

Prevention and screening

The majority of cancers are preventable. The goal of primary prevention is to avoid the development of cancer by reducing or eliminating exposure to cancer-causing factors. These include environmental carcinogens as well as lifestyle factors such as nutrition and physical activity. Secondary prevention aims at early detection at a stage when curative treatment is still possible. This is achieved by frequent medical check-ups of individuals or by population-based screening programmes to which all those belonging to a certain age group are invited. Chemoprevention seeks to reduce the risk of cancer development through the use of pharmaceuticals.



TOBACCO CONTROL

SUMMARY

- > Tobacco-induced death and disease are preventable: halving current smoking rates would avoid 20-30 million deaths before 2025 and 150 million by 2050.
- > Smoking cessation is very effective in reducing the risk of lung cancer even in later life.
- > The greatest saving of life would result if rates of smoking uptake by children and adolescents were decreased.
- > Comprehensive tobacco control, including implementation of regulatory measures and encouraging personal commitment, requires coordinated involvement of government and community organizations, health care professionals and planners.
- > The hazard posed by environmental tobacco smoke is significant. This justifies the demand for a tobacco-free environment, particularly at work and in public places.

Tobacco usage was estimated to account for an annual death toll of more than three million in 1990 (Table 4.1). The latest estimates from WHO put the annual number of deaths today at more than four million. If current smoking patterns continue, the total is predicted to increase to more than eight million in 2020 (Table 4.2). Thus current cigarette smoking will cause about 450 million deaths worldwide in the next 50 years. Accordingly, smoking is recognized as the most preventable cause of death of humankind. Apart from lung and several other cancers, respiratory heart disease, chronic obstructive lung disease, stroke, pneumonia, aortic aneurysm and ischaemic heart disease are caused by smoking and are, to that extent, preventable, as are a range of non-fatal diseases (Table 4.3) [1-3].

Attributable risk and years of life potentially saved

Apart from knowing the diseases caused by tobacco, increasingly definitive estimates may now be made of the number of lives lost and the extent to which those lives were shortened. For a time, knowledge of attributable risk and years of life lost was restricted to quite specific populations: the British doctors constituting the cohort established by Doll and Hill in 1951 and monitored thereafter [2] and the cohort of volunteers from the American Cancer Society [4]. Extrapolation from these relatively limited databases to, in some instances, the population of the whole world was inappropriate because, despite validity of the respective studies, the populations involved were predominantly male white upper class Western populations. Although this selection of the population may not invalidate establishing the list of diseases linked to use of tobacco, extrapolation is more uncertain in relation to quantitation of risk. The key quantities that need to be measured include the relative risk (measuring how much more frequent the disease is in tobacco smokers than in non-smokers) and the attributable risk in the total population (measuring the proportion of people suffering from the disease in the population whose disease may be attributed to smoking). Granted the limitations already noted, follow-up of the British doctors for 40 years [2] indicates that one smoker out of three died from a smoking-related illness, losing on average 7.5 years of life (Fig. 4.1). It should be noted that the outlook for smokers worsens the longer the follow-up lasts. Thus, based on the first 20 years of the study, the estimate was five years of life lost, but the period became 7.5 years when the result for the last 20 years were added. Most probably the final estimate will be close to ten years, with perhaps the death of one in two smokers being attributable to the habit. The impact of smoking on survival is dose-dependent; smokers of 25 or more cigarettes per day have a survival of

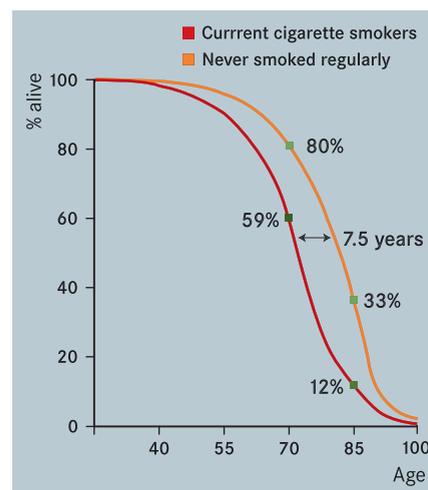


Fig. 4.1 Smoking significantly reduces overall survival. British Doctors Study. Estimates based on age-specific death rates for the entire 40-year period.^[2]

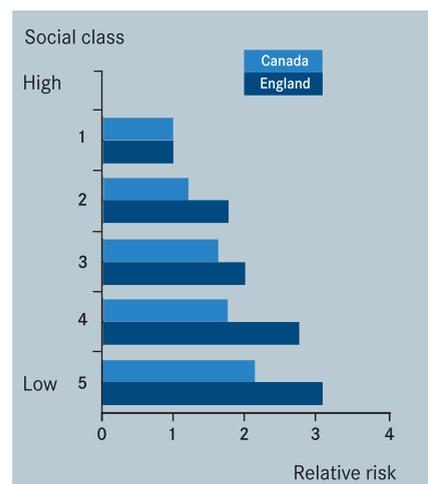


Fig. 4.2 Lung cancer mortality among men in Canada and England, late 1980s, by social class.

only about 50% at around the age of 70 years, whereas 80% of non-smokers are still alive.

World estimates for mortality caused by all diseases linked to tobacco have been produced [5] (Table 4.1). For the present, the most affected regions of the world remain

Europe and North America, but the burden is already high in China and recent studies suggest that there the disease and death toll will be heavy (Fig. 4.5). While in the United Kingdom and the USA, tobacco is responsible for about a third of all deaths at ages 35 to 69 years [6], for China the current estimate for men is about 12% to 20% but is predicted to increase to 33% by 2030 [7,8] with, for the time being, about equal proportions of lung cancers, other cancers and other diseases.

The numbers of lives lost to tobacco-induced disease and the extent to which lives are shortened may be regarded as indicative, at least in theory, of what could be saved by cessation of smoking. The effectiveness of preventive activity may often be assessed in terms of the number of lives able to be saved and these data taken into account when determining the allocation of resources. Clearly, total and immediate cessation of smoking is unachievable and can be set aside as a realistic goal. Even reducing current smoking rates by 50% would avoid 20-30

million premature deaths in the first quarter of the current century and about 150 million in the second quarter. The affected numbers of individuals in virtually all communities are so great that any incremental decrease in smoking rates will affect large numbers of individuals and have direct repercussions, for example, on health budgets. Accordingly, the efforts directed toward smoking cessation should not be balanced solely against an assessment of the numbers of lives saved, but must involve consideration of total community health care resources and the avenues through which such finite resources are most usefully expended.

Nature of intervention

Beyond being a primary concern for individual users, smoking or tobacco use has ramifications for the whole community. Therefore all sectors of society have to be mobilized against it. As a means of influencing an individual's decision to smoke, or to continue to smoke, responsibility has traditionally been accorded to doctors and

public health specialists. However, a critical influence may be exercised by teachers and all professionals in schools. In terms of action at a community level, a critical role may fall to legislators, who are responsible for design of legislation controlling tobacco use, and politicians, who enact relevant legislation.

Tobacco usage has massive economic ramifications for governments who derive benefits from taxes on tobacco trade, but these may be considered to be offset by the costs of diagnosing and treating diseases linked to tobacco, as well as other less direct costs. The broad economic impact of tobacco use involves traders dealing on world or national scales. The economic ramifications of tobacco control may involve agronomy insofar as alternative crops must be considered. Finally, the wider community may be influenced by the manner in which relevant issues are presented through the media [9].

Legislation is a crucial aspect of tobacco control and WHO has proposed a framework convention on this topic [10]. Key

Region	Deaths due to tobacco use (1,000s)	% of total deaths (all causes)	Years of life lost due to tobacco use (1,000s)	% of total years of life lost (all causes)
Established market economies	1,063	14.9	11,607	11.7
Former socialist economies of Europe	515	13.6	7,803	12.5
India	129	1.4	1,719	0.6
China	820	9.2	8,078	3.9
Other Asian countries and islands	223	4.0	2,638	1.5
Sub-Saharan Africa	78	0.9	1,217	0.4
Latin America and the Caribbean	99	3.3	1,340	1.4
Middle East	111	2.4	1,779	1.2
World	3,038	6.0	36,182	2.6
Developed regions	1,578	14.5	19,410	12.1
Developing regions	1,460	3.7	16,772	1.4

Table 4.1 The estimated burden of mortality attributable to tobacco use in 1990. Numbers of deaths and years of life lost due to tobacco use are shown. These figures are also expressed as a percentage of the total numbers of deaths and years of life lost from all causes.

Region	Deaths due to tobacco use (1,000s)	% of total deaths (all causes)	Years of life lost due to tobacco use (1,000s)	% of total years of life lost (all causes)
Established market economies	1,286	14.9	11,607	21.2
Former socialist economies of Europe	1,101	22.7	10,072	26.3
India	1,523	13.3	18,183	12.0
China	2,229	16.0	23,418	18.0
Other Asian countries and islands	681	8.8	7,475	7.7
Sub-Saharan Africa	298	2.9	3,945	1.7
Latin America and the Caribbean	447	9.4	4,888	8.8
Middle East	817	12.3	9,477	9.2
World	8,383	12.3	88,129	10.3
Developed regions	2,387	17.7	20,742	23.4
Developing regions	5,996	10.9	67,386	8.7

Table 4.2 The estimated burden of mortality attributable to tobacco use in 2020. Numbers of deaths and years of life lost due to tobacco use are shown. These figures are also expressed as a percentage of the total numbers of deaths and years of life lost from all causes.

areas include pricing, smuggling, tax-free products, advertising and sponsorship, the Internet, test methods, package design and labelling, agriculture and information sharing. These topics partly overlap with those necessary for any national tobacco control legislation, particularly actions to limit supply, including those calculated to modify the product and limit its availability or by modifying people's attitudes [11]. In respect of affecting supply, and apart from banning the product, options include modifying the composition of tobacco and in particular setting limits for selected constituents (tar content), changing the presentation (information provided, health warning, generic packaging), controlling advertising and sales promotion, and increasing the price paid by consumers through taxation. So far as demand is concerned, steps may be taken to restrict smoking in public places and at the workplace, to prevent youth from smoking and to make health education compulsory. Elements of legislation of special importance for young people

include restriction of advertising, banning of smoking in schools and other places where children and adolescents congregate and, finally, educating children. Approaches to control of tobacco-related cancer can be divided between those directed towards health protection and those acting through health promotion.

Health protection

Health protection approaches have been effective in reducing tobacco consumption in many countries. A 1% increase in the price of tobacco products is followed by a 0.5-0.8% decrease in sales. Tax increases that raise the real price of cigarettes by 10% are considered to reduce smoking by about 4% in high-income countries and by about 8% in other countries. Furthermore, increasing taxes on tobacco products is easy to implement. However, this measure can be seen as a "tax on the poor", in view of the increasing prevalence of smoking with lower social class (Fig. 4.2). Reducing subsidies for tobacco growing is an approach complementary to

increasing taxes. Subsidies for tobacco growing are very important: for example, in 1990, the European Union spent more than 700 million pounds sterling for this purpose, as compared to slightly more than 5 million pounds for tobacco control initiatives. In many developing countries, tobacco yields a higher net income for the producer than most food crops. Restrictions in sales of tobacco products concern mainly the youth. The rationale for this is that most smokers take up their habit before age 18. Restrictions may include a complete ban of sales, a ban of automatic vending machines, and banning free distribution of tobacco products. Promotion of a tobacco-free environment has focused on hospitals and other health services, schools, workplaces, as well as different public settings. Separate spaces for smokers are often provided; sometimes a workplace ban only concerns areas where clients or the public are present. The strongest resistance against any restriction often comes from owners and managers of settings receiving the public,

such as bars and restaurants, who fear a decrease in business. In fact, the limited evidence from cities in the USA where this measure has been implemented speaks against a negative economic impact. In general, however, there has been little assessment of the effectiveness of promotion of tobacco-free environments. It should be stressed that fire prevention is an important positive side-effect of promotion of tobacco-free workplaces and public settings.

Various forms of restrictions on advertising of tobacco products have been implemented in many countries. A recent survey of 22 countries with policies of either complete or partial ban on direct advertising concluded that a comprehensive set of tobacco advertising bans can reduce tobacco consumption, but that a limited set of advertising bans will have little or no effect [12]. However, tobacco companies have developed sophisticated forms of indirect advertising through subsidiaries. Sponsorship of cultural and sporting events can be seen as part of the same strategy of indirect advertising: several countries are currently discussing regulation of such sponsorship. Moreover, organizations involved in tobacco control (e.g. cancer societies) have developed a proactive advertising strategy, often using icons of tobacco advertisements such as cowboys and camels.

A final form of tobacco control through health protection is the requirement that warnings are printed on tobacco products. Such health warnings are now widespread (a 1991 survey listed 77 countries where they were requested, although in most cases they consisted of “mild” statements about health without requirement of rotation [11]). In almost every respect, residents in developing countries are receiving inferior information about the hazards of smoking than residents of more developed countries [13]. There is no formal evidence that health warnings on cigarette boxes contribute to a decrease in tobacco consumption.

Health promotion

Discouraging smoking

The epidemic of smoking-induced cancer and other disease, both present and antic-

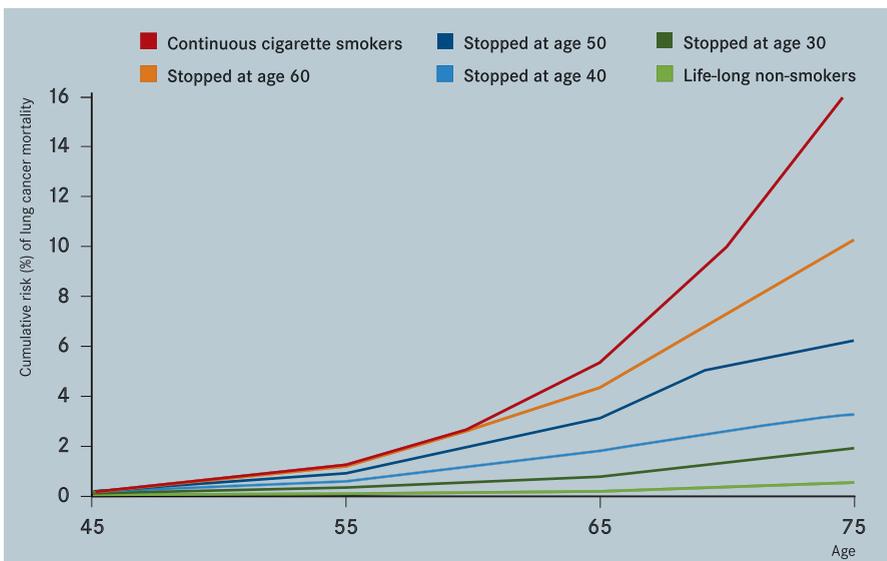


Fig. 4.3 Cessation of smoking greatly reduces the risk of death from lung cancer, and is even effective at age 60 (UK men, 1990) From: R. Peto et al. (2000) *BMJ* 321: 323-329.

Diseases associated with tobacco use	
Neoplastic diseases	Lung cancer Oral cancer Laryngeal cancer Pharyngeal cancer Oesophageal cancer Stomach cancer Pancreatic cancer Bladder cancer Kidney cancer Some leukaemias Liver cancer
Vascular diseases	Ischaemic heart disease Pulmonary heart disease Myocardial degeneration Aortic aneurysm Peripheral vascular disease Cerebrovascular disease
Respiratory diseases	Chronic obstructive lung disease Pulmonary tuberculosis Pneumonia Asthma Other respiratory diseases
Other	Peptic ulcer

Table 4.3 Diseases associated with tobacco use.

ipated, is primarily attributable to young people taking up the habit. Factors that lead youngsters to start smoking include smoking by parents and siblings and, most significantly, peer pressure. Thus, smoking by a best friend, or belonging to a group where a majority smoke has a strong influence [14]. The task of promoting non-smoking as a healthy lifestyle choice may be accorded to teachers in general or to

specialist educators. The goal must be to prevent schoolchildren from starting to smoke. Therefore, programmes must be initiated early (before the age at which experimentation is likely to start) and to achieve a positive impact, an intensive programme over several years should be integrated into the school curriculum. Limited interventions by health professionals from outside the school setting cannot be

expected to have a lasting impact. Unless interventions are strengthened with inclusion of booster sessions, the positive effects of most programmes will wear off. However, even under the best conditions, there seems little room for optimism. Under real life conditions, it has proved impossible to replicate the encouraging results from pilot trials [15]. While effort continues to be directed at health promotion campaigns aimed at youth, there is abundant recognition of the worth and need for development of campaigns directed towards women [16] and members of communities in the developing world [17].

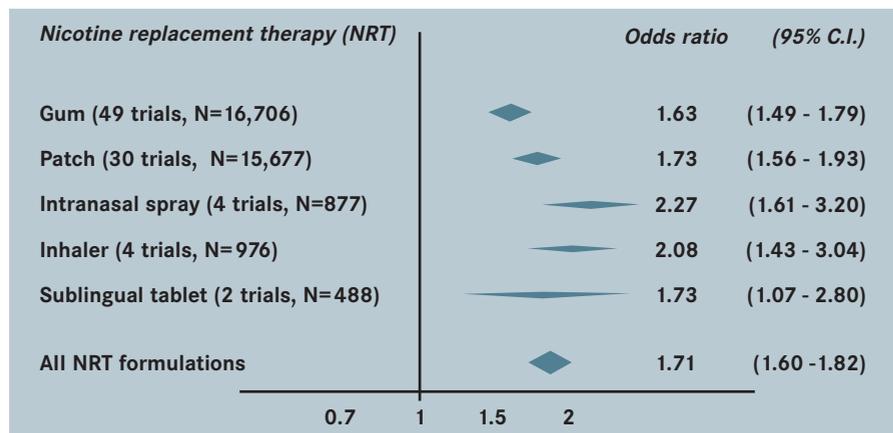


Fig. 4.4 Meta-analysis of nicotine replacement therapy trials; nicotine replacement therapy increases the chance of quitting smoking by more than one and a half times. T. Lancaster et al. (2000) *BMJ* 321, 355-358, with permission from the BMJ Publishing Group.

