

CANCER PATTERNS, TRENDS, AND BURDEN

Earshi

Bhopal



Breast

Cervix

Breast

Cervix

Delhi

Mumbai

Breast

Breast

Cervix

Cervix

Calendar year

CANCER PATTERNS, TRENDS, AND BURDEN

Describing cancer occurrence and mortality in populations is a fundamental task of epidemiology and has been a feature of IARC's work since its birth. These descriptions serve three distinct and important purposes. First, variations in cancer occurrence between populations in different places, at different times, or with different characteristics can provide clues to the factors causing such variations (see the chapter "Cancer registries: a worldwide endeavour"). Consequently, descriptive epidemiology data often constitute the starting point in the search for cancer causes. Second, these data, particularly time trends in cancer occurrence and in survival of people with cancer, provide conclusive evidence with respect to the effectiveness of interventions against cancer. If research correctly identifies a cause and it is then removed, a documentable fall in cancer occurrence must ensue. Similarly, if a treatment is effective it should produce a net increase in survival. In this way, descriptive epidemiology data put the final seal on a cycle of research and interventions against a cancer. Third, descriptive epidemiology is the absolutely essential tool for describing the cancer burden in a population in quantitative form, and the indispensable premise for rational planning of cancer control actions and services.

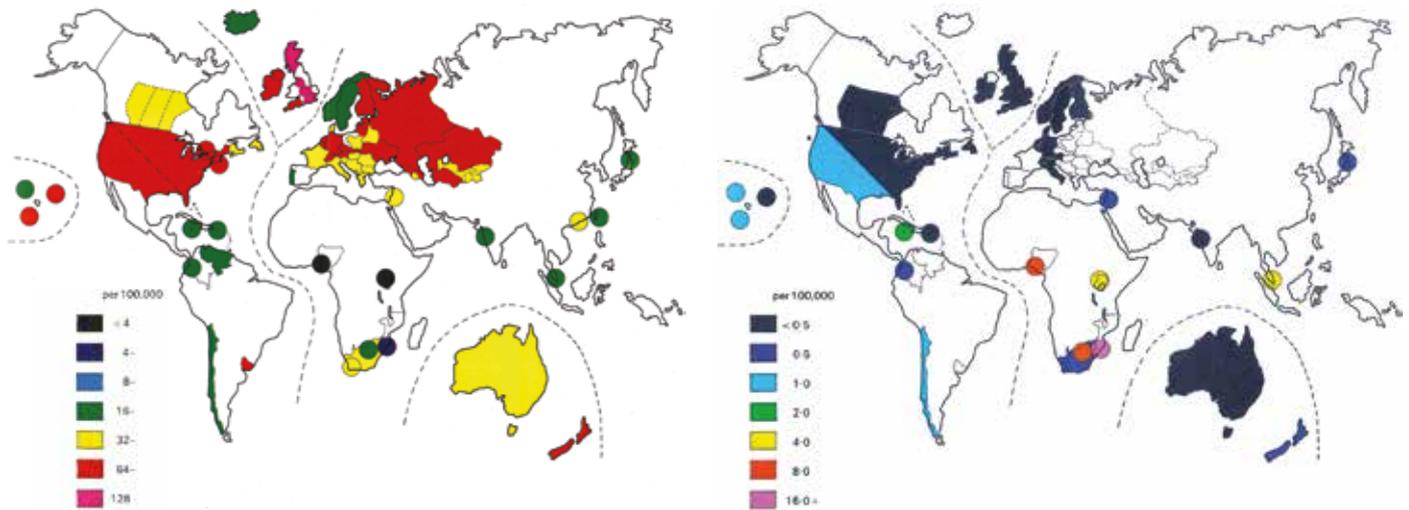
CLUES TO CAUSES

Exploring cancer occurrence systematically

Since its first volumes, *Cancer Incidence in Five Continents* has presented in a uniform way cancer incidence rates by age and sex for each cancer registry. In addition, tables are included of incidence rates, standardized by age to a common "world population" age structure, for each registry and each major type of cancer. These tables are a simple but valuable form of registry data analysis, enabling cancer occurrence in different geographical areas to be compared.

“
There was something completely incomprehensible: cancers of the upper aerodigestive tract were extremely common in southern Europe but rare in northern Europe while, conversely, lung cancer incidence was very high in the north and less so in the south. We conducted a large study, which showed the importance of alcohol consumption for cancer of the larynx in southern Europe. Certainly, the development of epidemiology in the Latin countries of Europe was also greatly helped by conducting this study.

– Jacques Estève, former IARC scientist



Maps of lung cancer incidence rates (left) and primary liver cancer incidence rates (right) in about 1965 (cases per 100 000 people per year). Some large areas were well covered by registries that provided incidence data; in other areas, only some localized registration existed (circles), and in others no data at all were available.

The information in the tables can be used to draw maps. The two maps shown here are from Richard Doll's 1967 book *Prevention of Cancer: Pointers from Epidemiology*. The first shows the geographical distribution of lung cancer incidence rates in about 1965. There are striking differences. The high rates in countries with industrialized lifestyles reflect chiefly the role of tobacco smoke and also the effect of urban air pollutants. When this map was produced, the causal role of tobacco smoking had already been established, but other maps raised questions. An example is the second one shown here. What were the causes of the variation in liver cancer incidence, with high rates recorded by registries in areas of Africa and Asia and low rates in industrialized countries? Agents in the environment were identified as obvious initial suspects, leading to IARC's research projects on aflatoxins (see the chapter "Carcinogens in the human environment") and hepatitis viruses (see the chapter "Viruses and vaccines"). The Agency used a similar approach in relation to variations in cancers of the lung and larynx across Europe, helping to establish the important role of alcohol in the case of cancer of the larynx.

