and the risk of
male breast cancer [24].

Detection
Rare cancers are often of low clinical and research interest, which may considerably
delay their diagnosis and consequently, worsen the prognosis. Their rarity and diversity fre-
quently challenge the diagnostic acumen of the clinician. Novel molecular biology techniques serve to enhance the diagnosis and classification of these tumours and are indispensable for application of tailored therapies [25].

Management
Surgical resection is probably the most com-
monly used therapy in rare cancers, with chemo-
therapy and radiation therapy as adjuvants. For rare tumours of the head and neck, new tech-
niques of irradiation (e.g. intensity-modulated radiation therapy) appear to improve the control of these tumours [26]. Radiation therapy has replaced resection as frontline treatment in anal cancer [27]. Progress in molecular biology techniques allows identification of new prognostic factors,
and development of molecular-targeted therapia-
ies. For cancers with very bad prognosis (e.g. salivary glands, sweat glands), systemic pallia-
tive therapy should also be determined in clini-
cal trials [10].

In a large European study, the population-
based 5-year relative survival ranged from
good to poor for 14 specific tumour types
(Figure 5.28.3) [3]. In another population-
based study, the 5-year relative survival for small intestine cancer was 54%, but varied with
the histological type: 83% for carcinoids, 62%
for lymphomas, 45% for sarcomas and 25% for
adenocarcinomas [9]. Large clinical series show
5-year relative survival of 86% for patients with
parathyroid carcinoma [28]. The relative 5-year
survival rates of patients with anal cancer in the
population covered by SEER registries is over
70% for women and 60% for men, with much
lower rates (less than 30%) among black men.
Earlier detection improves the survival of patients
with anal cancer [29]. Five-year relative survival
rates of vaginal carcinoma patients diagnosed
from 1983 through 1999 ranged from 96% for
stage 0 (in situ) to 36% for stages I–IV [10]. An even
lower five-year relative survival rate of 14% was
observed for women with vaginal melanoma
[30]. Five-year relative survival rates for vulvar
melanoma (N=223) diagnosed between 1985
and 1989 differed by stage, with 77% survivors
in stage I dropping to 24% for those with
stage IV, while recurrent disease was associ-
ated with 100% fatality [28].

For some rare cancers, treatment outcome has
been particularly successful. Examples include
hairy cell leukaemia, chronic myelogeneous
leukaemia, seminoma, gastrointestinal stromal
tumour, (del)5q myelodysplastic syndrome,
acute promyelocytic leukaemia. The reason for
this success may be the same as the reason for
their rarity, whereby a single molecular genetic
aberration needs to be targeted, in contrast to
multiple aberrations in the most common cancers
[31]. The limited numbers of patients within each
tumour type require large international trials to
allow identification of prognostic factors or to
compare the outcome. Translational research
and a multidisciplinary approach in
specialised centres are vitally important for rare
cancers. The Rare Cancer Network, initiated in
1993 to carry out large retrospective studies on
rare cancers with the participation of more than
70 institutions from 21 countries, may help in the
development of international standards for manage-
ment of these tumours [32].

A
B
C
D
Fig. 5.28.2 Age-specific incidence rates for some rare cancers in selected populations included in Volume IX of Cancer Incidence in Five Continents [7]. N, total numbers of cases contributing to the statistics in each graph.

Fig. 5.28.3 Five-year relative survival from some rare cancers in patients diagnosed during 1986–1994 in Europe, EUROCARE
[3]. 95% confidence intervals are shown as line sections.
REFERENCES


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