Smoking cessation

Preventing young people from starting smoking would cut the number of deaths related to tobacco, but not until after 2050. Quitting by current smokers is the only way in which tobacco-related mortality can be reduced in the medium term. The risk of lung cancer decreases inversely with the time since quitting smoking (Fig. 4.3). About 20% of smokers are prepared to make an active attempt to quit in the immediate future (within 30 days) [18].

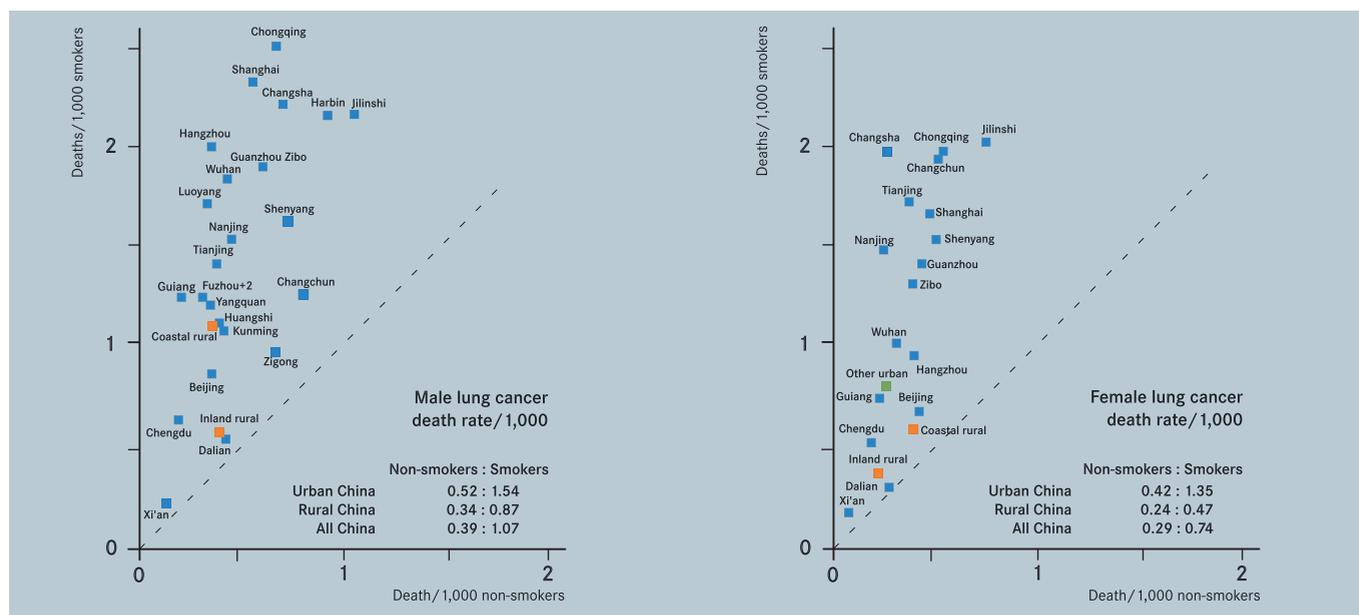


Fig. 4.5 Death rates at ages 35-69 from lung cancer in smokers versus non-smokers in various parts of China, 1986-88. Although lung cancer rates show wide variation between cities and between urban and rural areas, lung cancer mortality in smokers was consistently about three times higher in smokers than in non-smokers. Lung cancer mortality rates in some areas greatly exceed those found in the USA, which in 1990, similarly standardized for age, were 1.4 per 1,000 male and 0.6 per 1,000 female smokers, and 0.1 per 1,000 male or female non-smokers. R. Peto et al. (1999) *Nature Medicine* 5: 15-17.

However the challenge posed is daunting. Cigarette smoking is an addiction, as powerful in many respects as cocaine or opiate dependence. The rates of dependence for nicotine in the general population are higher than for alcohol, cocaine or marijuana. Among those who have ever tried even a single cigarette, almost one-third develop nicotine dependence. Although most smokers want to quit, they experience well-characterized barriers and withdrawal symptoms during their attempts and they are largely unsuccessful in quitting. In fact, spontaneous quit rates without any cessation intervention range from 2% to 5% [19]. The efficacy of a range of interventions calculated to increase the spontaneous quit rates have been evaluated, and for many options the results of ten or more trials have been published. Simple advice from doctors in the course of routine care in the context of primary care, hospital wards, outpatient consultations and industrial clinics increases the quit rate by a factor of 1.69. Nurses providing individual counselling, as distinct from general health promotion, are also effective. Likewise, counselling provided through quit clinics is effective whether provided on an individual or group basis. The relative efficacy of different psychological approaches that might be used in such a situation is poorly understood. In the absence of face-to-face contact, the efficacy of self-help material is not as great but is discernable. Increasingly, such self-help materials may be delivered through the Internet, though whether this will be more effective than publications, audiotapes or videotapes remains to be seen.

Nicotine replacement therapy is intended to provide the nicotine otherwise obtained from cigarettes, thereby reducing withdrawal symptoms associated with quitting. On the basis of more than 90 trials, this increases the chances of quitting up to two-fold (Fig. 4.4). The therapy is most effective if accompanied by at least some counselling. Nicotine may be delivered by various means (patch, inhaler, nasal spray, gum) and none has been identified as most effective; many protocols involve a combination of such prod-



Fig. 4.6 Posters from smoking cessation campaigns in France, Italy, Tunisia, Japan and China.

ucts. Apart from nicotine, a range of pharmacological agents have been proposed as expediting smoking cessation. Anxiolytics are not effective, but some antidepressants, specifically including bupropion, are. The drug may be used alone, or in combination with nicotine, and quit rates are increased by a factor of approximately 2.75. In more limited investigations, similar results have been claimed for the tricyclic antidepressant nortriptyline. Relevant mechanisms have not been demonstrated. A range of other pharmacological interventions are under evaluation and, not surprisingly, the field is one of intense activity.

Reduced exposure to environmental tobacco smoke

A tangential benefit of smoking cessation is decreased exposure of individuals apart from the smoker to tobacco

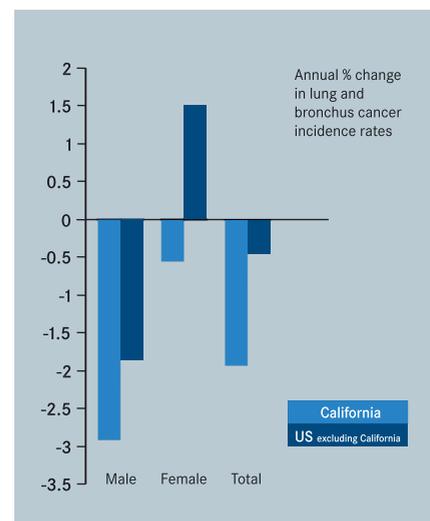


Fig. 4.7 Declining lung cancer rates in California by comparison with rates in other parts of the USA. Centers for Disease Control and Prevention (2000) *Mortality and Morbidity Weekly Report*, 49:1066-1069.

smoke. This may be achieved in part by health protection legislation which limits smoking indoors and the requirement to provide a safe workplace. In common with some other areas of tobacco control, it is possible that progress in this area may be influenced by the outcome of litigation and the associated financial risk incurred by those permitting or tolerating such exposure.

Outcome

The health benefits of smoking cessation are indisputable, and specifically include reduced risk of malignant disease. A classic example involves the

impact of anti-smoking publicity and health education in California, where smoking rates declined more than twice as rapidly as in the rest of the USA. It is now evident that during the period 1988-1997, age-adjusted lung cancer incidence rates in California declined significantly compared with stable incidence rates in other parts of the USA (Fig. 4.7). Thus, California is one of the few regions in the developed world where lung cancer mortality among women is declining.

The efficacy of smoking cessation, as a means of decreasing the risk of malignant disease, is not an issue requiring

further investigation. Hence, the immediate issue confronting governmental and other authorities is the amount and type of resources that should be allocated to this established means of cancer prevention. An important consideration is the limitation of those factors which tend to promote adoption of the smoking habit by the community in question.

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WEBSITES

- GLOBALink, the International Tobacco Control Network, UICC:
<http://www.globalink.org>
- Florida Tobacco Control Clearinghouse:
<http://www.ftcc.fsu.edu>
- CDC's Tobacco Information and Prevention Source:
<http://www.cdc.gov/tobacco/>
- List of smoking and tobacco control monographs from the National Cancer Institute:
http://rex.nci.nih.gov/NCI_MONOGRAPHS/LIST.HTM
- Tobacco Control Research Branch (NCI), information on spit tobacco:
http://dccps.nci.nih.gov/TCRB/less_default.html
- Tobacco Free Initiative, WHO:
<http://tobacco.who.int/>
- 11th World Conference on Tobacco or Health (August 2000):
<http://www.wctoh.org/>
- Smoking Cessation, "Live Smoke Free", Health Canada:
<http://www.hc-sc.gc.ca/hppb/cessation/>
- Framework Convention on Tobacco Control :
<http://www.who.int/gb/fctc/>
- Quit: the National Tobacco Initiative (Australia):
<http://www.quitnow.info.au>

REDUCTION OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

SUMMARY

- > The prevention of cancer attributable to occupational and environmental exposures is primarily achieved by regulatory action.
- > Relevant measures include replacement of carcinogens with alternative chemicals or processes, improved ventilation, re-engineered manufacturing processes and, if this fails, use of protective clothing and equipment.
- > A significant reduction in occupational cancer attributable to implementation of preventive measures has been demonstrated in many instances. However, there remains a burden of past exposure, particularly to asbestos.

In developed countries, it has been estimated that about 5% of all cancers are attributable to occupational exposures and about 1% to pollution [1] (*Occupational exposure*, p33; *Environmental pollution*, p39). These minor proportions might not command immediate attention. However, the cancers in question are immediately preventable, particularly those resulting from occupational exposures. In principle, an individual should not have to accept an increased risk of cancer which has been recognized as being caused by doing a particular job. It is notable that exposure to occupational carcinogens and to environmental pollutants is largely involuntary, as distinct from “lifestyle” exposures, such as active smoking, alcohol drinking and sun exposure, the extent of which are largely a matter of personal choice. Prevention of cancers attributable to occupational exposures and environmental pollution involves at least two stages: firstly, identification of the specific agent or situation responsible for an increased

cancer incidence and secondly, the imposition of appropriate regulatory controls. However, regulatory control of exposure to carcinogens or hazardous environments must vary according to the situation being addressed. Even in relation to the same agent, there may be several options and hence the procedures adopted by different countries may vary.

Occupational cancer

Prevention of exposure

The primary strategy for prevention of occupationally induced cancer involves preventing exposure to the recognized carcinogen in question. One option is to cease production, exemplified by the phasing out of 4-aminobiphenyl in the United Kingdom, following reports of increased risk of bladder cancer among exposed American workers [2]. Another approach is the adoption of protective measures, including those involving building design and ventilation systems. Consideration may be given to altered means of production (e.g. the use of “closed” rather than “open” engineering). As a general rule, reduced emissions and/or improved ventilation are more efficient than the use of protective equipment in achieving a durable reduction in exposure. Reduction of emission can often be achieved for chemicals generated incidentally in the course of production, such as intermediates formed during chemical manufacturing processes. However, reduction of exposure at source may be difficult to achieve when the hazardous material is the final manufactured product.

Adoption of protective clothing and “safe” handling procedures may be perceived as the last resort in a general assessment of preventive measures, but is recognized as being necessary and appropriate to particular situations. Safety equipment must be properly related to the hazard and be comfortable. Such equipment may include gloves, gowns, masks and/or respirators depending on the situation. Related meas-

ures include use of proper warning labels and secure storage arrangements. Activities of the International Labour Organization (ILO) aimed specifically at the prevention of occupational cancer include the adoption and promotion of the Occupational Cancer Convention and Recommendation (ILO, 1974) and the production of a publication concerning prevention and control of occupational cancer (ILO, 1988). The Occupational Cancer Convention specifies the principles to be adopted and had, in 2001, been signed by 35 Member States. Article 3 states that “Each Member which ratifies this Convention shall prescribe the measures to be taken to protect workers against the risks of exposure to carcinogenic substances or agents and shall ensure the establishment of an appropriate system of records.”

Screening

Screening of occupationally exposed workers for physical or biological indicators of exposure has been proposed, but



Fig. 4.8 Clothing to prevent contamination with chemical waste.

there is no evidence for the efficacy of this approach. This is specifically the case for lung cancer and mesothelioma among asbestos-exposed workers (screened using chest X-rays or cytological examination of sputum) and bladder cancer among workers exposed to aromatic amines (screened using cytological or mutagenicity analysis of urothelial cells in the urine). Education programmes directed at reducing any delay in examination and diagnosis of workers developing symptoms of disease are an option. These programmes not only require awareness and information campaigns, but also require appropriate facilities for diagnosis and treatment

[3]. In Finland, there is a policy of increasing awareness about carcinogens in the workplace and employers are required to maintain files on all employees, recording all exposures.

Actions and outcomes

Prompt regulatory action may be seen to have followed the identification of vinyl chloride as an occupational carcinogen. An occupational exposure limit of 500 parts per million (ppm) for vinyl chloride monomer was common during the 1960s, and was based on the explosive properties of the chemical. However, in 1974, several cases of an otherwise very rare cancer,

angiosarcoma of the liver, were described among workers exposed to vinyl chloride, and this was followed soon after by the results of animal experiments, confirming the carcinogenicity of this compound. These findings led to a rapid reduction in recommended exposure levels for vinyl chloride monomer to 10 ppm or less.

However, a similar quick response to accumulating evidence of an unacceptable hazard has not occurred for other occupational carcinogens. The history of occupational exposure to asbestos is illustrative of an unacceptable time-lag between identification of risk and regulatory action. Epidemiological results indi-

Country	Year	Butadiene concentration (mg/m ³)	Interpretation
Australia	1991	22 (Probable human carcinogen)	Time-weighted average
Belgium	1991	22 (Probable human carcinogen)	Time-weighted average
Czechoslovakia	1991	20	Time-weighted average
		40	Ceiling
Denmark	1993	22 (Potential occupational carcinogen)	Time-weighted average
Finland	1998	2.2	Time-weighted average
France	1993	36	Time-weighted average
Germany	1998	34 (Human carcinogen)	Technical exposure limit
		11	
Hungary	1993	10 (Potential occupational carcinogen)	Short-term exposure limit
The Netherlands	1996	46	Time-weighted average
The Philippines	1993	2200	Time-weighted average
Poland	1991	100	Time-weighted average
Russia	1991	100	Short-term exposure limit
Sweden	1991	20 (Suspected of having a carcinogenic potential)	Time-weighted average
		40 (Suspected of having a carcinogenic potential)	Ceiling
Switzerland	1991	11 (Suspected of being a carcinogen)	Time-weighted average
Turkey	1993	2200	Time-weighted average
United Kingdom	1991	22	Time-weighted average
United States:			
ACGIH (Threshold Limit Value) ^a	1997	4.4 (Suspected human carcinogen)	Time-weighted average
NIOSH (Recommended Exposure Limit)	1997	(Potential occupational carcinogen: lowest feasible concentration)	Time-weighted average
OSHA (Permissible Exposure Limit)	1996	2.2	Time-weighted average

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). ^a Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

Table 4.4 International occupational exposure limits and guidelines for butadiene (which is classed by IARC as a probable human carcinogen, Group 2A).

cating that exposure to asbestos caused lung cancer accumulated from the 1930s and the evidence became conclusive during the 1950s and 1960s. However, only during the late 1970s were effective steps for limiting exposure initiated in some countries [4]. Even so, relatively little action concerning asbestos-induced cancer has been taken in many countries (notably in the developing world, see below) until recently.

After introduction of preventive measures, a progressive decrease in the risk of cancer among relevant workers may be evident. This may be seen by comparing groups of workers who were employed in different time periods. For example, the risk of lung cancer decreased among cohorts of American workers who were potentially exposed to chloromethyl ethers. This hazard was reduced after 1971, when a closed manufacturing system was introduced [5]. Among relevant workers, lung cancer incidence was greatest in the 1960s, and decreased after 1974. Change in risk of cancer is also evident amongst Norwegian workers employed in a nickel refinery smelter from the beginning of operation in the 1910s until the 1960s [6] (Fig. 4.9). Major changes in the process occurred during this time, particularly after 1950. [7]. Risk of nasal cancer has decreased; excess risk of lung cancer has also decreased but to a lesser degree, which may be attributable to the effects of increased smoking.

The situation in developing countries

Most documented examples of successful prevention of occupational cancer involve developed countries. To some extent, these examples have also led to improvement in conditions of occupational hygiene in developing countries. The quality of industrial hygiene in the Chinese chemical industry improved markedly during the 1970s such that by 1981, air concentrations of vinyl chloride monomer were similar to those in industries in Europe and North America [8]. However, lack of economic resources and health services may limit the adoption of preventive measures. Often, exposure levels in the informal employment sector and in small workshops, where a large propor-

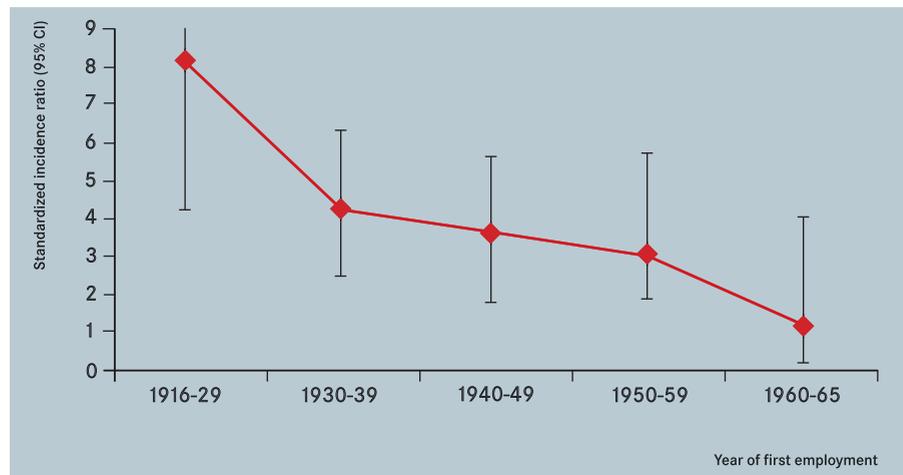


Fig. 4.9 Risk of lung cancer among nickel refinery workers, by year of first employment.