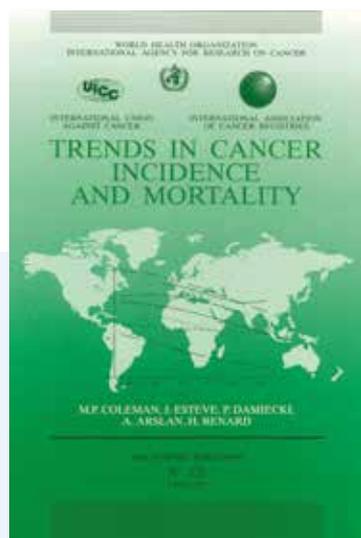
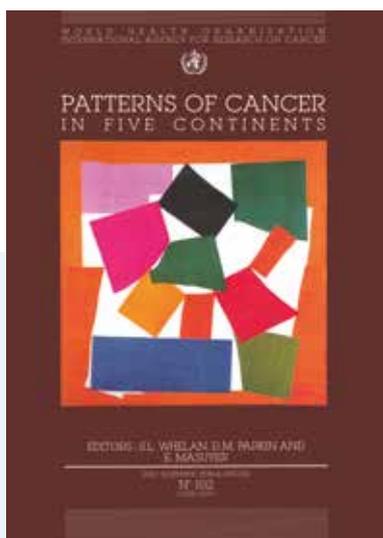
Over the decades, IARC has supported the systematic development of cancer registries throughout the world, in cooperation with the International Association of Cancer Registries (see the chapter "Cancer registries: a worldwide endeavour"). This has enabled the scope of cancer incidence analyses to expand in three directions: (i) a more complete coverage of countries, for many of which no data had been available in the first rounds of the exercise; (ii) more reliable estimates of incidence rates based on larger numbers of cancers recorded, a feature of special importance for the less frequent types of malignancies; and (iii) the possibility of observing, for the first time, trends in cancer incidence in the medium and long term, over periods of up to several decades.

IARC was swift in supporting and developing these opportunities for data analyses on a global scale, as evidenced by two books, published in 1990 and in 1993. *Patterns of Cancer in Five Continents* (IARC Scientific Publication No. 102) summarizes in graphical format, for easy comparability, the incidence data collected in *Cancer Incidence in Five Continents*, Volume V (mostly recorded between 1978 and 1982). *Trends in Cancer Incidence and Mortality* (IARC Scientific Publication No. 121) is the first comprehensive analysis of changes in cancer incidence and mortality around the world over a 30-year period. For cancer incidence, the analyses covered 60 populations in 29 countries.

As Max Parkin remarked, not only were increasingly reliable data flowing in to IARC from registries all over the world; the evolution of computerized data processing was also making faster, more flexible, and more complete analyses feasible (see “Global cancer surveillance: a job for IARC”). The latest product of this evolution is the GLOBOCAN 2012 database (globocan.iarc.fr), which contains incidence, mortality, and prevalence estimates for 27 site-specific cancers and for all sites combined in 184 countries worldwide. Building on earlier versions in 2002 and 2008, GLOBOCAN 2012 provides users with access to information on the data sources and reliability as well as summary statistics for each country. An “Online Analysis” option enables the production of more detailed tables and graphs as well as projections of cancer burden over the next two decades.

Current questions and clues

The data in successive volumes of *Cancer Incidence in Five Continents* can be used to derive graphs showing the time trends in cancer incidence and mortality rates over decades. These data are readily available in the “Online Analysis” facility of the *CI5plus* website (ci5.iarc.fr/CI5plus). The simultaneous comparison of incidence and mortality in different populations and over time, using the data of *Cancer Incidence in Five Continents*, can generate both questions and clues as to the factors producing the observed patterns.

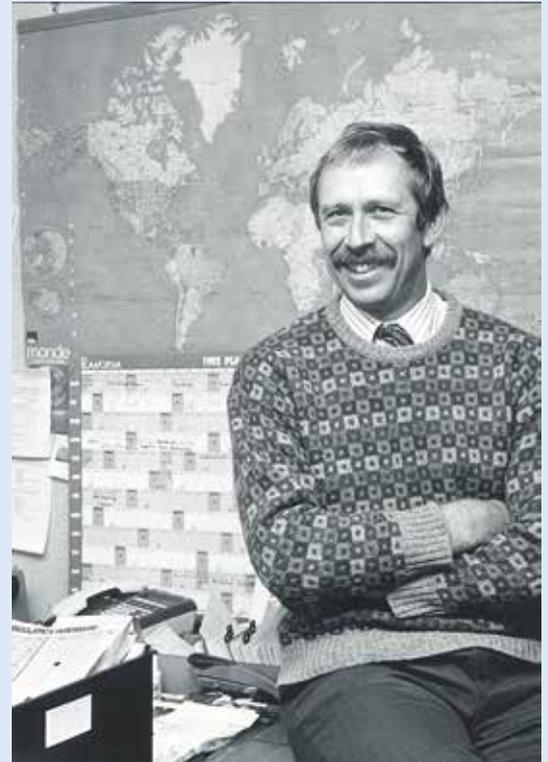


GLOBAL CANCER SURVEILLANCE: A JOB FOR IARC

Max Parkin worked at IARC from 1981 to 2004, and for almost 20 years he was the head of descriptive epidemiology research. Within this broader activity, his commitment ensured the production at regular intervals of up-to-date and reliable estimates of cancer occurrence around the world. These IARC estimates have become the standard reference internationally and are today available online in the user-friendly form of GLOBOCAN. Parkin recalls working at IARC in the 1980s.

“In the Descriptive Epidemiology Unit, we were concerned primarily with exactly the same mission as the Cancer Surveillance Section today. We were looking at cancer occurrence around the world. It is difficult to look back now: there was no Internet, no rapid communication when I came in the 1980s. Of course we had computers, but it was all mainframe computers at that time. The Agency had a central computer with terminals in one room. That is how it worked. Everything was produced from the paper records coming in; it was obviously a slow and hard process.

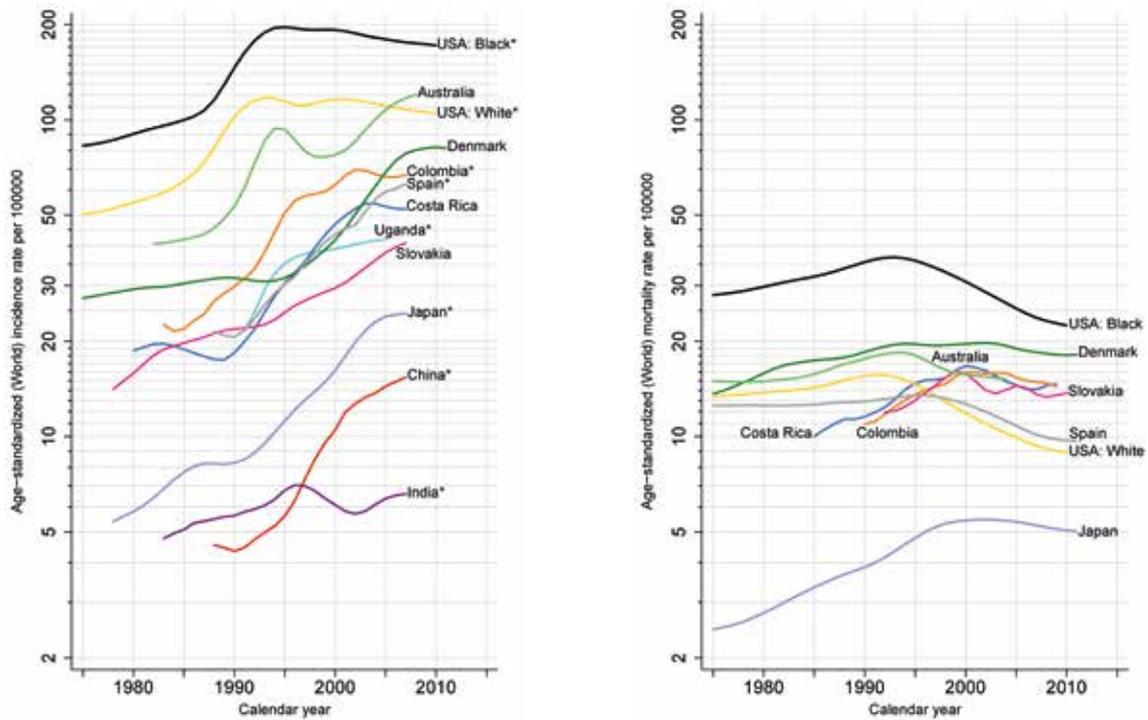
“However, working at IARC represented a great benefit in getting international collaborations. IARC was regarded as a trusted partner, which was not going to abuse its role of coordinator in having access to scientific data from individual partners around the world. So that was a huge advantage that would have been very difficult to replicate for any other institution.”