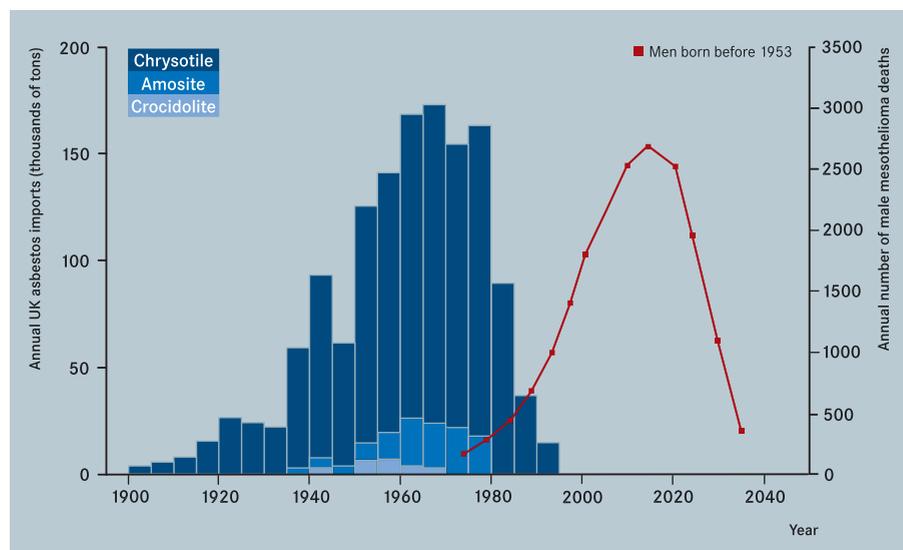


Fig. 4.10 UK asbestos imports and predicted mesothelioma deaths in British men. Mortality from mesothelioma reflects past exposure to asbestos. Despite the ban on the use of asbestos in the early 1990s, mesothelioma cases will continue to increase, with approximately 250,000 expected deaths in Europe over the next 35 years.

tion of workers are located in developing countries, are high compared to “best practice” adopted in large facilities [9]. Protective clothing may have limited effectiveness in some developing countries because of discomfort arising from its use in hot, humid climates. Exposure to asbestos, crystalline silica and pesticides are recognized priorities for control of occupational cancer hazards in developing countries. The greatest impact in terms of pre-

vention of disease is likely to come from the establishment and enforcement of national and international regulatory controls. Child labour is another cause for concern. Even where regulations to protect workers from exposures to carcinogens are adopted, such regulations may not apply to children, who are often not employed legally [8]. Some nations have established legislation that applies specifically to the employment of children: for example, a detailed list of

industries, processes and occupations that are deemed to be dangerous for children has been set out by the Philippines. Prevention of occupational cancer may

positively affect general environmental conditions. A study of conditions at the Huannan coal mine, China, established that from 1953 to the 1980s underground dust

levels decreased from 266 mg/m³ to 1.3 mg/m³, and this coincided with marked improvement in housing conditions, water quality, nutrition and sanitation [8].

Environmental pollution

The prevention of cancer caused by environmental pollution might be expected to follow the same principles and approaches adopted for prevention of occupational cancer. However, control of carcinogenic hazards in the general environment is usually more complex than at the workplace. Among other things, environmental pollution usually derives from many sources. Moreover, exposure levels vary greatly over space and time. Measures to reduce pollution can rarely be correlated with reduced cancer incidence. A decreased incidence of lung cancer, for example, cannot be attributed to reduced air pollution against a high background of tobacco

Pollutant	Decrease
Carbon monoxide (CO)	37%
Lead	78%
Nitrogen dioxide (NO ₂)	14%
Ozone	6%
Particles of ≤10 µm diameter (PM-10) PM-10 measurements began in 1988	22%
Sulfur dioxide (SO ₂)	37%

Table 4.5 Percent decrease in air concentrations of six key air pollutants, USA (1986-1995).

Compound	Average ambient air concentration [mg/m ³]	Cancer associated	IARC classification
Acetaldehyde	5	Nasal tumours in rats	2B
Acrylonitrile	0.01 - 10	Lung cancer in workers	2A
Arsenic	(1 - 30) x 10 ⁻³	Lung cancer in humans	1
Benzo[a]pyrene	No data	Lung cancer in humans	1
Bis(chloromethyl)ether	No data	Epitheliomas in rats	1
Chloroform	0.3-10	Kidney tumours in rats	2B
Chromium VI	(5 - 200) x 10 ⁻³	Lung cancer in workers	1
1,2-Dichloroethane	0.07 - 4	Tumour formation in rodents	2B
Diesel exhaust	1.0 - 10.0	Lung cancer	2A
Nickel	1 - 180	Lung cancer in humans	1
Polycyclic aromatic hydrocarbons (benzo[a]pyrene)	(1 - 10) x 10 ⁻³	Lung cancer in humans	1
1,1,2,2-Tetrachloroethane	0.1 - 0.7	Hepatocellular carcinomas in mice	3
Trichloroethylene	1 - 10	Cell tumours in testes of rats	2A
Vinyl chloride	0.1 - 10	Haemangiosarcoma in workers Liver cancer in workers	1

Table 4.6 WHO guidelines (1999) for air pollutants with carcinogenic health end-points. These substances have been classified by IARC as either human carcinogens (Group 1), probable human carcinogens (Group 2A) or possible human carcinogens (Group 2B).

co-induced disease, including the impact of environmental tobacco smoke. However, such limitations do not detract from the value of initiatives to reduce environmental pollution. Such measures may reasonably be presumed to contribute to prevention of cancer, even in the absence of definitive data.

Air pollution

Air pollution has decreased in most developed countries during recent decades. In some Central and Eastern European countries, such as Poland, there has been a significant reduction in emissions of air pollutants as a result of the implementation of environmental protection programmes [10]. However, even when an increased risk of cancer is attributable to environmental pollution, appropriate preventive measures may not be adopted. People living in villages in Cappadocia, Central Turkey, where the local stone used for house construction was contaminated with the carcinogenic fibre, erionite, were burdened with a very high incidence of pleural mesothelioma [11]. Attempts to relocate exposed individuals away from contaminated houses were hampered by economic constraints and there is anecdotal evidence that migrants from poorer parts of the country moved into some of the houses left empty.

Regulation is the primary approach to preventing pollution-induced cancer. Improvements in air quality have been achieved by means of adopting guidelines and legislation, examples of which include the *WHO Air Quality Guidelines for Europe*, the *National Ambient Air Quality Standards* (US Environmental Protection Agency) and *Council Directives on Air Quality* (European Union). The Environmental Health Criteria series of the International Programme on Chemical Safety currently assesses the health risks of some 120 chemical compounds and mixtures. Limits have been set on motor vehicle exhaust emissions in many parts of the world. The Council of the European Communities has adopted a phased programme for the implementation of emission standards for carbon monoxide, hydrocarbons and nitrogen oxides from

gasoline and diesel-powered vehicles [12]. One aspect of the control of atmospheric pollution in relation to cancer concerns the limiting of ozone depletion. The 1987 Montreal Protocol (mediated by United Nations Environment Programme and signed by 150 countries) has resulted in the cessation of production and consumption of a significant proportion of all ozone-depleting substances in industrialized countries. The worldwide consumption of ozone-depleting substances

decreased by nearly 75% in the seven years to 1996. As a result of the subsequent decline in the rate at which global ultraviolet radiation is increasing, it has been estimated that 1.5 million cases of melanoma may be prevented in the next 60 years [13].

Indoor air pollution is a major public health challenge, which demands action in terms of research and policy-making [14]. The greatest burden of disease resulting from exposure to smoke from cooking

Standard (mg/L)	Countries (concentration and date standard was established, if known)
< 0.01	Australia (0.007, 1996), European Union (1998), Japan (1993), Jordan (1991), Laos (1999), Mongolia (1999), Namibia, Syria (1994)
0.01 -0.05	Canada (0.025, 1999)
0.05	United States (considering lowering standard from 0.05, 1986), Mexico (considering lowering standard, 1994) Bahrain, Bangladesh, Bolivia (1997), China, Egypt (1995), Indonesia (1990), Oman, Philippines (1978), Saudi Arabia, Sri Lanka (1983), Viet Nam (1989), Zimbabwe

Table 4.7 Currently accepted national standards for arsenic in drinking water.

Operative measure	Examples
<p>Preventing exposure Use of gloves and face mask Full respirator</p>	<p>Pharmacists handling cytotoxic drugs Specified emergency procedure for spillage of hazardous material</p>
<p>Controlling exposure Environmental monitoring</p>	<p>Measurement of asbestos fibre level in breathing zone Film badge to assess radiation exposure</p>
<p>Assessing uptake and excretion</p>	<p>Urinary measurement of metabolite, e.g. dimethylphosphate in workers exposed to dichlorvos Urine analysis for haematuria Determination of protein adducts and screening for preneoplastic lesions in MOCA {4,4'-methylenebis(2-chloroaniline)}-exposed workers Determination of DNA adducts in coke oven workers exposed to polycyclic aromatic hydrocarbons</p>

Table 4.8 Means to either prevent or determine the level of exposure to occupational carcinogens.

stoves arises in rural areas of developing countries. Exposure may be reduced by introducing improved stoves, better housing and cleaner fuels. Environmental exposure to tobacco smoke is a key aspect of atmospheric pollution and reducing this hazard is discussed elsewhere (*Tobacco control*, p128).

Soil and water pollution

The United Nations Environment Programme establishes warning systems for countries in which the environment and human health may be affected by the export of hazardous substances and pesticides from where they are manufactured. The Rotterdam Convention, 1998, which

replaced various voluntary systems, obliges an importing country to give explicit informed consent before specific chemicals (such as DDT and polychlorinated biphenyls) can cross its borders. This measure is particularly important to countries with limited scientific expertise or equipment to deal with hazardous materials.

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WEBSITES

- International Labour Office:
<http://www.ilo.org/>
- UK Health and Safety Directorate: Preventing or controlling exposure to substances which can cause occupational cancer:
<http://www.hse.gov.uk/hthdir/noframes/cancers.htm>
- The Air Management Information System, WHO's Healthy Cities Programme:
<http://www.who.int/peh/air/amis.html>
- EPA National Center for Environmental Assessment, Cancer Guidelines:
<http://www.epa.gov/ncea/cancer.htm>
- United Nation Environment Programme:
<http://www.unep.org>
- National Institute for Occupational Safety and Health (USA):
<http://www.cdc.gov/niosh/homepage.html>

REDUCTION OF EXPOSURE TO ULTRAVIOLET RADIATION

SUMMARY

- > Encouragement of sun-protective behaviour is the most effective public health measure to reduce incidence of skin cancer, particularly in highly susceptible white populations, and especially in children.
- > Available options include sun avoidance by using shade, wearing protective clothing and using sunscreens.
- > Often, the protective effect of sunscreens is counteracted intentionally-extended periods of sun exposure, notably during vacations.
- > Downward trends in melanoma incidence in some countries reflect a successful implementation of prevention policies.

Skin cancer is the most common cancer worldwide, although only one form, melanoma, is comprehensively documented (*Melanoma*, p253). Over 100,000 cases of melanoma occurred worldwide in 1990. It is estimated that 2.75 million basal and squamous cell carcinomas were diagnosed in 1985, which may be equated with 30% of all newly diagnosed cancer [1]. Such non-melanocytic cancers are usually not life-threatening, but are cause for the provision of medical services, including hospital admissions.

Solar radiation is established as a cause of skin cancer and may account for 80-90% of such disease [2]. The incidence of skin cancer in different communities varies according to skin type and distance from the equator. The highest rates occur in Australia, where cancer incidence is dominated by skin cancer that, in terms of incident cases, outnumbers all other forms of cancer by more than three to one [3].

The scope of sun-protection strategy

The extent of individual exposure to sunlight is, in the first instance, determined by personal behaviour. Two types of exposure can be distinguished: intentional exposure (usually in the context of achieving a tan) and unintentional exposure in the course of daily life. The immediate goal of sun protection programmes is to affect individual behaviour, specifically in relation to intentional exposure. Programmes may be targeted to particular population groups or to the community as a whole. Epidemiological evidence indicates that sun exposure during childhood and adolescence contributes markedly to lifelong risk of skin cancer [4]. The intensity and duration of targeted intervention largely determines the impact of such programmes. Individual sun-related behaviour may be influenced by mass media campaigns and the provision of educative material. Thus the “Sun Awareness” programme in Canada used strategies for improving community knowledge about skin cancer and sun protection, which included mass media, distribution of educational brochures and development of a school curriculum to promote sun protection [5].

Prevention programmes may appropriately focus on young people, parents, caregivers and the settings in which young people spend time outdoors. In relation to children and adolescents, relevant agencies to be engaged in sun protection programmes include early childhood services, schools and those involved in providing sport and recreational activity. Attention should also be paid to adults with high intermittent or cumulative sun exposure, specifically including workplace exposure for those involved in agricultural, forestry, fishery, construction and outdoor electricity transmission and similar work [6]. General practitioners and community health nurses may be encouraged to play a role in educating specific sections of the community to adopt improved sun protective behaviour.

Provision of structural and environmental support to reduce sun exposure necessitates an infrastructure that is responsive and well resourced to steer relevant programmes and strategies [7].

Means of intervention

Public health programmes developed to reduce skin cancer focus on a range of means to reduce sun exposure. The means to be used may vary between areas of high and low sunlight. Relevant strategies may include dissemination of knowledge about the intensity of sunlight in the local environment, scheduling activity or work to be indoors around solar noon, minimizing the time spent outdoors in sunny seasons, and advice as to how to avoid direct sunlight exposure during times when the ambient intensity is high. Protection when in direct sunlight may be achieved by wearing protective clothing, hats or sunglasses and using sunscreens [8].



Fig. 4.11 Sun-protective behaviour can be taught at a young age.



Fig. 4.12 T-shirt and sign advertising the “SunSmart Campaign” on a beach in Australia.

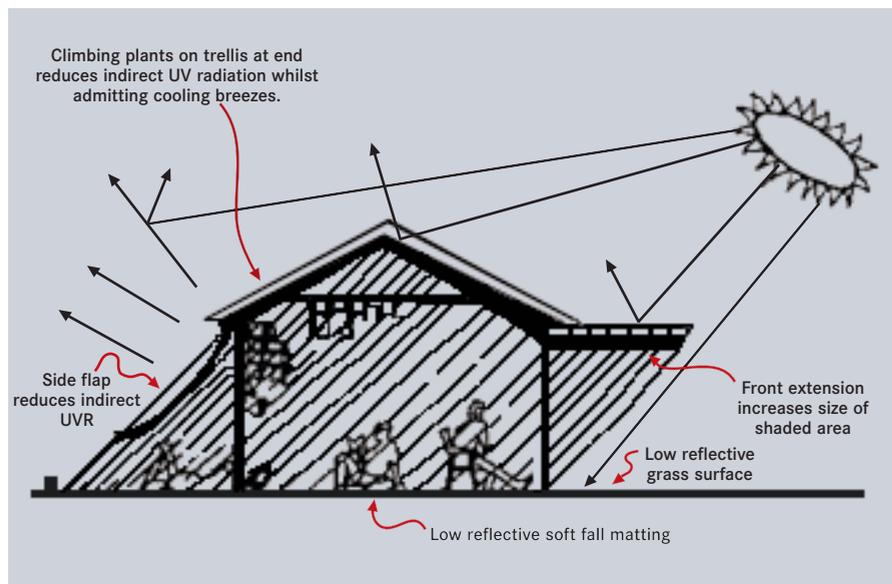


Fig. 4.13 Structural and other design features of a garden shelter designed to provide protection from exposure to the sun.

Means of sun protection include the provision of shade that falls in the right place at the right time of day (Fig. 4.13). Shade barriers, which may be either structures or trees, need to be of sufficient size, and provide at least 94% protection against direct ultraviolet radiation [9]. Natural shade is attractive because of its aesthetic appeal, cooling effect and fewer disposal problems than with built shade. Advantages of the latter include the precision with which shade needs can be met and other uses including rainwater collection and solar power generation. Provision of adequate and appropriate shade requires planning, an aspect of which is a “shade audit” to determine the adequacy of existing shade. Planning additional shade requires consideration of safety, site usage patterns, climatic conditions, aesthetics, sightlines and the possibility of vandalism. Most summer clothing provides protection factors against sunburn of greater than 10; more than 85% of fabrics tested have protection factors of 20 or more. Factors that affect the protection offered by fabrics against sunlight include weave, colour, weight, stretch and wetness [10]. By comparison with other options, scant attention

is given to sun-protective clothing in relevant groups [11].

Sunscreens are available worldwide as consumer products; the European Union and USA account for 75% of the world market. Sunscreens are regulated either as cosmetics (European Union, Japan, South Africa and South America) or as drugs (USA, Canada and Australia). Investigations of sunscreen usage have included determination of who uses them, in what circumstances are they used, why sunscreens are used, and what has been the experience of users. It is evident that sunscreen usage affects other sun-related behaviour, such as deliberate engagement in sun exposure, the duration of such exposure, and the duration of incidental or intentional sun exposure [12].

Sunscreens absorb ultraviolet radiation across the 290-400 nm spectrum. Efficacy is expressed through the “sunscreen protection factor” (SPF) which is the ratio of the least amount of ultraviolet energy required to produce minimal erythema on skin protected by the sunscreen in question to the energy required for the same effect on unprotected skin. Most commercial preparations are presented as

having SPF values of up to 15-20. “Active” ingredients of sunscreens are the chemicals included to reduce the amount of ultraviolet radiation that reaches viable cells of the skin. Sunscreen formulations typically contain UVA absorbers (examples being cinnamates and derivatives of para-aminobenzoic acid) and UVB absorbers (such as the benzophenones) together with solvents, wetting and suspending agents and preservatives [13].

Outcome

A range of end-points may be employed to assess the efficacy of sun-protective activity as a means of preventing skin cancer. A high proportion of sun protection campaigns incorporate some measure of outcome, although few studies of large-scale community interventions have been reported. In assessing the results of particular campaigns, it is important to consider whether people change their behaviour in ways that counteract the benefits of a sun protection campaign [13].

The efficacy of particular interventions in reducing risk of cancer has been most comprehensively studied in relation to sunscreens. Sunscreens undoubtedly prevent sunburn. In experimental studies, sunscreens have been definitively shown to prevent squamous cell carcinoma induced by solar-simulated radiation in mice. The prevention of skin cancer in humans is less clearly established, determination of the issue being complicated by a number of factors. These include the consideration that use of the sunscreen may determine (and perhaps even encourage) sun exposure. Approximately half the relevant case-control studies recently reviewed by IARC (8/15) recorded significantly higher risks for melanoma in users of sunscreens than in non-users, while a minority of such studies showed lower risk for melanoma in users compared to non-users [13]. Some findings imply that sunscreen use may encourage prolonged sun exposure, a scenario which obviously complicates attempts to demonstrate protective effects of sunscreens. In contrast to the data concerning risk of melanoma, corresponding studies in relation to squamous cell carcinoma constituted “limited” evi-

dence for the preventive effect of topical use of sunscreens [14]. In respect of the efficacy of all sun protection behaviour, the high incidence of

skin cancer in Australia may constitute a sensitive indicator. In this regard, some positive results are already available. The incidence of basal cell carcinoma and

melanoma in younger people (under 55), especially among women, is no longer increasing and, in some age groups, has begun to decline [15].

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WEBSITE

Anticancer Council of Victoria SunSmart programme:
<http://www.sunsmart.com.au/>

HEPATITIS B VACCINATION

SUMMARY

- > Persons chronically infected with hepatitis B virus are at high risk of developing chronic liver disease (cirrhosis) and hepatocellular carcinoma.
- > The likelihood of infection is greatest for infants and decreases with age.
- > Childhood vaccination against hepatitis B is a cost-effective measure to prevent adult morbidity and has been shown to prevent the development of chronic carrier status in more than 95% of vaccinated children.
- > Hepatitis B vaccine is the first and at present the only cancer-preventive vaccine. It has already been demonstrated to reduce the risk of hepatocellular carcinoma in some high-incidence areas.

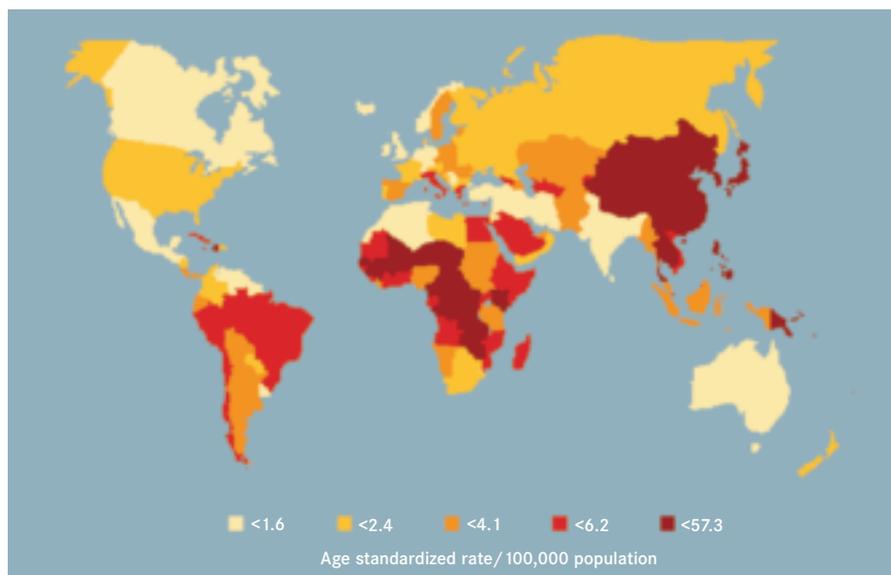


Fig. 4.14 Global incidence of liver cancer in women.

Hepatocellular carcinoma is one of the most common and most lethal cancers worldwide. The disease more commonly affects males, and generally those in their most economically productive years. There is striking geographical variation in incidence, with very high rates in South-East and East Asia, the Pacific rim and sub-Saharan Africa and much lower rates in North America and Europe (*Liver cancer*, p203).

The geographical distribution of chronic hepatitis B virus (HBV) infection and hepatocellular carcinoma is very similar (Figs. 4.14, 4.15). First discovered as a cause of acute fulminant hepatitis in 1969, HBV has since been identified as the major etiologic agent in hepatocellular carcinoma (Fig. 4.18). Subsequent research has documented variations in disease outcomes based on age of exposure, defined differences in HBV transmission patterns and provided estimates of the risk for chronic liver disease and hepatocellular carcinoma associated with long-term HBV

infection. It is estimated that 20-25% of all chronic carriers will die from liver disease associated with HBV infection (*Chronic infections*, p56).

Most individuals infected with HBV will develop no symptoms and subsequently will demonstrate complete resolution and lifelong immunity to the virus. A small portion of exposed persons will have an acute symptomatic infection with jaundice, malaise and flu-like symptoms, with a small subset of these individuals developing fulminant hepatic failure with significant mortality. The other possible outcome from HBV infection is chronic persistence of the virus and the development of the carrier state, defined by the expression of hepatitis B surface antigen (HBsAg) in the blood. The age of exposure to the virus is the primary determinant of infection outcome (Fig. 4.21). Younger children are extremely unlikely to develop any acute symptoms but have much higher rates of chronic persistent infection. The converse is true of adolescents and adults with more frequent symptomatic

acute infection but lower rates of chronic HBV infection. Children born to an HBV-infected mother have a 90% or greater chance of chronic infection. With increasing age of exposure, the risk of chronic HBV infection decreases markedly from a risk of up to 90% for infants to around a 30% risk for children around 5 years of age, decreasing to <5% for young adults [1].

The high HBV carriage rates in endemic regions result in a large pool of infectious individuals, which perpetuates horizontal and vertical transmission and ensures that children are exposed to the virus at a young age. Consequently, the age of infection is lower with resulting higher rates of chronic HBV infection, higher hepatocellular carcinoma incidence and a younger median age of cases. Unfortunately, the resources required to identify, treat and palliate affected individuals in many of these highly endemic regions are largely unavailable. In regions of low and intermediate endemicity, parenteral transmission is more common, through contaminated

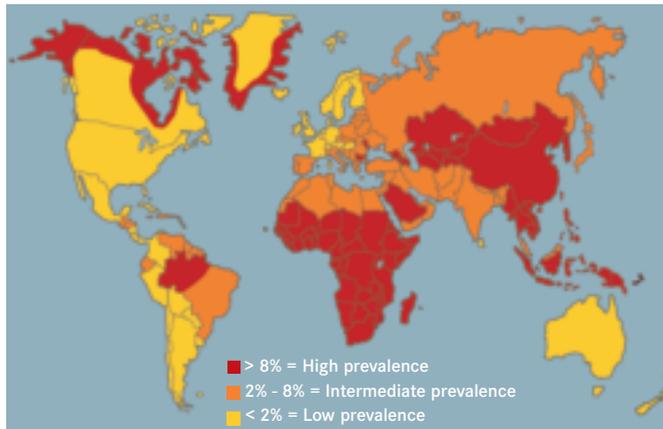


Fig. 4.15 Global prevalence of chronic hepatitis B virus (HBV) infection 1997, based on HB surface antigen serology.

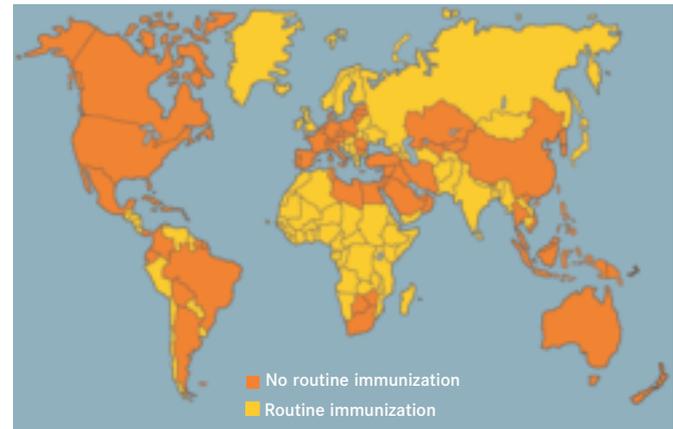


Fig. 4.16 Global distribution of countries using HBV vaccine in their national immunization programme, 2000.

blood products, sharing contaminated needles during intravenous drug use and through sexual transmission.

Currently, there are around 350 million chronic carriers of HBV worldwide and, based on conservative assumptions, an estimated 70 million of these individuals are likely to die from HBV-related liver disease. Because of the relatively low cost of the hepatitis B vaccine and the uniformly fatal outcome of hepatocellular carcinoma, childhood hepatitis B vaccination in highly HBV endemic areas is one of the most cost-effective measures available for prevention of early mortality in adults [2].

Nature of the intervention

Vaccination efforts have historically concentrated on preventing acute infectious diseases, particularly those of childhood. Hepatitis B vaccine is the first vaccine designed to prevent a major human cancer and currently the only one in widespread use. The vaccine was initially developed by purifying the viral envelope component of the surface antigen particle (HBsAg) of the virus from the blood of individuals with chronic HBV infection. This plasma-derived vaccine undergoes intensive treatment to destroy any live virus, as well as to remove any other potential contaminants, and is then combined with an alum adjuvant to stimulate the immune system. Second-generation vaccines involved production of HBsAg particles

through yeast or mammalian cells using recombinant DNA technology. Both plasma-derived and DNA recombinant vaccines are equally safe and effective. Since the early 1980s, hundreds of millions of doses of hepatitis B vaccine have been administered worldwide. Adverse reactions are uncommon and generally mild in nature, with this vaccine considered among the safest of vaccines. Hepatitis B vaccine is generally administered in sequential doses with at least four weeks between doses. An appropriate response to the vaccine is the development of antibodies to the surface antigen and is termed seroconversion. Three doses of vaccine will generally produce seroconversion rates in excess of 90%.

Vaccination campaigns aimed at reducing HBV-related hepatocellular carcinoma must take into consideration the patterns of HBV transmission. Because the highest risk for development of chronic HBV carriage occurs at the youngest ages, hepatitis B vaccine is most efficacious when given as close to birth as possible. This early vaccination benefit will be most pronounced in those high-endemicity countries with significant mother-to-child and early horizontal transmission. Hepatitis B vaccine does not interfere with other vaccines and can be administered simultaneously with many of the other routine childhood immunizations, including diphtheria, tetanus and whole-cell pertussis vaccine, oral attenuated poliomyelitis vac-

cine and BCG (bacille Calmette-Guérin). Integration of hepatitis B vaccine into the routine “Expanded Programme on Immunization” (EPI) efforts of individual countries provides the most appropriate strategy for global hepatitis B vaccination.

In addition to the focus on hepatitis B vaccination to prevent primary infection with HBV, new therapeutic vaccines have been designed to treat chronic HBV carriers and hopefully prevent progression to cirrhosis or cancer. Several novel vaccines, including DNA-based vaccines which incorporate the hepatitis B surface antigen gene, have been designed to stimulate the immune system of HBV-infected individuals, through induction of either a T-cell response or production of neutralizing antibodies [3]. Although therapeutic vaccines demonstrate potential, these trials are in the earliest stages and it remains to be seen what level of efficacy in reducing or stopping HBV replication and preventing progression can be achieved. The frequency and degree of serious adverse effects from these vaccines must also be demonstrated to be acceptably low.

Implementation of preventive measures

In the early 1990s, WHO/EPI recommended integration of hepatitis B vaccination into the routine EPI and this was subsequently endorsed by the World Health Assembly. Earlier, hepatitis B vaccine was utilized sporadically, with fewer than 20 countries routinely administering the vac-

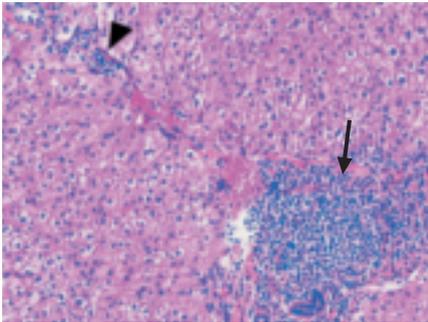


Fig. 4.17 Chronic active HBV-associated hepatitis is associated with risk of hepatocellular cancer. Inflammatory infiltrates are present in the parenchyma (arrowhead) and in the periportal space (arrow).

cine. Initial implementation strategies varied based on the local epidemiology. Routine childhood immunization was the recommendation for high-endemicity countries, having over 8% of the population with chronic HBsAg carriage. Low-endemicity regions (<2% HBsAg carriage) with delayed patterns of transmission may focus on vaccinating adolescents before their likely exposure through sexual contact or needle-sharing. Alternative “high-risk” strategies were also employed, focused on vaccinating individuals with behaviour (needle-sharing, multiple sexual partners) or occupations (health care workers) which put them at significant risk for HBV exposure. Although these targeted approaches were beneficial in some risk groups, they did not lead to any measurable reduction in HBV infection rates at a regional or national level.

The most effective preventive strategy worldwide is routine immunization as part of the regular EPI programme. Timing of doses of hepatitis B vaccine can be adjusted to conform to the childhood immunization schedule of the individual country with little decrease in seroconversion rates. Countries with limited maternal-child health services and low vaccine coverage for the other EPI vaccines may be hard-pressed to add any additional vaccines. The cost of the hepatitis B vaccine compared to other childhood vaccines is

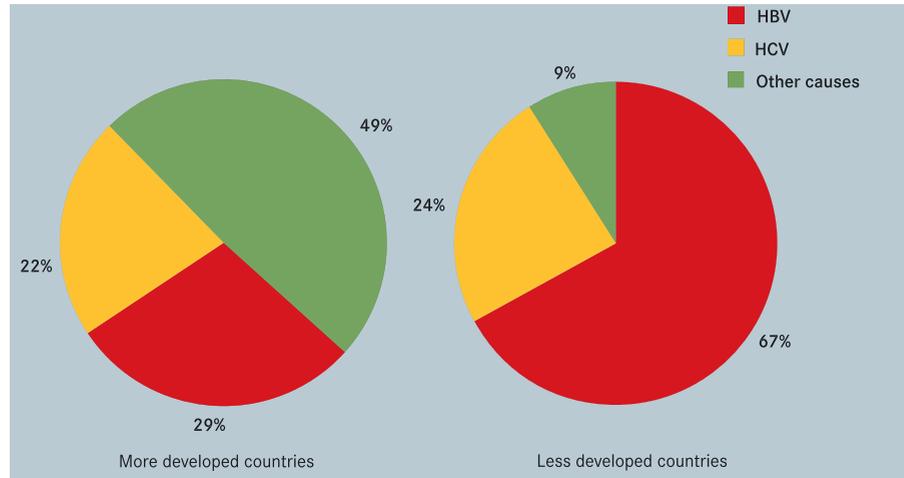


Fig. 4.18 Estimate of the risk of hepatocellular carcinoma attributable to hepatitis viruses and other causes (e.g. alcohol cirrhosis).

also a significant impediment to global implementation. However, over the last decade a dramatic decline in cost from over US\$ 100 to as little as US\$ 0.50 per paediatric dose in developing countries has greatly increased the feasibility of large-scale HBV control efforts.

Evidence of outcome

Protection against both acute and chronic HBV infection is related to the development of protective levels of antibody in response to vaccination. Hepatitis B vaccine has been used in numerous field trials throughout the world with documented immunogenicity in the 90-95% range. Despite rapidly declining levels of antibody following immunization, protection among vaccine responders is almost universal. Long-term protection against acute and chronic infection has been demonstrated in a variety of settings with follow-up ten years after vaccination [3]. One of the largest on-going cohort studies has shown that 80-90% of all HBV infections and 90-95% of chronic HBV infections can be prevented through immunization [4]. Similar rates of vaccine efficacy have been demonstrated in studies from other populations.

Prevention of chronic HBV carriage should lead to subsequent decreases in the rates of hepatocellular carcinoma after several decades – the period of time generally

required for chronic persistent HBV infection to develop to hepatocellular carcinoma [5]. Validation of this premise is under way in the Gambia, West Africa, where both vaccinated and unvaccinated individuals will be followed for 25-35 years to document the effectiveness of the vaccine

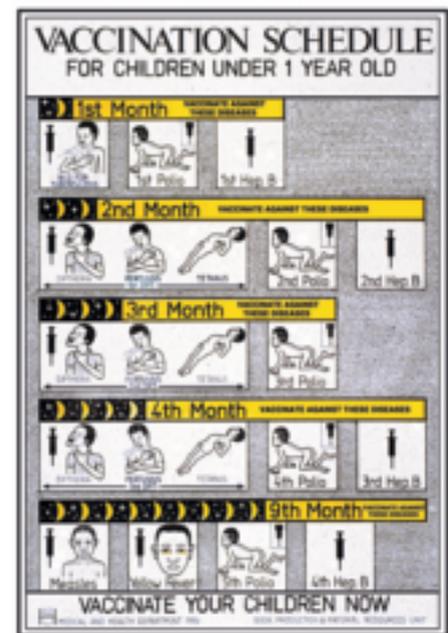


Fig. 4.19 Public health poster publicizing vaccination against HBV for children under one year old in the Gambia.