Max Parkin headed the descriptive epidemiology activities at IARC for many years and initiated the first global estimates of cancer burden.

The “Online Analysis” option in the GLOBOCAN 2012 database.





Prostate cancer incidence rates (left; cases per 100 000 men per year) and mortality rates (right; deaths per 100 000 men per year) in selected populations, age-standardized to a common world population.

An example is prostate cancer. The graphs derived from *CI5plus* data display the comparison of incidence and mortality rates for prostate cancer among 12 populations over a 30-year period. Prostate cancer is the second most frequently diagnosed cancer among men worldwide, and its incidence varies more than 25-fold between the high values of the USA and Australia and the low value of India. Rates of newly diagnosed cases increased rapidly in the late 1980s in North America as the prostate-specific antigen (PSA) screening test was introduced, and a similar pattern arose in many of the highest-resource countries during the 1990s. In contrast, prostate cancer mortality rates underwent little change or tended towards a modest decline.

Does the combined evidence of markedly rising incidence and steady or diminishing mortality indicate that spectacular advances have occurred in treatment? Or is it the case that PSA testing has increased the detection of all prostate cancers, including indolent ones that would never have progressed and caused the patient's death? The answer is still the subject of investigation, but it appears that the evidence leans mostly towards the PSA test detecting a substantial proportion of indolent cancers, with a search continuing for improved markers to better distinguish these cancers from the aggressive ones. In turn, the question remains open as to whether part of the observed increase in incidence may be due to factors other than enhanced detection of cases – for instance, as a result of affluent lifestyles in the countries most affected.

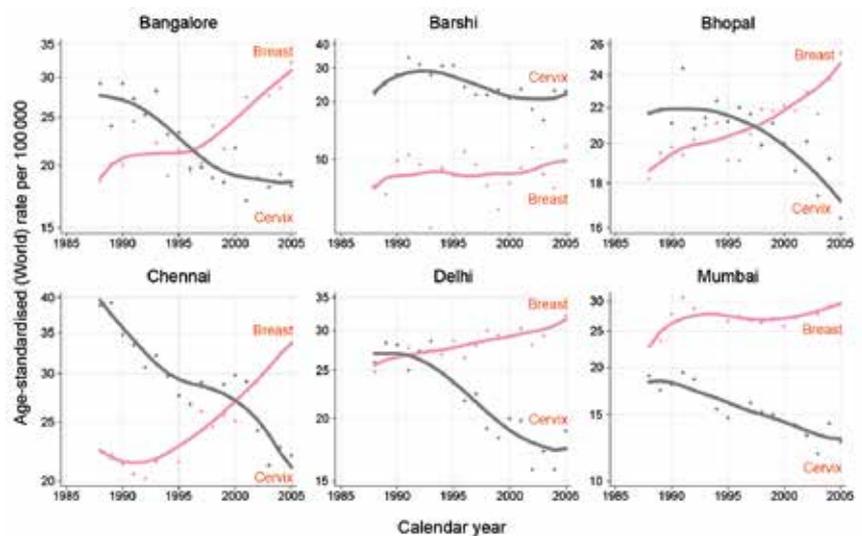
Cancer in migrants

Among the many populations that can be studied, those of migrants are of special interest. Studies of cancer in migrant populations permit comparisons of cancer incidence in populations of similar genetic background living in different environments. Differences in incidence between the migrant population and the population of origin point to the influences of environmental factors to which migrants are exposed in the host country.

“ The most significant achievement of the Agency is the description of the variation in cancer rates between different populations and over time. That description of the geography of cancer changed the way in which people think about the avoidability of cancer. IARC has done an enormous service over the decades in its descriptive statistics from different parts of the world. – Richard Peto, long-term IARC collaborator

IARC epidemiologists have participated in analyses of cancer mortality in various migrant populations. Examples include Polish-born migrants to England and Wales as well as North African migrants to France. More systematic work has been collated in two IARC publications, one on Jewish people migrating to Israel from many countries (see “*Cancer Incidence in Jewish Migrants to Israel 1961–1981*”) and the other on Italian migrants to various countries. From both, the trend clearly emerges of an increasing incidence of cancers like those of the lung, colon and rectum, and female breast with migration to environments with prevailing lifestyle habits typical of industrialized countries.

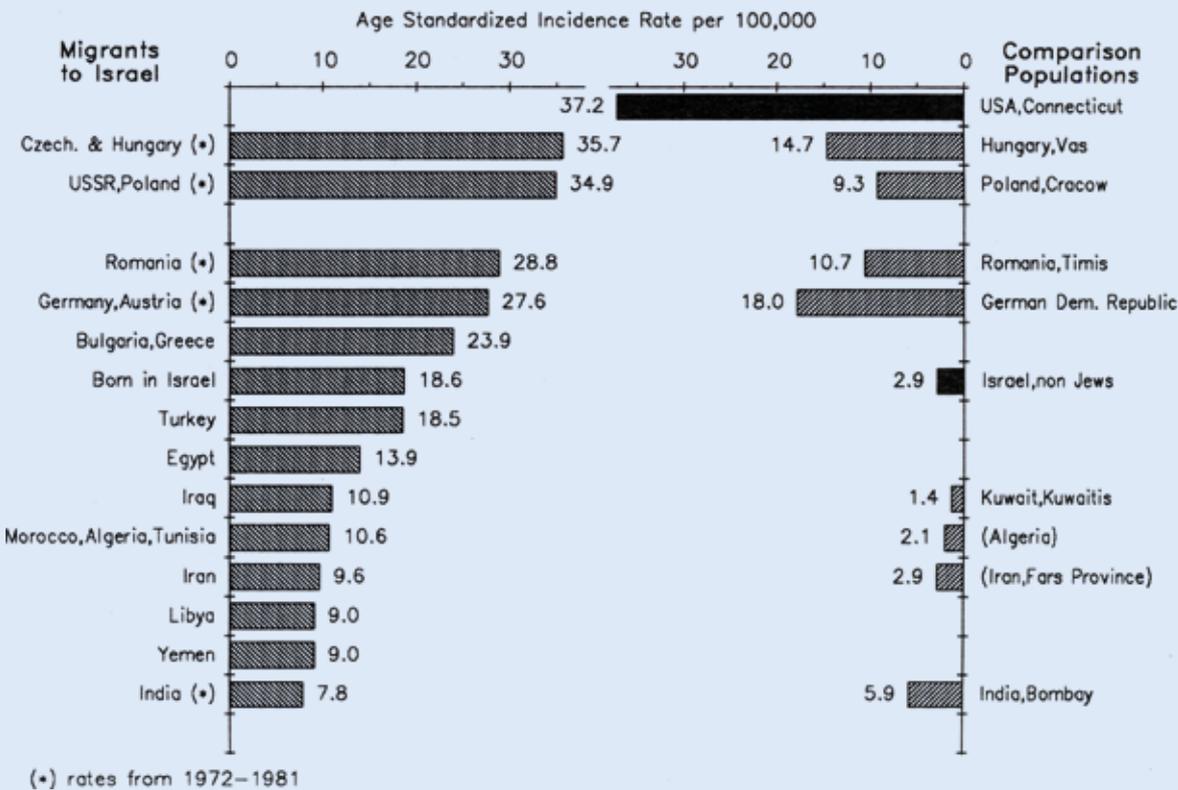
Inequalities within a population with regard to cancer incidence and survival can also be observed from cancer registry information. A good example of this is a recent set of IARC studies of indigenous peoples of North America and Australasia. These show higher incidence rates among the indigenous peoples of some cancers associated with industrialized lifestyles, for example lung cancer linked to smoking, but also of infection-related cancers such as cervical and liver cancers. In a further example, trends in breast cancer incidence (increasing) and cervical cancer incidence (decreasing) in India demonstrate the changing patterns with improving human development, and how this transition lags behind in rural areas (e.g. Barshi) compared with urban areas (e.g. Delhi). These within-country comparisons can provide policy-makers with important indicators as to where additional emphasis needs to be placed on cancer control measures to serve more vulnerable, and often disadvantaged, sectors of society.



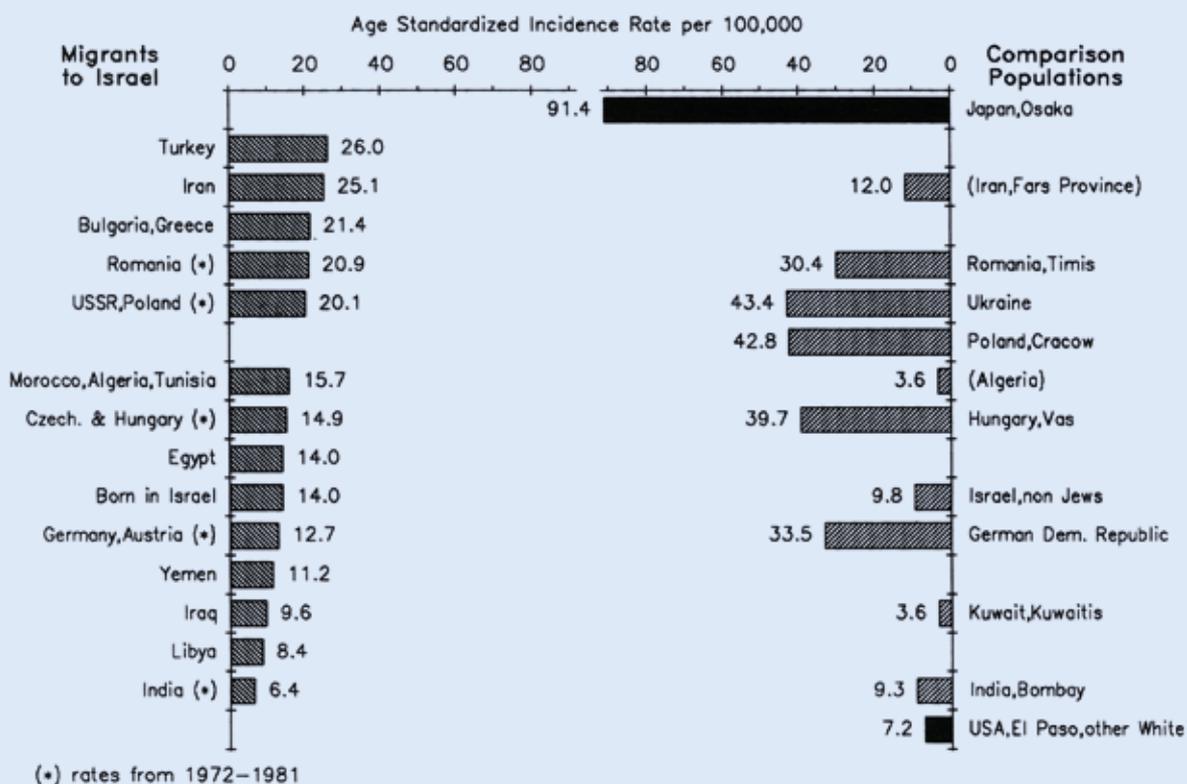
Trends in cervical and breast cancer incidence rates in six cancer registration areas in India. The Barshi area remains mostly rural and exhibits only minor variations in rates, whereas in the other five areas socioeconomic transitions have been accompanied by marked changes in cancer incidence rates, particularly a major decrease in cervical cancer occurrence.

CANCER INCIDENCE IN JEWISH MIGRANTS TO ISRAEL 1961–1981

IARC Scientific Publication No. 98, *Cancer Incidence in Jewish Migrants to Israel 1961–1981*, was published in 1989. It used the database of the Israel Cancer Registry (active since 1960) to compute age-standardized cancer incidence rates for 13 Jewish migrant populations as well as the population of Jews born in Israel. For comparison purposes, rates from cancer registries in the country of origin of the migrants were derived from data in *Cancer Incidence in Five Continents*, Volume III. Results were presented in the form of tables and graphs.