Fig. 4.20 HBV vaccination of infants in the Gambia.

in preventing chronic liver disease and hepatocellular carcinoma at the individual level. Taiwan, which has high HBV carriage rates and a high hepatocellular carcinoma incidence, was one of the first countries to introduce routine vaccination in 1984. A nationwide statistically significant reduction in childhood hepatocellular carcinoma has already been observed in Taiwan among the vaccinated cohort of children aged 6-14 compared to the cohort of chil-

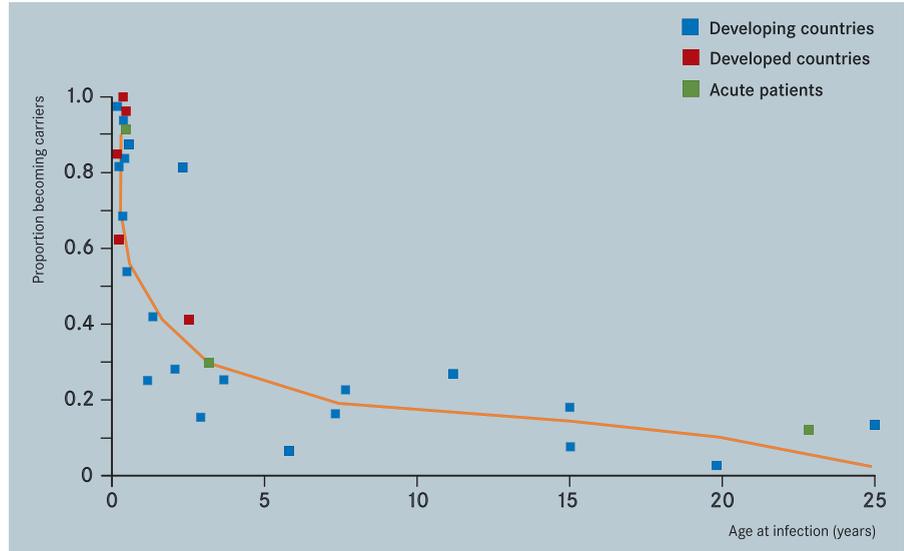


Fig. 4.21 Risk of becoming a chronic carrier of HBV based on age at infection. Risk is highest in very young children.^[1]

dren born before implementation of the vaccination programme [6].

Over 80 countries have now integrated hepatitis B vaccine into their routine immunization programme, with varying levels of coverage (Fig. 4.16). Hepatitis B vaccine may now be available to around half the world's children. However, children from countries with the highest risk of HBV infection are frequently the same countries with limited resources or infrastruc-

ture to provide the vaccination. Despite the decline in vaccine cost, limited health budgets in poorer countries make ability to purchase vaccine a primary obstacle to global immunization. WHO and other donor and non-profit agencies have focused on developing a vaccine support strategy to aid those needy countries with an adequate vaccination infrastructure to purchase and provide hepatitis B vaccine to the world's children.

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WEBSITES

- WHO fact sheets on vaccination against HBV and HCV: <http://www.who.int/health-topics/hepatitis.htm>
- CDC National Center for Infectious Diseases: <http://www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm>

HUMAN PAPILLOMAVIRUS VACCINATION

SUMMARY

- > Infection with human papillomaviruses is common and causes some benign lesions as well as cervical and other cancers.
- > Vaccines based on human papillomaviruses may be prophylactic, therapeutic or a combination of both, and are potentially a safe and effective means of preventing or controlling disease.
- > Technical difficulties associated with the development of such vaccines are considerable, but several phase I, II and III trials are under way.

From a public health perspective, there is an overwhelming case to justify the development of human papillomavirus (HPV) vaccines. At least 50% of sexually active adults have had a genital HPV infection. So-called “low-risk” HPV types cause benign lesions or genital warts, while others, called “high-risk” or “oncogenic” types, are the principal cause of cervical cancer and are also associated with other cancers of the anogenital region, and possibly with cancers of the upper aerodigestive tract and of the skin (*Chronic infections*, p56; *Cancers of the female reproductive tract*, p215). Since both genital warts and cervical cancer rates are rising in young women in some populations, the burden of HPV-associated disease is likely to increase in coming decades. HPV-associated lesions can regress spontaneously due to cell-mediated immunity. This is indicated by an increased risk of HPV infection and of HPV-associated lesions in immunosuppressed patients, and the observation that neutralizing antibodies can block HPV infection *in vivo* and *in vitro* [1]. On the other hand, the occurrence of chronic HPV infections and reinfections suggests that in some individuals natural immunity is not effective in controlling HPV

infection. Although the exact mechanisms of immune evasion are not fully understood, the development of effective vaccines for papillomaviruses in various animal models [2-4] has stimulated the development of similar vaccines for humans. Three main types of HPV vaccine are being developed: prophylactic vaccines, therapeutic vaccines and combined or chimeric vaccines which have both effects.

Prophylactic vaccines

Vaccines based on the induction of neutralizing antibodies against the HPV structural proteins L1 and L2 are termed “prophylactic”. The generation of virus-like particles (VLPs), which are morphologically indistinguishable from authentic virions, apart from lacking the viral genome [5], has greatly accelerated the development of these vaccines (Table 4.9). VLPs for HPV 6, 11, 16, 18, 31, 33, 39, 45 and 58 have been produced in various laboratories. At least five HPV VLP-based vaccines have been developed and have gone through pre-clinical evaluation. Phase I-II clinical trials to assess safety, immunogenicity, dose, schedule, route of administration and adjuvants for these vaccines are being planned or have been initiated. The US National Cancer Institute (NCI) vaccine has been shown, in a phase I study of 58 women and 14 men, to be able to induce serum antibody titres that are approximately 40-fold higher than that

observed during natural infection [6]. However, certain basic issues need to be solved before the mass use of these vaccines can commence [7,8]. Such issues include the HPV types to be included (HPV 16 accounts for 50% and HPV 18, 31 and 45 for a further 30% of cervical cancers), the route of administration, the target population (ideally infants) and the cost (Table 4.10). The ideal HPV vaccine will have to be polyvalent (i.e. contain the VLPs of the HPV types most commonly associated with cancer in a given population, Fig. 4.22), inexpensive, and able to confer a long-lasting protection for infants of both sexes. Although HPV-associated genital tumours are much more frequent in women than men, men act as vectors of the virus.

While the problems already outlined are being solved, phase III trials to assess the efficacy of available VLP-based vaccines to prevent HPV infection and cervical intraepithelial neoplasia are being planned. For example, the NCI vaccine will be used in a phase III trial in Costa Rica in the context of a large cohort study on the natural history of HPV in Guanacaste province.

Therapeutic and combined vaccines

Vaccines based on the induction of cellular immunity directed against cells expressing viral proteins are termed “therapeutic” and are intended to induce

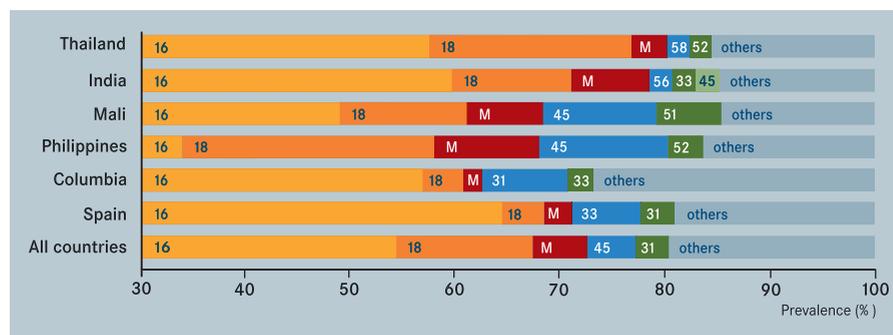


Fig. 4.22 The most common HPV types found in cervical carcinoma biopsies, by country. M = multiple infections with HPV 16 and/or 18.

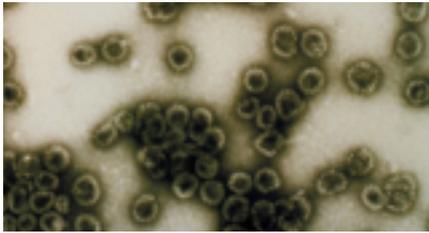


Fig. 4.23 Proteins which make up the HPV particle are used in the manufacture of a vaccine.



Fig. 4.24 Collecting blood from a participant in an HPV prevalence study, Ibadan, Nigeria.

regression of HPV-associated lesions. The E6 and E7 proteins (*Oncogenes and tumour suppressor genes*, p96) are the natural targets for these vaccines because such proteins are consistently expressed in cervical cancer cells. Since neither protein is located on the cell surface, the most effective mechanism for the destruction of cancer cells is likely to be through the action of cytotoxic T cells which recognize intracellular processed peptides in complex with major histocompatibility complex (MHC) class I molecules. Candidate therapeutic vaccines are constituted using either synthetic peptides, recombinant proteins or live vectors coding for HPV proteins [8].

Several vaccines that target the E6 and E7 oncoproteins of HPV 16 and 18 are now available and are being used in phase I-II trials (Table 4.11). These trials have been, or are being carried out in patients with advanced cervical cancer or in patients with genital precancerous lesions. Some of the vaccines are peptide-based while others are based on a recombinant vaccinia vector expressing E6 and E7 from both HPV 16 and 18 [9]. Results from only one of these trials have been published in full [10]. As is the case for prophylactic HPV vaccines, in order to develop safe and

Organization (vaccine name)	HPV type and antigen	Vaccine type	Current status
Medimmune SmithKline Beecham (MEDI-501)	HPV-11 L1	VLP	Phase II trials under way; safety and immune response proven in Phase I trials
Medimmune SmithKline Beecham (MEDI-503, 504)	HPV-16, 18 L1	VLP	Phase II trials under way
Merck, CSL Limited	HPV-16 L1	VLP	Phase II trials under way in USA, UK and Australia; Phase III to begin soon
National Cancer Institute, NIAID	HPV-16 L1	VLP	Phase II trials under way; large-scale efficacy trial planned to begin in Costa Rica in 2002
Medigene	HPV 16 L1, E7	VLP	Phase I/II trial

Table 4.9 Prophylactic HPV vaccines under development in clinical trials. VLP = virus-like particles

effective therapeutic vaccines, serious technical difficulties must be overcome. Such vaccines must be tailored to the MHC antigens of the recipients and must elicit a stronger anti-tumour response than that produced without vaccination. Combined or chimeric vaccines are designed to have the ability to both protect against HPV infection and induce regression of HPV-associated lesions [8]. The first approach considered was to develop an L1 or L1-L2 VLP-based vaccine capable of inducing a cytotoxic T-cell response. Another approach being used is the production of chimeric VLPs that con-

tains both L1 or L1-L2 and E6 or E7 proteins [9]. Such vaccines should induce a protective response elicited by L1 or L2 proteins and a cytotoxic T cell-mediated response elicited by the E6 or E7 proteins. There are still many technical and practical problems to be solved before safe, effective and inexpensive HPV vaccines are produced for mass use in the general population. Although these problems appear to be greater for therapeutic vaccines, their production has moved into an industrial phase. Lessons learnt from the slow introduction of hepatitis B virus vaccine into routine immunization pro-

Issue	Comments
HPV types to be included	At least 30 oncogenic types exist, but HPV 16 accounts for 50% and HPV 18, 31, and 45 together for a further 30% of cervical cancers
Route of administration	Oral or nasal spray
Target population	Ideally infants, girls and boys
Cost	It should be low, perhaps using bacterial vectors or transgenic plants

Table 4.10 Open issues in the development of prophylactic HPV vaccines.

Vaccine	Site of trial	Number of patients	Condition of patients
Recombinant vaccinia HPV 16 and 18 E6 and E7 proteins (Cantab Pharmaceuticals, UK)	UK (University of Wales)	8	Advanced cervical cancer CIN III lesions Advanced cervical cancer Early invasive cervical cancer
	UK (University of Wales)	10	
	US (NCI)	14	
	UK, The Netherlands, Belgium, Germany and Sweden	18	
HPV 6-L2 E7 fusion protein (Cantab Pharmaceuticals, UK)	UK (London)	36	Genital warts
HPV 16-E7 protein	Australia (Queensland)	5	Advanced cervical cancer
HPV 16-E7 peptide	The Netherlands (Leiden University)	15	Advanced cervical cancer
HPV 16-peptide	US (Norris Cancer Center, USC)	45	CIN II-III lesions VIN lesions
		15	
HPV 16-E7 peptide	US (NCI) (Cytel Co, US)	15	Recurrent or refractory cervical cancer

Table 4.11 Phase I-II clinical trials with HPV therapeutic vaccines.

grammes should help to reduce the period between availability of an appropriate HPV vaccine and its introduction for routine

use. However, it is unlikely that this will happen within the next 15-20 years. Meanwhile efforts should continue to

introduce or improve existing screening programmes for cervical cancer (*Screening for cervical cancer*, p167).

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WEBSITE

Vaccines, Immunization and Biologicals (WHO):
<http://www.who.int/vaccines/en/hpvrd.shtml>

CHEMOPREVENTION

SUMMARY

- > Chemoprevention is defined as reduction of the risk of cancer development through the use of pharmaceuticals or micronutrients.
- > The breast cancer drug tamoxifen reduces the risk of developing a second cancer in the other breast.
- > A lower risk of colon cancer has been observed following regular use of aspirin and related non-steroidal anti-inflammatory drugs which reduce the risk of recurrence of adenomas.
- > Trials to establish chemopreventive activity by micronutrients, including carotenoids and retinoids, among people at high risk, have been inconclusive.

The goal of chemoprevention is to prevent or reverse the process of carcinogenesis, or to enhance regression of abnormal cells or tissue to normality with minimal or no side-effects. Relevant mechanisms vary, and in many cases have not been determined. Although the carcinogenic process is often characterized as being dependent on mutation, epigenetic changes are also involved. These may be perturbed during the 20-year (or longer) latent period before invasion and metastasis occur (*Multistage carcinogenesis*, p84) and appear to provide the basis for chemopreventive activity by a variety of agents. Chemoprevention may have great potential for control of cancer.

The scope of chemopreventive agents

Many studies have shown that people who consume more vegetables and fruit than persons at otherwise the same risk who consume less or none, have a reduced risk of cancer (*Diet and nutri-*

tion, p62). Although the results of intervention trials of dietary augmentation with fibre and fruit and vegetables to reduce the occurrence of colonic polyps have so far been negative, there is considerable evidence, particularly from experimental studies, that some chemicals present in the diet at low concentrations play an important role in protecting against cancer. Some examples include folate, curcumin, genistein, selenium and tea catechins. Micronutrients (defined as nutrients present in the body in amounts less than 0.005% of body weight) which appear to protect against cancer include β -carotene, α -tocopherol and ascorbic acid. The preventive activity of vegetables and fruit is partially credited to micronutrients. However, intake of these agents as vitamin pills or diet supplements is yet to be established (through trials) as preventing cancer in humans. So, although the evidence suggests that modification of diet can lower cancer risk, the same effect is not yet

achievable using easy-to-take, pre-packaged natural or synthetic compounds. Putative chemopreventive agents include pharmaceutical drugs and hormonally active agents. There is conclusive evidence that tamoxifen reduces the risk for contralateral breast cancer in women with a previous diagnosis of breast cancer. Observational studies indicate a moderately reduced risk for colorectal cancer in people using aspirin regularly, and an indication of greater reduction in risk with



Fig. 4.25 The aim of chemoprevention is to prevent cancer by the administration of easy-to-take, pre-packaged natural or synthetic compounds typically in the form of a pill.

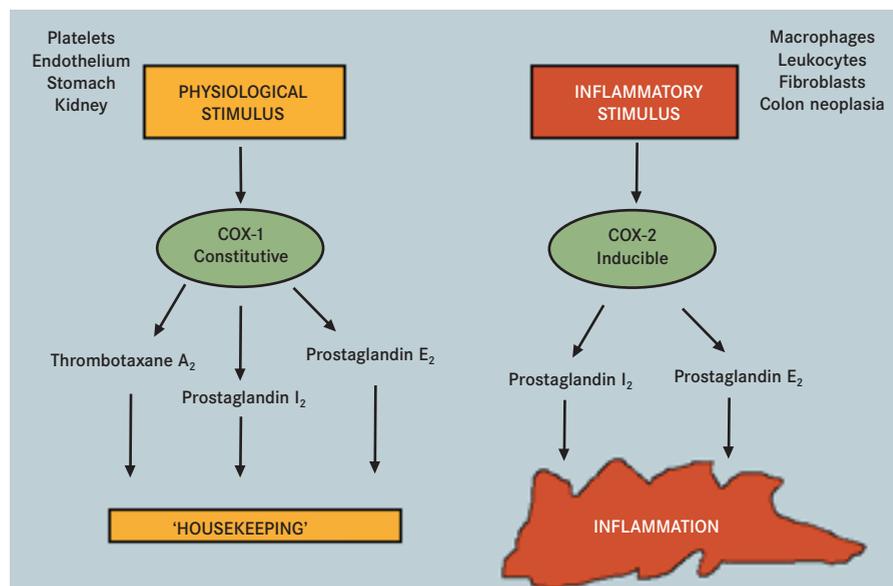


Fig. 4.26 COX-1 and COX-2 cyclooxygenases: COX-1 is constitutively expressed and regulates the homeostasis of various tissues, including the generation of cytoprotective prostaglandins. Inflammatory stimuli induce COX-2, which is also highly expressed in colorectal neoplasia in the absence of stimulation.

prolonged use. Similar drugs, that is other non-steroidal anti-inflammatory drugs, appear to have this effect, and cancers at sites apart from the bowel may be susceptible. In respect of these and similar agents, the IARC began a series of *Handbooks of Cancer Prevention* in 1997 by considering the cancer-preventive activity of non-steroidal anti-inflammatory drugs [1]. Subsequent volumes have been published on carotenoids [2], vitamin A [3], retinoids [4] and use of sunscreens [5], the latter being substances that reduce exposure to a carcinogenic agent (in this case, sunlight).