The bars in the first figure indicate the rates of cancer of the colon and rectum for female migrants to Israel (bars at left) and for the population of the corresponding country of origin (bars at right; at the top is shown the highest recorded rate, for USA, Connecticut). A pattern is evident of increasing incidence as people migrated from less-developed countries to Israel, where lifestyle habits – including diets – more typical of industrialized countries were adopted. The pattern for male migrants was closely similar.



The second figure shows the rates of stomach cancer for male migrants to Israel. Here, a picture appears that is reversed with respect to that for cancers of the colon and rectum (and the pattern for female migrants was the same). Higher rates occur in the less-developed country of origin (at right) than among the migrants to Israel (at left). This points to environmental factors in Israel that are less conducive to the development of stomach cancer or have a more protective effect.

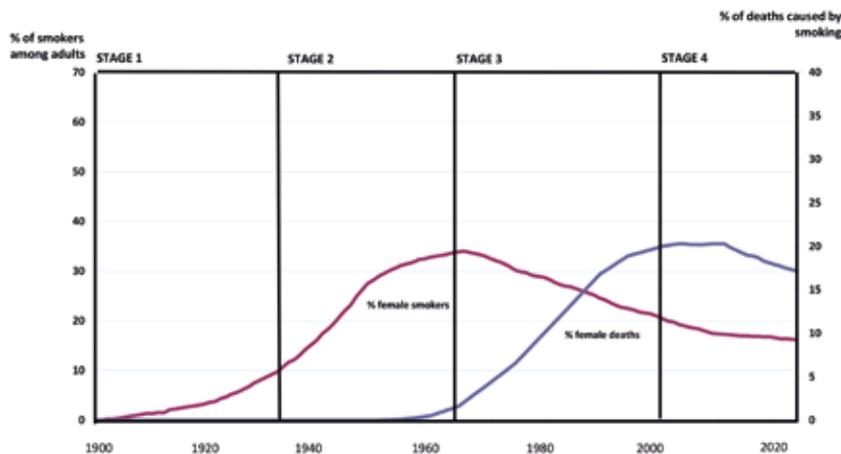
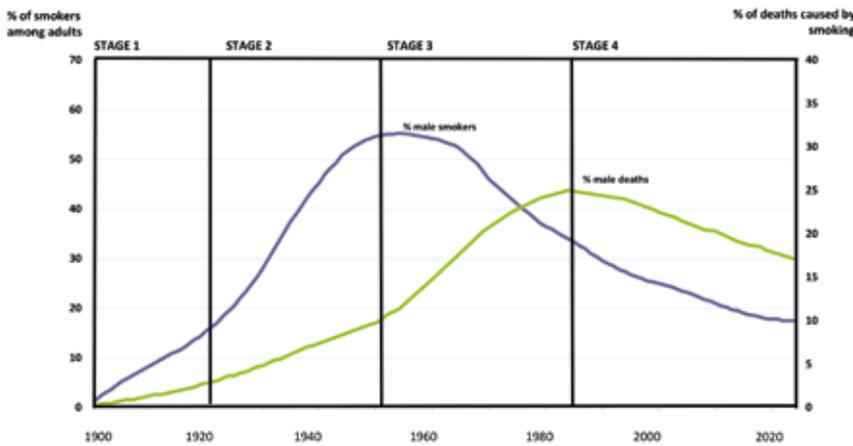
CANCER CONTROL IS EFFECTIVE

Appropriately designed studies are usually carried out to test whether a preventive intervention against cancer or a therapeutic treatment in patients actually works. If this is the case and the intervention or treatment becomes generalized on a large scale, its positive effect should be visible in the decline of the incidence of the cancer in the whole population or in an improved outlook for patients.

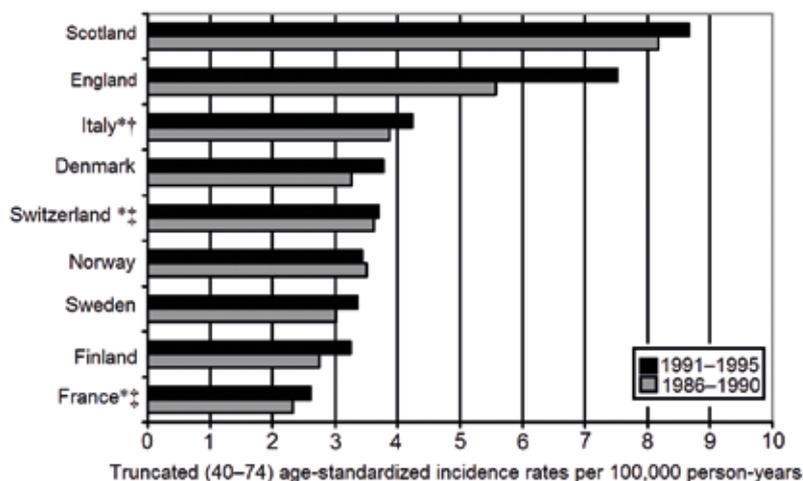
The best example of an effective preventive intervention is the campaign against smallpox, the first disease to have been fought on a global scale. After the World Health Organization (WHO) introduced the Smallpox Eradication Programme in 1966, the number of recorded cases – still sizeable in the late 1960s in some parts of Africa – progressively declined to zero. Smallpox was officially declared eradicated throughout the world in 1980.

Trends in cancer incidence

Statistics from cancer registries are a key instrument to demonstrate the effectiveness of preventive interventions. For example, as shown schematically in the figure, they can be used to monitor in various countries the stages of the epidemic of lung cancer and other tobacco-related diseases as a result of the increase in the prevalence of tobacco smoking in the country and, later, the decrease in prevalence, due to effective preventive interventions.



Stages of the tobacco epidemic in men (top) and women (bottom). In both sexes, the increase and decrease in the percentage of people smoking is paralleled some 20 years later by an increase and a decrease in tobacco-related deaths from diseases, including cancers, that take decades to develop.



Mesothelioma incidence rates (cases per 100 000 men per year) age-standardized to a common population in two time periods. In all countries except Norway, an increase was observed from 1986–1990 to 1991–1995.

* Selected areas only.
 † First period = 1987–1990.
 ‡ First period = 1988–1990.

For less common cancers, more targeted investigations are required. Mesothelioma is a malignant tumour of the pleura and peritoneum that develops several decades after exposure to asbestos, the only well-established cause. A collaborative study by epidemiologists from IARC and European mesothelioma registries showed the increase in mesothelioma incidence rates between two successive time periods. This increasing trend has continued into the 21st century, reflecting high exposure to asbestos in the past, mostly as a result of the occupations of the people affected. It can be expected that as a result of the ban on the use of asbestos, mesothelioma incidence rates will stop increasing and start decreasing. A hint of this may be the slight decline seen in the figure for Norway, the first country to introduce the ban (in 1984).