Relevant mechanisms

The appropriate use of a chemopreventive agent may depend on an understanding of the mechanism of action at all levels, in animals and humans. Without this knowledge, selection of preventive agents is intuitive or the product of chance. The

trend in the field of chemoprevention has therefore been to develop new agents based on known mechanisms of action.

COX-2 inhibition

One aspect of tumour development is the release of arachidonic acid and its metabolism to eicosanoids, including prostaglandins. Down-regulation of the cyclooxygenases (COX-1 and COX-2) by pharmacological means may result in reduced incidence of cancer, because cyclooxygenases catalyse the formation of prostaglandins, which have multiple effects that favour carcinogenesis [7] (Fig. 4.26). A number of prostaglandin synthesis inhibitors are effective in counteracting tumorigenesis. Compounds such as anti-inflammatory steroids (i.e. glucocorticoids) are potent inhibitors of experimental skin carcinogenesis [8]. These compounds are effective inhibitors of phospholipase A₂, which may explain their abil-

ity to decrease the amount of arachidonic acid available for metabolism to pro-inflammatory prostaglandins. Aspirin and aspirin-like drugs can inhibit colorectal tumorigenesis and are among the few agents reported to be useful for chemoprevention of neoplasia [1]. The cyclooxygenase pathway is a major target for prevention by non-steroidal anti-inflammatory drugs, primarily because COX-2 plays a role in inflammation as well as in apoptosis and angiogenesis. From the perspective of chemoprevention, the recent finding that overexpression of the gene for COX-2, a key enzyme for the formation of prostaglandins from arachidonic acid, is an early and central event in colon carcinogenesis provides an important target for the development of chemopreventive agents [9]. Overexpression of COX-2 in epithelial cells inhibits apoptosis and increases the invasiveness of tumour cells [10]. Treatment of colon tumour cells

Agent	Humans	Animals
Non-steroidal anti-inflammatory drugs Aspirin Sulindac Piroxicam Indomethacin	Limited Limited Inadequate Inadequate	Sufficient Sufficient Sufficient Sufficient
Carotenoids β-Carotene (high dose supplements) β-Carotene (usual dietary levels) Canthaxanthin α-Carotene Lycopene Lutein Fucoxanthin	Lack of activity Inadequate Inadequate Inadequate Inadequate Inadequate Inadequate	Sufficient Sufficient Sufficient Limited Limited Limited Limited
Retinoids all- <i>trans</i> -Retinoic acid 13- <i>cis</i> -Retinoic acid 9- <i>cis</i> -Retinoic acid Fenretinide (4-HPR) Etretinate Acitretin N-Ethylretinamide Targretin LGD 1550 Preformed vitamin A	Inadequate Limited Inadequate Inadequate Inadequate Inadequate Inadequate Inadequate Inadequate Lack of activity	Inadequate Limited Limited Sufficient Limited Inadequate Lack of activity Inadequate Inadequate Limited
Sunscreens	Limited (squamous cell carcinoma) Inadequate (basal cell carcinoma) Inadequate (malignant melanoma)	Sufficient - -

Table 4.12 Evidence of cancer preventive activity: evaluations from the IARC *Handbooks of Cancer Prevention* series.

with non-steroidal anti-inflammatory drugs results in a dramatic increase in arachidonic acid concentration, which, in turn, stimulates the conversion of sphingomyelin to ceramide, a known mediator of apoptosis. The activity of non-steroidal anti-inflammatory drugs to inhibit tumour growth may also be related to their induction of lipoxygenases [11].

New pharmacological agents, such as celecoxib, have recently been developed that are selective for inhibition of the enzymatic activity of COX-2, while not affecting the constitutive form of the enzyme, COX-1. Celecoxib has been shown to prevent colon carcinogenesis in a rodent model. In 2000, celecoxib was approved by the US Food and Drug Administration as an adjunct to standard care in patients with familial adenomatous polyposis, in whom *APC* gene defects result in a 100% chance of developing colorectal cancer. It is now in clinical trials in cohorts of patients at high risk of other cancers apart from the colorectum.

Estrogen receptor modulation

Through clinical trials, tamoxifen has been definitively shown to prevent contralateral breast cancer in women previously diagnosed with the disease [12], although an effect on survival has yet to be confirmed. Extensive trials are under way to determine whether a preventive effect may be achieved in women who have not had a previous breast cancer. Although tamoxifen and its derivatives have come into clinical use recently, they were synthesized well over 20 years ago, before the estrogen receptors were cloned. The mechanism of action of these drugs is now understood on the basis of the receptors. The demonstration of occurrence of the estrogen receptor- β , as contrasted with estrogen receptor- α , in the prostate, colon and ovary suggests that it may be useful to develop estrogen analogues that will selectively bind to this isoform of the receptor.

Retinoid receptors

Compounds related to vitamin A (retinoic acid and similar substances termed “retinoids”) were initially shown to modu-

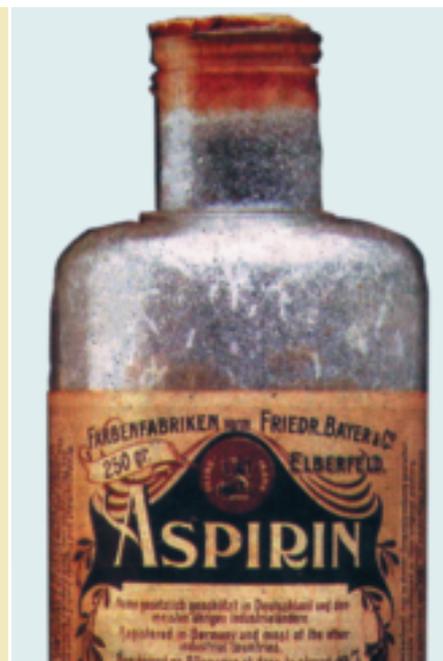
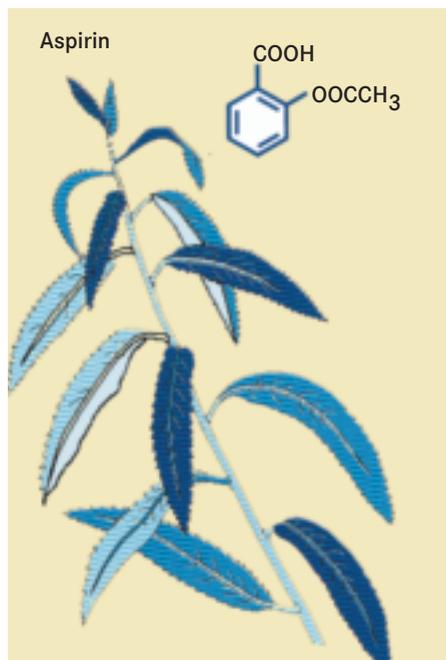


Fig. 4.27 The ancient Greeks chewed the bark of willow trees to alleviate pain and fever, but it was not until the last century that the active ingredient in willow bark, salicin, was isolated and commercially produced as aspirin. Observational studies have shown that regular use of aspirin reduces the risk of cancer of the colon and rectum.

late differentiation in many experimental systems [13]. Retinoids that are selective for binding to the three retinoid X receptors (RXRs), while not binding to the three retinoic acid receptors (RARs), may represent a specific class of chemopreventive agents. The retinoid X receptors are of particular importance in the nuclear receptor superfamily because of their ability to heterodimerize with many other members of this family, including retinoic acid receptors, the vitamin D receptor, the thyroid receptor, as well as with newly discovered “orphan” receptors, such as peroxisome-proliferator-activated receptor- γ .

Analytical epidemiology studies

Since 1970, the role of dietary fibre in colorectal cancer has been explored in many case-control studies, with relatively consistent results suggesting a reduced risk with higher consumption. A meta-analysis of these studies showed both an inverse association and a dose-response relationship [14]. The results of the cohort studies have been much less convincing.

In a recent prospective study of almost 90,000 female nurses who were followed up for more than 16 years, colorectal cancer developed in 787 women, and neither total dietary fibre nor dietary fibre from vegetables, fruit and cereals separately was associated with the risk for distal colonic or rectal adenomas. In fact, greater consumption of vegetable fibre was associated with a small increase in risk [15].

Both case-control and cohort studies have tended to show a reduced risk for colorectal cancer after prolonged use of aspirin [16]. Of 15 studies that specifically addressed the association between regular use of aspirin and/or other non-steroidal anti-inflammatory drugs and colorectal cancer, nine case-control and five out of six cohort studies recorded a lower risk for colorectal cancer; one cohort study showed an increased risk for colorectal cancer among users of non-steroidal anti-inflammatory drugs [1]. As observational epidemiological studies can be subject to bias, chemoprevention with

aspirin and other non-steroidal anti-inflammatory drugs should only be considered established if there are appropriate results from a randomized trial.

Human intervention trials

A number of studies have been performed in which the serum concentrations of β -carotene or dietary intake of

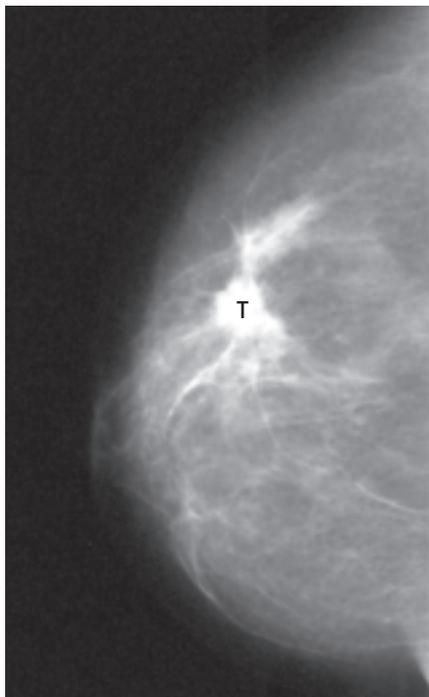


Fig. 4.28 Mammogram showing the location of a tumour (T). Treatment of invasive breast cancer with tamoxifen reduces the risk of a second tumour in the contralateral breast.

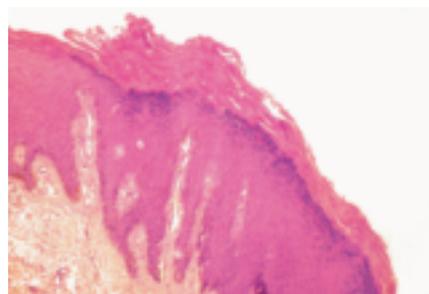


Fig. 4.29 Histopathology of oral leukoplakia which has been assayed in cancer chemopreventive trials with retinoids (see Box: Precursor lesions in chemoprevention trials, p87).

β -carotene were assessed in observational epidemiological studies in relation to cancer risk [17]. The results of these studies suggest that β -carotene has preventive effects against cancers of the lung, oral cavity and pharynx. In order to confirm this interpretation, three large intervention trials were started in the 1980s. Enthusiasm for use of β -carotene in chemoprevention was substantially dampened by the outcomes of these trials. In the two largest, β -carotene use significantly increased the risk for lung cancer among smokers and/or asbestos-exposed workers within three to six years after the start. The third trial, conducted among physicians in the USA who were primarily non-smokers, showed no increased risk for lung cancer [18]. In one of the trials, α -tocopherol supplementation had no effect on the occurrence of lung cancer [19].

A 32% reduction in the incidence of prostate cancer and a 41% reduction in deaths from this cancer were recorded among the smokers randomly assigned to a daily dose of α -tocopherol (vitamin E) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. There was, however, a 50% increase in the occurrence of cerebral haemorrhage among those men taking vitamin E [19]. Thus, before use of vitamin E can be recommended for the prevention of prostate cancer, another trial should be conducted in an independent setting, with careful attention to possible side-effects. The chemoprevention of prostate cancer is otherwise under active evaluation. A number of ongoing randomized trials are comparing the effects of selenium, soy protein, finasteride and other agents. None of these trials have yet yielded unequivocal evidence for the efficacy of any particular agent. It is hoped, however, that dietary supplements will limit the progression of the ubiquitous latent prostate hyperplasia associated with the ageing male to aggressive, malignant disease.

Several combinations of vitamins and salt were tested in a large Chinese trial, and one of these combinations (β -carotene plus vitamins plus selenium)

led to a 13% reduction in total cancer mortality, significant 21% reduction in stomach cancer mortality, but no significant reduction in oesophageal cancer, which was the primary target of the study. Recently a clinical trial on men with a history of non-melanoma skin cancer found that the incidence of prostate cancer was 63% lower among those treated with selenium compared to men receiving a placebo [20].

The future of chemoprevention trials

An issue which is of primary concern for investigations on diet and cancer is to what extent the rather disappointing results from trials of cancer chemoprevention and antioxidants (with the possible exception of those on selenium) negate the results obtained in observational epidemiological studies on the same compounds and on fruit and vegetables. There are at least two important differences between these clinical trials and studies on diet. The first is the dose: the clinical trials used doses of β -carotene (15 to 25 mg per day) which led to blood concentrations 10 to 20 times higher than those achievable through high dietary intake of fruit and vegetables. The second is that clinical trials generally tested one or two compounds at a time, at high doses, while fruit and vegetables represent a complex mixture of hundreds of natural compounds.

The use of the double-blind, placebo-controlled randomized trial design for evaluating preventive actions is important. Many examples are now available of chemopreventive agents which appear to have a beneficial effect in observational studies, but which have failed in randomized trials. Regarding future research in this area, the contradictory results of clinical trials suggest that observational studies combining dietary data and biological markers of diet should be exploited more thoroughly to identify combinations of nutrients potentially associated with cancer prevention and which may be candidates for experimental studies on laboratory animals and, eventually, for chemopreven-

tion trials in humans. We also need more knowledge of the concentrations of chemopreventive agents and their metabolites that prevent cancer in

rodents and how such concentrations relate to those achievable in target human tissues. Finally, the selected intervention agents should be tested in

pilot clinical studies before embarking on large-scale randomized efficacy trials.

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WEBSITES

The NCI's Rapid Access to Preventive Intervention Development (RAPID) Program:
<http://www.cancer.gov/prevention/rapid/#1>

Medscape Drug Info (for information on aspirin, β -carotene, celecoxib, tamoxifen, vitamin A):
<http://www.medscape.com/druginfo>

SCREENING FOR BREAST CANCER

SUMMARY

- > The epidemic increase in breast cancer incidence has led to the introduction of population-based mammography screening.
- > The analysis of large randomized trials has shown that in women aged 50 to 69 years, mammography screening can reduce mortality from breast cancer by 25-30%. For women in the age group 40-49 years the screening efficacy is significantly less.
- > The benefits of mammography in regional or national screening programmes is lower. Under optimal conditions with a high compliance rate, a mortality reduction of 20% appears achievable.
- > There is only indirect evidence that screening by clinical breast examination will reduce the number of breast cancer deaths.

Cancer of the breast is the most common cancer in women worldwide and in many regions, including Europe and Australia, it is still the most common cause of death from cancer in women. Until recently, there has been little change in mortality rates in spite of the steady improvement in prognosis observed in recent years.

Breast cancer is characterized by early systemic dissemination. As a result, awareness of symptoms, and subsequent diagnosis, often occur when disease is advanced and metastatic. Mammography (an X-ray examination of the breasts) can detect preclinical cancer, that is, detect the tumour before it is palpable, or before it causes symptoms. Tumours detected and treated at an early stage, can be expected to be associated with a better survival rate than those detected symptomatically. Early diagnosis may permit breast-conserving surgery (stage I disease), reduce the need for adjuvant thera-

py or decrease complications related to intensive treatment and recurrence [1]. Population-based mammographic screening programmes were introduced in this context.

The impact of screening

Since the 1970s, the incidence of breast cancer has continued to increase. Only in 4 out of 70 populations assessed worldwide was there an average change between 1975 and 1990 of less than 0.5% per year [2,3]. Steep increases of the order of 3-5% per year have occurred in some Asian countries (e.g. Japan, Singapore), in Asian migrants to the USA (Japanese, Chinese and Filipino) and Southern Europe (Spain) (Fig. 4.31). In some developed countries (e.g. England and Wales, Finland, Denmark, The Netherlands, USA), a clear change in the speed of increase can be linked to the introduction of mass screening that occurred at different times in different countries, e.g. in the early 1980s in the USA, 1987-88 in England and Wales, early 1990s in The Netherlands. Some increase is attributable to reduced fertility and changing dietary habits. However, mam-

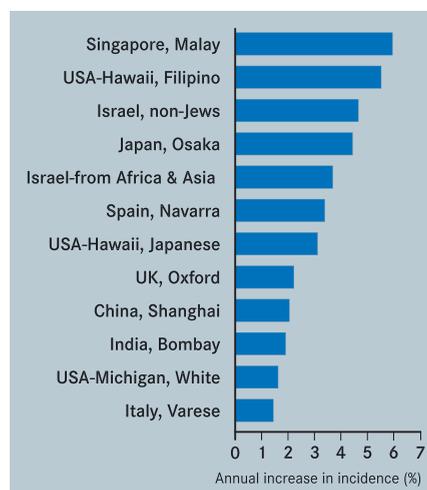


Fig. 4.31 Populations exhibiting the largest increases in the incidence of breast cancer between 1975 and 1990.



Fig. 4.30 Mammography, an X-ray examination of the breasts, is used to screen for breast cancer. ©GE Medical Systems

mography is the main determinant of these relatively recent increases as indicated by trends in the incidence of *in situ* cancers [4,5].

Mortality has not consistently paralleled incidence trends everywhere. In fact, in some developed countries rates have been rather stable, even with incidence on the increase. No clear overall decline in mortality had been observed in any place before the late 1980s, when a smooth downturn occurred in Europe, North America and Australia. Such changes before the era of mammography can be attributed to a progression towards early diagnosis that took place in the 1970s, particularly in young generations. More recently, in the early 1990s, a drastic fall in mortality was seen in the UK and North America [6,7]. However, the fall occurred too soon after the widespread availability of mammography to be a consequence of it; rather, the success of adjuvant therapy based on chemotherapy and tamoxifen is the likely major cause of this trend.

Protocols for screening

As currently practised, population-based screening for breast cancer is based on mammographic examination, at prescribed intervals, of all women within a

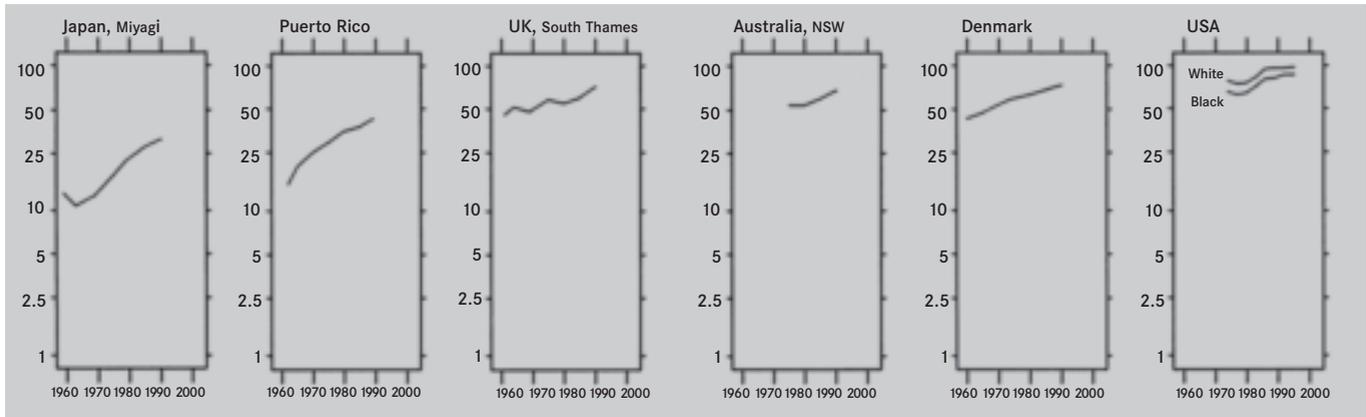


Fig. 4.32 Trends in breast cancer incidence. D.M. Parkin et al. (2001) *Eur J Cancer* 37, suppl. 8: S4-66.

specified age group. As of 1995, at least 22 countries had established national, sub-national or pilot population breast cancer screening programmes [8]. The specification of an eligible age range, and the “repeat interval”, are matters for national (or other authoritative) policy and vary accordingly. All programmes screen women by age 50 and repeat intervals are between one and three years. Establishment of the programmes depends on national or other health policy. There is considerable variation between screening programmes in relation to factors such as sociopolitical status of the screened population, public health priorities and funding sources. Implementation of population-based screening necessitates the provision of technical resources

and the availability of trained personnel, together with a media campaign to publicize the service. The latter may be directed in part toward particular groups, including the elderly and/or women of low socioeconomic status, or who are members of minorities, since such groups are known to undergo mammography less frequently than the general population [9]. The evaluation of individual mammograms requires appropriate expertise and quality assurance standardization. Independent double reading of mammograms is recommended, but not carried out in all screening programmes [8,10]. It is also essential to provide for adequate “follow-up” procedures in respect of initial mammographic results not categorized as satisfying the criteria for normality. Follow-up necessi-

tates contact with the individuals concerned, repeat and more comprehensive mammography, physical examination, ultrasonography and potentially biopsy. Cancers diagnosed after a negative mammogram are known as “interval” cancers. Mammographic breast density appears to be a major risk factor for interval cancer, worst risk being associated with extremely dense breasts [11]. Clinical examination and self-examination, whilst not proven to show a benefit in terms of reduction in breast cancer mortality, may aid in the detection of interval cancers, and are being evaluated for screening in countries that cannot afford mammography programmes. The International Breast Cancer Screening Network provides a basis for international collaborative effort designed

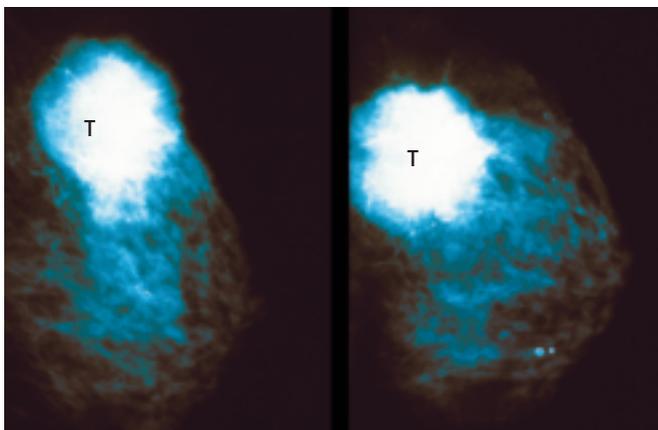


Fig. 4.33 Mammograms (2 views) from a patient displaying evidence of breast cancer. T = tumour.



Fig. 4.34 The evaluation of mammograms requires appropriate expertise and standardization.

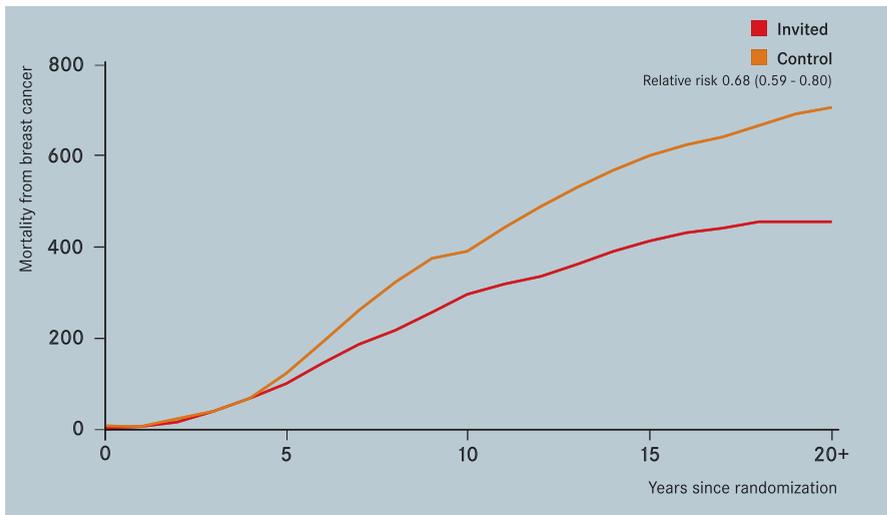


Fig. 4.35 Cumulative mortality from breast cancer in the Swedish Two-County screening trial. A reduction in mortality from breast cancer of 30% was found in the group of women that was invited for screening relative to the control group.

to document the varying breast cancer screening programmes, in order to produce international data on policies, administration and results of population-based breast cancer screening [7].

Evaluation of screening

Screening by mammography began to be widely adopted in the late 1980s following the publication of results of randomized trials. In fact, these studies gave heterogeneous results ranging from no reduction in mortality [12,13] to 30% of deaths prevented in women aged 50 or above [14]. In contrast, no significant reduction in mortality has been proven in younger women, which has led to differing recommendations and policies in various countries [15]. In most countries (e.g. United Kingdom,

Netherlands, Israel), screening is initiated in women of age 50 and above, whereas screening of women of ages 40-49 is performed in others (e.g. USA, Australia, Sweden). Several factors have been identified as possible sources of poorer performance in young women, including a lower sensitivity of the test due to greater density of the breast parenchyma (resulting in a higher risk of false positive and false negative results [16]) and faster tumour growth rate enhanced by circulating estrogen levels in premenopausal women [17]. Screening at more frequent intervals, every 12-18 months, may be required to obtain significant benefit in this age group [16].

Several countries have established organized screening programmes at the national or regional level, targeting women above the age of 50 [15]. These programmes were planned to reduce mortality by 25% and the effect was expected to become apparent about five years after implementation. So far, based on the results of randomized trials, the impact of screening interventions on older populations has been inferior to that expected, and the utility and justification of public financial support have been questioned [18,19]. IARC recently concluded that trials have provided sufficient evidence for the efficacy of

mammographic screening of women between 50 and 69 years old. Women who were invited to be screened showed a 25% reduction in breast cancer mortality. Since not all women accepted the invitation, the reduction among those who chose to participate in screening programmes is slightly higher, being estimated at 35%. For women aged 40-49, there is only limited evidence for a reduction [20].

By the time mammography was implemented for the general population, some benefit of early diagnosis was already being observed as an unplanned phenomenon, so the effect of the population-based programme was less than would have otherwise been expected. An impact of mammography is apparent from the increased relative frequency of *in situ* ductal carcinoma. If the lead time determined by modern mammography is significantly longer than that which characterized the test 20 years ago, a further reduction of mortality may be predicted. The natural history and biology of ductal carcinoma *in situ* is, however, poorly understood and the risk of over-treatment is at present of great concern [21]. Organized screening programmes should therefore be maintained and monitored until their full effect is clear.



Fig. 4.36 A positive mammogram requires comprehensive follow-up, including fine needle biopsy.

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WEBSITES

- Information from the US NCI on testing for various cancers, including breast:
<http://www.cancer.gov/cancerinfo/screening>
- NCI's Division of Cancer Prevention:
<http://cancer.gov/prevention/>
- FDA's Mammography Programme:
<http://www.fda.gov/cdrh/mammography/mqsa-rev.html>

SCREENING FOR PROSTATE CANCER

SUMMARY

- > Prostate-specific antigen (PSA) testing is widely used for the early detection of prostate cancer.
- > Elevated levels of PSA are closely, but not definitively, associated with prostate cancer; false positive results may lead to unnecessary treatment.
- > Assessment of population-based PSA screening suggests a reduction in mortality in countries with access to urological follow-up and treatment.

Secondary prevention of prostate cancer is feasible, but is subject to controversy, since the capacity to detect early disease must inevitably result in overtreatment for the individual patient, with substantial costs to society, in exchange for decreased mortality [1]. The lack of effective, appropriate markers of disease and any reasonable consensus on subsequent treatment necessitates extensive patient counselling as an important prerequisite, with some degree of prudence until the outcomes of the ongoing randomized trials in Europe and North America have been evaluated and audited [2].

Biological basis of secondary prevention

Prostate-specific antigen (PSA), a glycoprotein, is a proteinase that is responsible for the liquefaction of semen. PSA analysis has replaced prostatic acid phosphatase as the preferred serum marker of prostate cancer. The fact that PSA is highly tissue-specific and the consideration that few prostatic conditions result in a sustained, elevated level of serum PSA have made it the most efficacious marker currently available for the detection of prostate cancer. A serum “cut-off level” of 4 ng/ml for normality was used to demon-



Fig. 4.37 A physician in discussion with a patient: informed consent is a prerequisite for PSA testing.

strate the efficacy of PSA as a diagnostic tool [3]. Unfortunately, 25% of patients diagnosed with prostate cancer have levels of serum PSA that are less than 4 ng/ml. Of men with PSA levels between 4–10 ng/ml, 25% have cancer, and 60% have cancer when PSA levels are greater than 10 ng/ml.

PSA analysis should be combined with a digital rectal examination, the latter providing an assessment of the volume of the gland, since PSA is also released into the bloodstream of patients with benign prostate hyperplasia and other prostatic diseases. To improve the sensitivity of the PSA analysis, a number of parameters

may be assessed, most of which relate to concomitant benign prostate hyperplasia and also include age-specific reference ranges [4], typical values being: 40–49 years, <2.5 ng/ml; 50–59, <3.5 ng/ml, etc. A patient who proposes to have PSA assessed should be counselled about the relative risks and benefits that must be considered in relation to the procedure and its outcome (Table 4.13).

Other screening tests for prostate cancer focus on the different molecular forms of PSA, variously referred to as free PSA, total PSA, PSA-ACT complex assays and certain others. The ratio of free PSA to total PSA is reported to discriminate between cancer and benign prostate hyperplasia, thereby saving men from the prospect of intrusive biopsies, but always at the expense of missed cancers. For some of these newer forms of PSA analysis, the pre-analytical conditions for handling the blood sample should be closely monitored, since separation of the serum should be performed within three hours and the analyte then be determined within 24 hours. If this is difficult, the serum must be frozen for analysis at a later date. The efficacy of all these tests must be evaluated against prostatic biopsies that

Advantages	Disadvantages
Prostate cancer is an important public health problem	Available tests may detect innocuous and non-neoplastic lesions
Tests available are among the best screening tools in medicine	No consensus on optional early treatment
Advanced prostate cancer cannot be cured, early prostate cancer may be	Treatment morbidity may be high relative to benefit
Diagnosis at an earlier stage and lengthened survival are evident in many studies using PSA for early detection	Mortality reduction from screening has not yet been confirmed in prospective randomized trials

Table 4.13 A summary of the arguments in favour of, and against, prostate cancer screening.

Abnormal findings in digital rectal examination of the prostate

Induration of part of the gland

Asymmetry of the gland

A palpable nodule in the gland

Decreased mobility due to fixation of the gland

Table 4.14 Prostate characteristics indicative of abnormality in the context of digital rectal examination.

are positive, since the true prevalence of cancer in any cohort remains unknown (up to 20% of cancers can be missed). Continuous research to identify better markers is necessary, and in this regard studies of the kallikrein gene family are ongoing [5]. Prostate-specific membrane antigen has been seen to offer potential due to its consistent expression in prostate cancer, thereby opening possibilities for its use as a diagnostic, staging and predictive marker [6].

Development of screening protocols

The fate of patients with advanced stages of prostate cancer stands in sharp contrast to the outcome of treatment of patients with localized stages of the disease. The introduction of serum PSA

analysis significantly changed the pattern of diagnosis of prostate cancer to include the non-palpable, non-visible tumours referred to as T1c tumours in the TNM classification (Box: *TNM classification of malignant tumours*, p124). In North America, Europe and other developed countries, evidence from the widespread application of digital rectal examination, serum PSA determination and subsequent transrectal ultrasound directed biopsy, has led to a significant shift in the time of diagnosis of prostate cancer to the earlier, confined stages of the disease. Recorded incidence rates have increased dramatically as an immediate result of earlier diagnosis of asymptomatic cancers through the introduction of PSA testing (Fig. 4.38). Subsequently, incidence rates have decreased in some populations, such as the USA, probably because the proportion of the population with latent tumours which can be detected by opportunistic screening has been exhausted [7].

Digital rectal examination is the simplest, safest and cheapest means of detecting prostate cancer provided that the tumour is localized in the gland. Although advanced local prostate cancer can be obvious, only one-third of suspicious abnormal findings on examination are actually confirmed as cancer (Table 4.14). Transrectal ultrasound was introduced as a possible refinement to digital rectal examination; prostate cancer may be detected as a hypo-echoic lesion. Wider

adoption of the technique has revealed a false positive level comparable with that of digital examination, with only about one-third of all suspicious cases being confirmed as prostate cancer.

Evidence of outcome

A number of biases may complicate evaluation of any screening programme, and prostate cancer screening programmes in particular. These include lead-time bias, increasing survival as a consequence of earlier detection in the natural history of the disease and sampling that favours detection of less threatening cancers. Patient self-selection and overdiagnosis of preclinical cancers also tend to confuse outcome analysis. Even in the absence of trials, uncontrolled studies and the large numbers of specimens removed at radical prostatectomy have yielded important information about screening. These data indicate the extent to which diagnostic tests are performed and how such testing has led to a shift in disease stage at diagnosis and increased survival rates.

Some national authorities have recommended screening for the detection of prostate cancer by performing annual digital rectal examination and PSA tests, starting at the age of 50 (45 for high-risk patients), for men with at least a 10-year life expectancy [8]. These recommendations are generally being incorporated into men's health care programmes in many parts of the world. A slight but definite

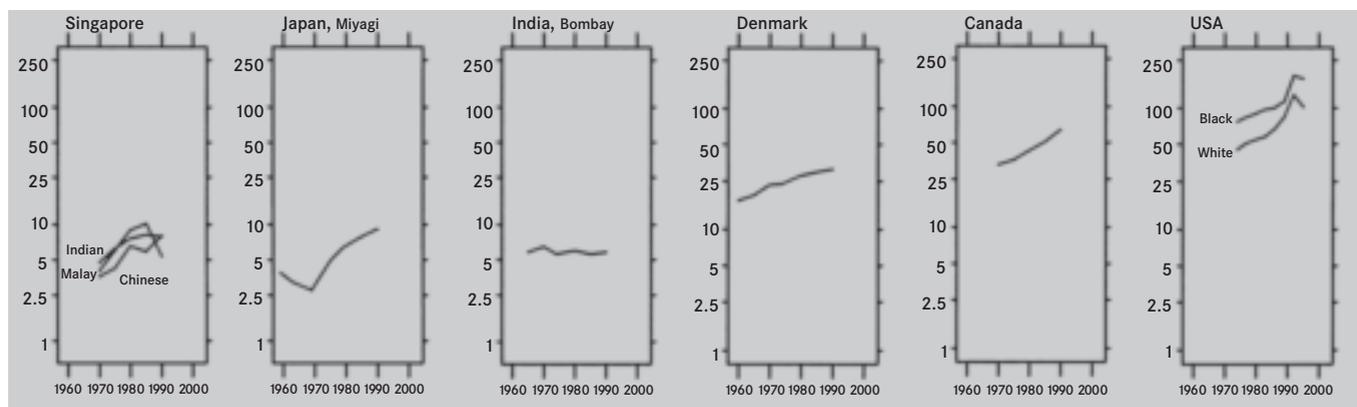


Fig. 4.38 Trends in the incidence of prostate cancer show a marked increase in many world regions, largely due to improved detection methods.