Another example in which the removal of an exposure from a population led to a subsequent decline in cancer rates came from work conducted by IARC with colleagues in Australia. The painkiller phenacetin, which causes kidney disease and was marketed in particular to women, was banned in Australia in the late 1970s. A corresponding decline in the incidence of a rare type of kidney cancer was observed some 30 years later using data from cancer registries that covered 95% of the Australian population.

Survival of cancer patients

Improved survival of cancer patients is the yardstick of success of treatments. However, the survival as measured from the statistics of a specialized oncology service may be quite different from the survival measured for all patients with, say, lung cancer in a given population, wherever they have been taken care of and whatever the treatment they have actually received. Often the average survival time is longer for patients treated at specialized cancer centres than for all patients considered together. This is because some patients may have had delayed diagnoses, less optimal treatment, and less systematic follow-up for relapses and complications. However, from a public health viewpoint, the average survival time of all patients is considered because it reflects the experience of the population as a whole.

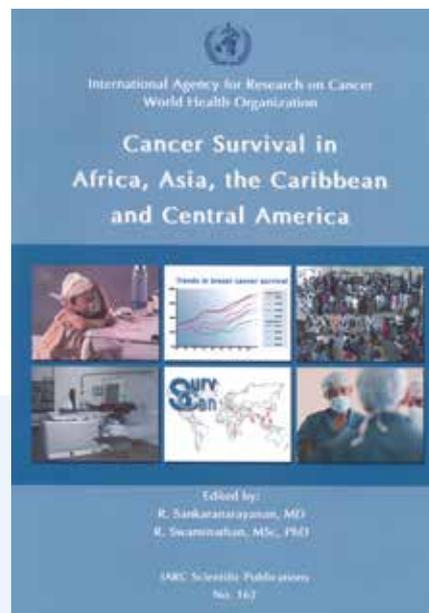
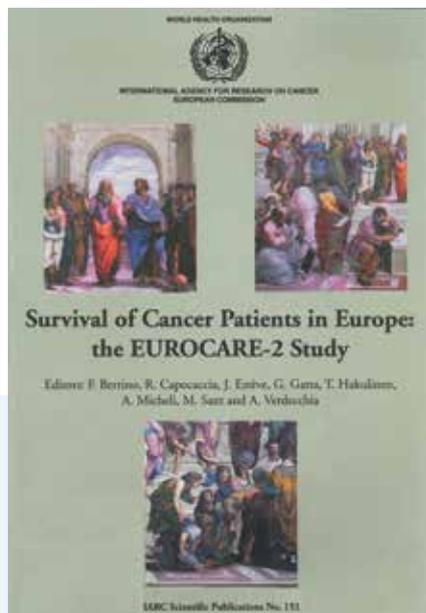
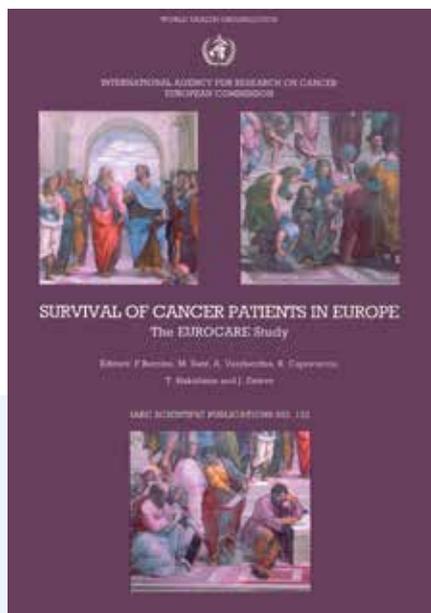
IARC has catalysed the collection of such cancer survival statistics in Europe, and more recently in Africa, Asia, the Caribbean, and Central America. Information on survival of cancer patients in developing countries is relatively rare. This emphasis by IARC has been important in highlighting the poor situation in

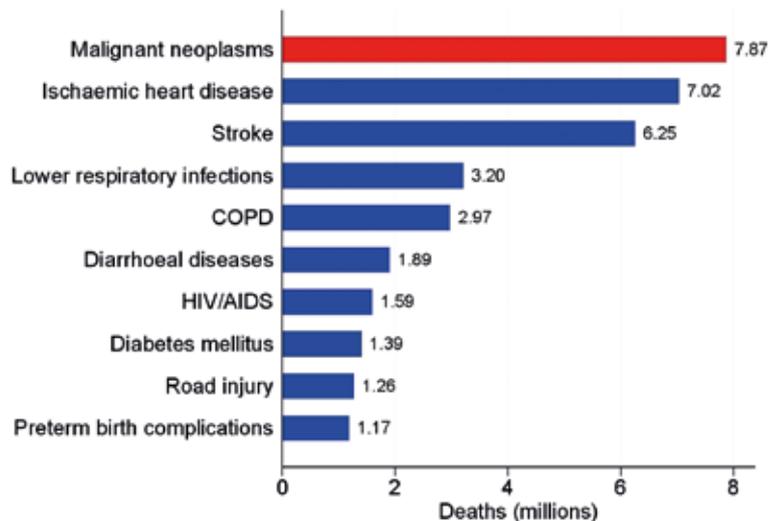
some countries and also in indicating how significant improvements can be made, even in countries with limited resources, if these are directed towards the early detection and treatment of the disease.

In Europe, the EUROCARE study, which was started in 1989, has developed into an autonomous research project that by 2014 had produced five successive cycles of survival analyses. EUROCARE has documented both a general improvement over time and important differences between countries. IARC epidemiologists participate in studies investigating the determinants of such differences. A recent example is an investigation that points to early management, immediately after diagnosis, as the likely reason for a difference in 1-year survival between patients with colorectal cancer in England and in France.

THE BURDEN OF CANCER

In 1984, IARC and WHO epidemiologists produced a first estimate of the frequency of occurrence of 12 major cancers worldwide in about 1975. The world was subdivided into 24 areas, and incidence figures were derived either directly (where data on cancers recorded by cancer registries were available) or, for several large areas, only indirectly via mortality data. The total number of new cancer cases per year was close to 6 million. In men, lung cancer was the most frequent, followed by cancers of the stomach and of the colon and rectum. In women, cancers of the breast, cervix, and stomach ranked highest. Of the 6 million new cases per year, it could be roughly estimated that up to 1 million were attributable to tobacco smoking and were therefore, in principle, preventable. Already at that time, the authors noted that in most developing countries the impact of cancer had been underestimated but that the decrease in mortality from infectious diseases resulted in increasing numbers of people of middle age and older at risk of developing cancer.

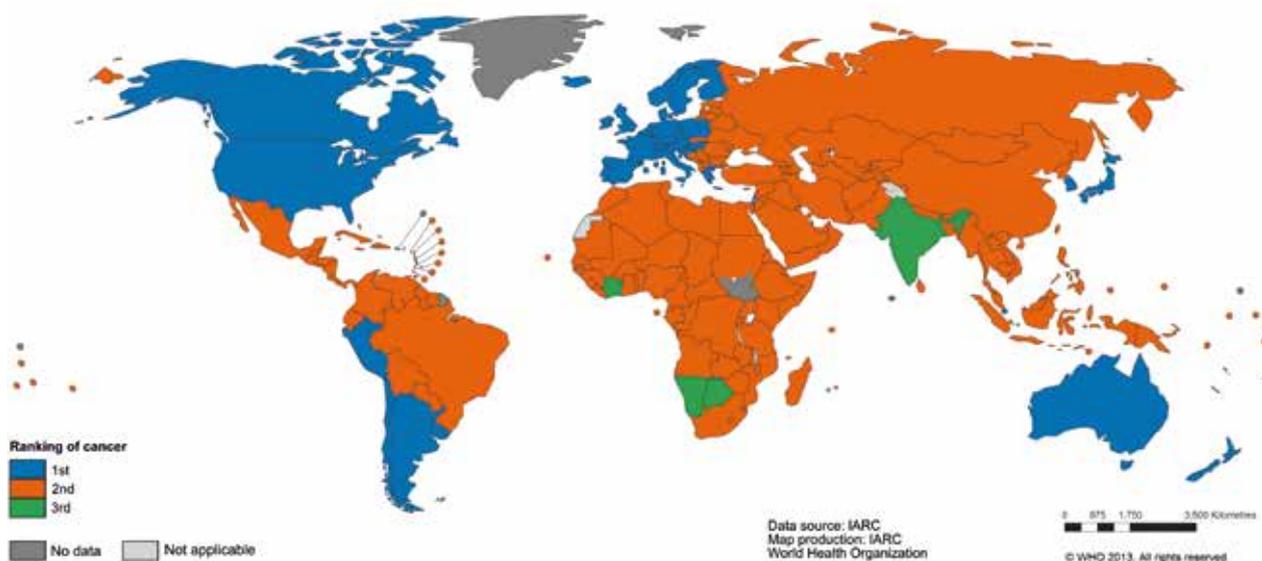




The 10 leading causes of death worldwide in 2011 (COPD, chronic obstructive pulmonary disease).

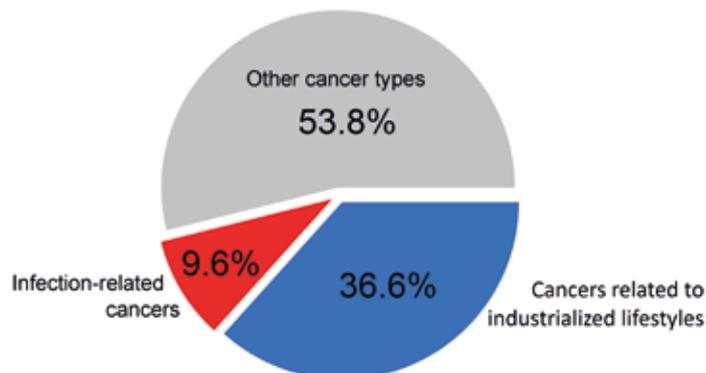
With the expansion of cancer registry coverage throughout the world, better estimates of cancer incidence became possible, and these were published by IARC for 1980 and subsequently at about 10-year intervals. Estimates of prevalence were also added (i.e. the number of living people who have been diagnosed with cancer), an important indicator of the burden on health services from people in need of clinical surveillance and, often, of treatment.

In 2011, there were nearly 8 million cancer-related deaths. All cancers, taken together, are now a leading cause of death worldwide, responsible for 14% of the total of 55 million deaths from all causes. When all main cardiovascular diseases (i.e. ischaemic heart disease and stroke) are similarly taken together, they are responsible for more than 13 million deaths, about 25% of the total. It is estimated that 14 million new cancer cases are diagnosed each year worldwide, and about 33 million living people have been diagnosed with cancer within the previous 5 years.

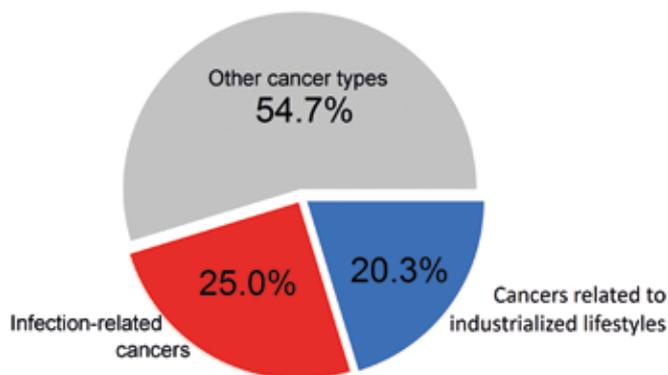


Ranking of cancers as a cause of premature mortality (ages 30–69 years), compared with cardiovascular disease and diabetes (combined) and chronic obstructive pulmonary disease, for both sexes, estimated for 2011.

High/Very High HDI: 7.9 million new cases



Low/Medium HDI: 6.2 million new cases



Estimated number of new cases of cancer in 2012 by categories of Human Development Index (HDI). Within each HDI category are shown the percentages of cancers attributable to infections (cervical, liver, and stomach cancers and Kaposi sarcoma) and related to industrialized lifestyles (colorectal cancer, female breast cancer, and prostate cancer).

The economic and demographic changes that are under way have blurred the categorization of countries as economically “developed” or “developing”, the terms used by IARC for decades when presenting the estimates of cancer burden by broad regions. Recently, a categorization in terms of Human Development Index (HDI) has been introduced, and was used in the third edition of IARC’s *World Cancer Report* (in 2014). HDI captures three dimensions of human development: life expectancy at birth, educational level attained, and purchasing power. With HDI, populations can be reclassified in a more meaningful way than with the traditional “developed”/“developing” dichotomy. With this new categorization, close to 8 million new cases of cancer occur per year in countries with high or very high HDI, whereas the annual burden on countries with low or medium HDI is about 6 million. In countries with low or medium HDI, a quarter of cancers are infection-related, and in countries with high or very high HDI, more than a third of cancers are related to industrialized lifestyles.

John Higginson, the first IARC Director, was among the first to put forward, in the 1960s, the concept that the great majority of cancers are primarily caused by environmental agents in the broad sense, i.e. agents that are not constitutive of a person's genetic make-up (see the chapter "Carcinogens in the human environment"). Since then, a vast literature has flourished that attempts to quantify the "great majority" and to divide it among major categories of causes (tobacco smoking, alcohol consumption, type of diet, workplace environment, etc.). Obtaining accurate and precise estimates of the proportion of cancers attributable to each category entails major methodological challenges. Notwithstanding these challenges, the best available measures were presented and discussed in the first and second editions of IARC's *World Cancer Report* (in 2003 and 2008). More recently, IARC has placed great emphasis on providing reliable estimates, reporting on the number of cancers worldwide linked to infections and to overweight (see "Overweight and cancer").

Incidence rates (new cases per 100 000 people per year), age-standardized to a common world population, for the seven most common cancers

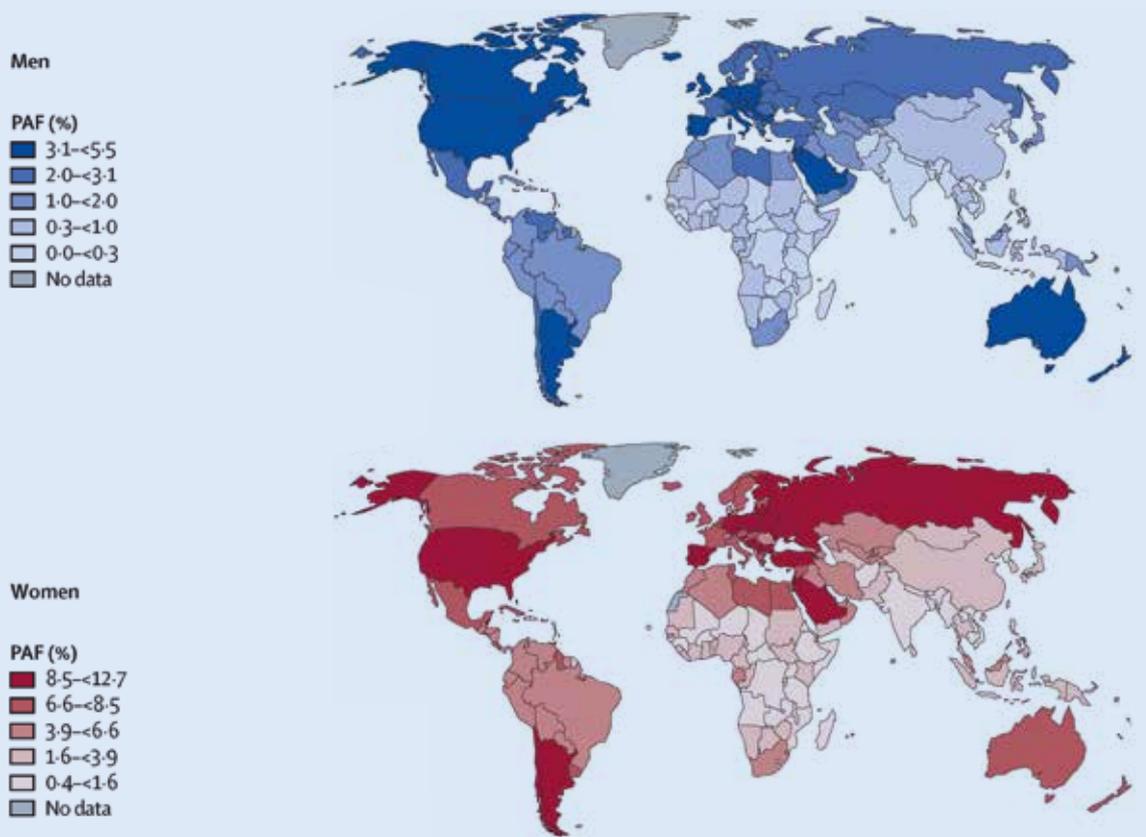
Cancer	Incidence rate in men			Incidence rate in women		
	Highest	Lowest	Ratio	Highest	Lowest	Ratio
Lung	87	3	29	61	1	61
Breast	2	0	—	107	9	12
Colon and rectum	64	3	21	45	2	22
Prostate	190	1	190	—	—	—
Stomach	111	2	56	46	1	46
Liver	61	2	30	22	1	22
Uterine cervix	—	—	—	65	2	33

The table shows the variation of incidence rates for the seven most common cancers worldwide. From the rates reported for each of the individual cancer registries in *Cancer Incidence in Five Continents*, Volume X (2013), the highest and the lowest have been selected (and rounded) for men and women. The rates vary widely between populations, with ratios of the highest to the lowest of one to two orders of magnitude, pointing to variations in the environment of the populations as the likely main causal factors of the cancers.

OVERWEIGHT AND CANCER

In most developed countries, a substantial proportion of people are overweight, an observation confirmed by recent statistical estimates that the global frequency of excess body weight in adults increased by more than 25% between 1980 and 2013. Overall, about 35% of the adult population of the world is overweight. This is an obvious cause for concern, given the established knowledge – based on numerous and consistent studies – that overweight increases the risk not only of cardiovascular diseases and diabetes but also of several cancers, including cancers of the colorectum, pancreas, gall bladder, and breast.

What proportion of all cancers can be attributed to overweight? This proportion, called the population attributable fraction, was calculated using figures for cancer incidence from GLOBOCAN 2012 and survey data for overweight, expressed in terms of body mass index, as available from the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group. Body mass index is calculated as weight (in kilograms) divided by the square of height (in metres); a value of 25 or more is generally accepted as indicating excess weight, and a value of 30 or more indicates obesity. The world map shows that the proportion of cancers attributable to overweight varies from less than 0.3% to more than 5% for men and from less than 1.6% to more than 12% for women. Overall, an estimated 3.6% (i.e. more than 480 000) of all new cancer cases in adults in 2012 were attributable to excess weight or obesity. These quantitative findings stress the pressing need to control the spread of the overweight epidemic globally.



Population attributable fraction (PAF) of new cancer cases in 2012 caused by high body mass index (a value of 25 or more) in men and women, by country.

The important message emerging from these analyses is that – as stated in the preface to *World Cancer Report 2014*, edited by Bernard W. Stewart and Christopher Wild – “Since the middle of the last century, enormous progress has been made in identifying the causes of cancer, so that more than 50% of cases could be prevented based on current knowledge.” However, one should not forget that the global variations in cancer incidence, as obtained from cancer registries, imply that the overall proportion of cancers that are potentially preventable is even higher than this figure. Thus, the search for causes of cancer continues, still stimulated in many cases by the intriguing variation in patterns seen when comparing one population with another.