D.M. Parkin et al. (2001) *Eur J Cancer* 37, suppl. 8: S4-66.

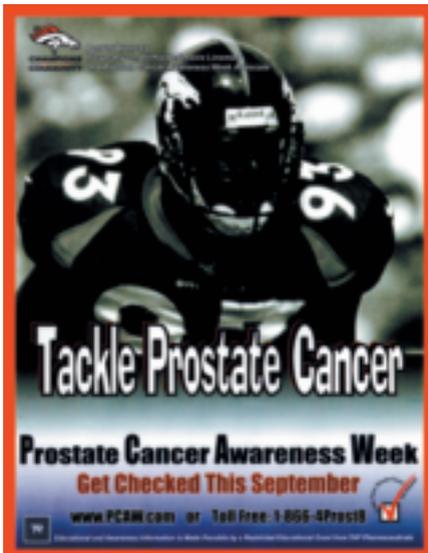


Fig. 4.39 Poster designed for an annual Prostate Cancer Awareness Week in the USA.

decrease in prostate cancer mortality has been recognized in countries where PSA was widely used in screening different

cohorts of men. The decrease in mortality has become a major subject of discussion. A community-based randomized trial in Quebec suggested a mortality decrease of 69% in screened men, which provoked comment to the effect that a correct analysis by intention to treat showed no benefit [9]. There is a general expectation that the earlier detection of prostate cancer inevitably provides a unique chance for cure. The understanding of “cure”, however, must include assessment of the quality of life experienced by the patient. Complications currently inherent in the management of prostate cancer include those associated with procedures for diagnosis and treatment, the clear prevalence of over-diagnosis and the lack of any consensus on the appropriate treatment. Ultimately, resolution of many of these matters can only be achieved on the basis of the results of randomized controlled trials.

A multinational controlled trial in Europe has recruited 180,000 men randomized between diagnosis and treatment in

screened men versus controls. In the USA, 74,000 men have been enrolled in a large controlled trial of screening for prostate, colorectal and other cancers. Collaboration between researchers concerned with these two trials has led to the development of the International Prostate Screening Trial Evaluation Group. The strength of the prospective planning and coordinated quality control will provide a sound basis for the scientific evidence required to answer the questions posed on the need for large population-based screening [10]. Currently, despite more than a decade of PSA-based screening, the impact of screening on mortality due to prostate cancer continues to be controversial, although some evidence of a decline in age-adjusted mortality rates for prostate cancer may be attributable, at least in part, to screening [11].

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WEBSITE

Preventing and detecting prostate cancer (NCI): http://www3.cancer.gov/prevention/spec_cancer.html#prostate

SCREENING FOR COLORECTAL CANCER

SUMMARY

- > Faecal occult blood test (FOBT) is the most cost-effective and comprehensively-applicable screening method available, but its specificity and sensitivity are limited.
- > Endoscopy provides the best method for detecting colorectal cancer and its precursor lesions, e.g. polyps. However, its application to population-based screening is limited by cost and availability of qualified specialists.
- > For individuals at average risk in developed countries, screening may be recommended.

Colorectal cancer is one of the few internal cancers that are amenable to secondary prevention, that is, prevention by detection of preclinical lesions. A small proportion of colorectal cancers occurs among those with a family history of the disease. The main aim of screening is to detect the 90% of cases of colorectal cancer that occur sporadically, most of these in patients above the age of 50. The precursor of advanced colorectal cancer is either an adenomatous polyp or a flat neoplastic area (Fig. 4.40). In order to prevent premature deaths, people aged 50-

Registry	Number of cases (%)			
	Total	0-49 yrs	50-69 yrs	70-85+ yrs
Osaka Cancer Registry, 1987-89	8,051	1,016 (12.6%)	3,849 (47.8%)	3,185 (39.5%)
Denmark Cancer Registry, 1989	3,222	180 (5.5%)	1,146 (35.5%)	1,896 (58.8%)
Norway Cancer Registry, 1996	2,910	140 (4.8%)	954 (32.7%)	1,816 (62.4%)

Table 4.15 Age at diagnosis of colorectal cancer in Japan and Scandinavia, both sexes.

69 years, among whom 35% of incident cases occur, are the main focus of attention (Table 4.15). Older age classes account for 60% of cases in developed countries, colorectal cancer being of relatively minor concern in developing countries. Simulation studies [1] conducted in the USA suggest small variations in cost and results with different strategies. The gain in life expectancy per person screened is small (1-4 weeks), but the benefit is great for the 5% destined to have cancer.

The faecal occult blood test

Screening by the faecal occult blood test (FOBT) is currently considered the optimal screening strategy in terms of cost-effectiveness. FOBT identifies persons at risk, though falling short of being definitive for cancer [2-7]. Guaiac resin-based slide

tests indirectly measure haemoglobin levels in the faeces by the determination of peroxidase activity (Fig. 4.42). When a drop of water is added to the slide (i.e. the slide is rehydrated, as opposed to being non-hydrated) the test has been found to be more sensitive, although at the expense of a higher false positive rate. A false positive result to the guaiac resin reaction occurs after ingestion of dietary haemoglobin or peroxidase-containing foods. Between trials there is considerable variation in quantitative findings. Generally however, the test should be positive in no more than 2% of those screened. The sensitivity of the test is around 50% for cancer (of all screened persons who have cancer, 50% will be detected) but is low for polyps, at around 10%. The predictive value of a positive test

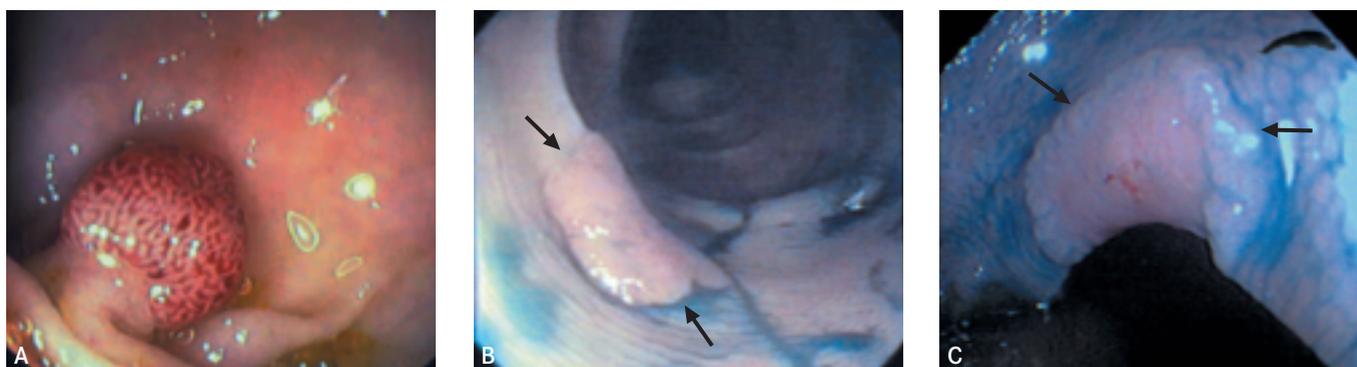


Fig. 4.40 Endoscopic features of (A) polypoid (B) slightly elevated and (C) flat adenoma of the colon.

is around 10% for cancer (out of every ten persons detected as positive, nine will not have cancer). An immunological FOBT for human haemoglobin is on trial; it is proving more specific, but also more costly. Screening procedures may be based on the malignant character of exfoliated cells. Genetic testing of stool samples for the *KRAS* oncogene and for p53 protein is not yet cost-effective.

Individuals at above average risk for colorectal cancer on the basis of family history may be stratified depending on the extent to which disease affects first-degree relatives. Having such a relative diagnosed at age 55 or over increases risk two-fold (by comparison with an individual with no family history), while one relative diagnosed under age 55, or two first degree relatives diagnosed at any age increases risk three- to six-fold. Persons at such increased risk should be monitored by annual FOBT. In some cases, familial predisposition may be dependent on a known gene defect. Genetic testing for adenomatous polyposis coli (*APC*) gene mutation diagnoses familial adenomatous polyposis. The test for microsatellite instability (replication error positive, RER, test), designed to establish a genetic basis for heritable nonpolyposis colon cancer, is also positive in 15% of sporadic cancers.

Endoscopy

Endoscopy [8], using either the flexible sigmoidoscope or the colonoscope [9-11],

is the most definitive means of detection, but has limitations. The false negative rate for flat neoplastic lesions has been recognized and remains high [12]. Improved detection of flat neoplastic lesions is achieved using a high-resolution video-endoscope, with a contrast enhancement system and the use of chromoscopy (Fig. 4.40). A major advantage of endoscopy is in the potential for tissue sampling and interventional procedures. Population-based eradication of pedunculate or sessile adenomatous polyps may reduce cancer incidence.

With a depth of insertion varying from 48-55 cm, the limited reach of the flexible sigmoidoscope is its major weakness. In usual examinations, the instrument does not reach the splenic flexure and may not advance beyond the sigmoid colon. Accordingly, sigmoidoscopy may achieve 70% of the penetration that would be attained by colonoscopy. The colonoscope permits exploration of the colon with a low false negative rate for polypoid lesions of at least 10 mm in diameter. For this reason, the intervals allowed before re-examination are relatively long (up to ten years) after a negative assessment or up to five years after polypectomy. Patient compliance with such recommendations for re-examination after colonoscopy is poor, the cost of the procedure is high and the associated morbidity (perforation in about 0.3 examinations per 1000 performed by experienced gastroenterologists) may be

of consequence in large series. To decrease costs, colonoscopy without sedation is being investigated. An imaging procedure which uses a camera system-on-a-chip (CMOS, which is cheaper than a closed-circuit display, CCD, camera) placed in a swallowed disposable capsule, is now suitable for exploration of the small intestinal lumen, but not that of the colon. Barium enema is rarely used in screening protocols; it is proposed when endoscopy is not available or has failed. "Virtual" endoscopy, a new imaging development, has not yet proved a reliable screening tool.

Mass screening protocols are generally recommended to be initiated in people of age 50 and above. Considerable uncertainty concerns the upper age limit, which has been recorded as high as 85 years for the first test. In general, screening may be stopped at age 70 after repeated negative tests. All protocols for follow-up of positive FOBT (Table 4.16) conclude with a colonoscopy, in a ratio varying from 4 to 100 % of those screened, depending on the strategy. Screening performed outside protocols is designated "opportunistic"; in this context endoscopy is the primary means of assessment.

Implementation of screening measures

Screening protocols have been evaluated through epidemiological studies. In respect of cost-effectiveness ratio (cost

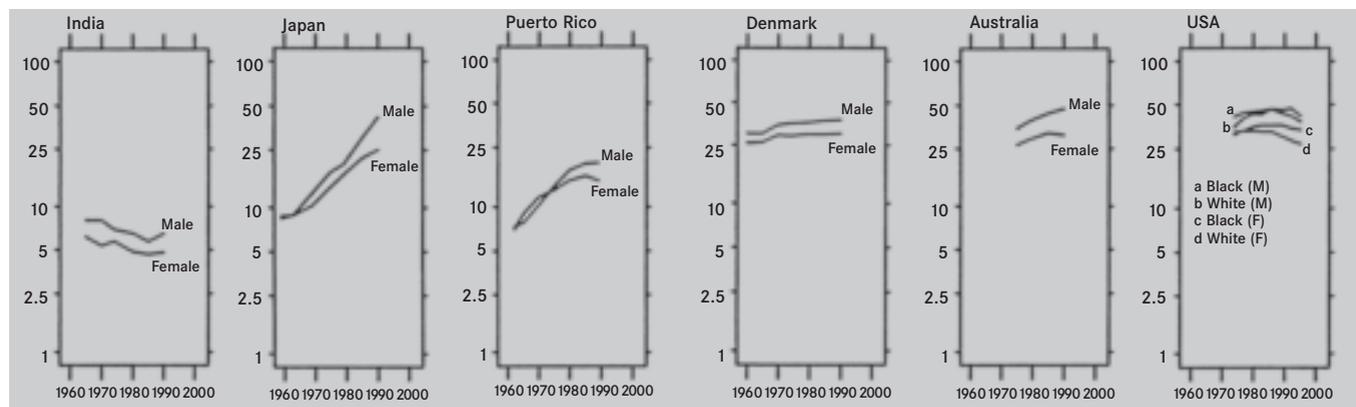


Fig. 4.41 Trends in the incidence of colorectal cancer. The increase is most prominent in countries which have most recently acquired the Western lifestyle. D.M. Parkin et al. (2001) *Eur J Cancer* 37, suppl. 8: S4-66.



Fig. 4.42 The FOBT test for colorectal cancer (shown here is a Hemocult II[®] test). Three consecutive stools samples are applied to the test card. After addition of the reaction solution, a blue coloration indicates the presence of blood. A single positive result among the three samples indicates the need for a clinical examination of the colon.

per year per life saved), screening for colorectal cancer in the USA has been evaluated as being below an arbitrary financial threshold adopted in screening (US\$ 40,000 per year of life gained) and in this regard compares favourably with protocols for breast or cervical cancer screening. It has been estimated that screening 200,000 people in Australia using the FOBT would detect 250 colorectal cancers and prevent as many as 55 deaths. The FOBT gives the most cost-effective programme, but prevents fewer deaths than other programmes. A single colonoscopy has a greater impact on cancer mortality. Some health authorities in developed countries acknowledge the legitimacy of a screening protocol for colorectal cancer. However, the high cost of a generalized intervention and the limited acceptance of the tests by the population explain its limited application. It has been shown that nurses can perform sigmoidoscopy as competently as doctors, as indicated by the duration of the procedure, the ability to detect neoplasia and the risk of complications. When a lesion is detected in these circumstances, a colonoscopy is performed by a specialist.

Evidence of outcome

FOBT has been assessed in randomized trials. An American trial [2] was based on an annual rehydrated FOBT in volunteers.

The compliance was high (90.2%) and 38% of individuals screened underwent colonoscopy. There was a 33% reduction in specific mortality in the screened group (Table 4.17). Reduction in cancer incidence also occurred. In the two European, population-based, randomized trials [3,4] conducted in the UK and in Denmark with a biennial non-rehydrated FOBT, the compliance was lower (around 60%), only 4% of individuals tested had colonoscopy and the reduction in mortality was less (15%).

Screening by sigmoidoscopy has been evaluated in case-control studies. In the Kaiser study [13], rigid sigmoidoscopy was associated with a 59% reduction in mortality from cancer of the rectum and distal colon. Scandinavian trials have shown less compliance and a higher yield of detection with sigmoidoscopy than with the FOBT. A

Screening protocols
Annual faecal occult blood test
Biennial faecal occult blood test
Annual faecal occult blood test + fibrosigmoidoscopy every 5 years
Fibrosigmoidoscopy every 5 years
Colonoscopy every 10 years
Colonoscopy once in a lifetime

Table 4.16 Options for population-based screening protocols for colorectal cancer (in males and females, from the age of 50 years).

cohort study in the USA has shown that screening by endoscopy reduces mortality from colorectal cancer by 50% and incidence by 40% [8]. Primary endoscopic screening is increasingly favoured as compared to the FOBT protocol [9].

There is indirect evidence that primary colonoscopy may reduce cancer mortality. The National Polyp Study in the USA has shown a 75% reduction in the risk of colorectal cancer after polypectomy [10,11]. Among persons of average risk, above age 50, screening by colonoscopy reveals cancer in 0-2.2% and large adenomas in 3-11%. The number of colonoscopies needed to detect one cancer in screening is estimated at 143 for individuals of either sex, aged at least 50, and 64 for males aged at least 60 years. The number of colonoscopies needed to detect one cancer in patients with a positive FOBT is

	Screened annually	Unscreened
Number of people	15,550	15,394
Number of colorectal cancers detected	323	356
Number of deaths from colorectal cancer	82	121
Mortality ratio (deaths in screened/deaths in unscreened)	0.67	1.00

Table 4.17 The efficacy of screening by FOBT as reflected by the reduced mortality due to colorectal cancers diagnosed in the group subject to annual screening in comparison with the unscreened group.

45 with one positive rehydrated FOBT, 9.8 with one positive non-rehydrated FOBT and only 2.7 if two positive non-rehydrated positive FOBT are required. The chance of finding a cancer in the five years after negative colonoscopy is very small. This justifies the tendency towards screening with primary endoscopy to explore at ten-year intervals or once in a lifetime. A recent comparative but non-randomized Finnish study on the endoscopic detection of neoplasia in families fulfilling the Amsterdam

criteria for hereditary nonpolyposis colon cancer has suggested efficacy of colonoscopy in reducing the risk of and mortality from colorectal cancer.

International comparisons

In countries with a high rate of colorectal cancer, secondary prevention is justified. Mass screening with the FOBT is proposed and reimbursed in Japan, Germany and the Czech Republic for example, but implementation depends upon the accom-

panying awareness campaign. In the USA, an annual FOBT and/or sigmoidoscopy every five years is recommended. Screening with primary sigmoidoscopy is encouraged in Scandinavian countries and in the United Kingdom. Application of any large-scale endoscopic screening programme is hampered by a shortage of specialists and the high cost of their expertise.

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WEBSITES

- Colorectal cancer prevention and control initiatives CDC: <http://www.cdc.gov/cancer/colorct/colorect.htm>
- Colorectal cancer screening, the American Gastroenterological Association: http://www.gastro.org/public/brochures/cc_screening.html

SCREENING FOR CERVICAL CANCER

SUMMARY

> In most developed countries, cytological screening (Pap test) has led to a significant reduction in the incidence of and mortality from cervical cancer. In countries with lower participation compliance and a less developed health care system, screening has been much less or not at all effective in reducing mortality.

> In developing countries, the cost of infrastructure and initial investments for organized cytological screening may be prohibitive. The cost-effectiveness of screening programmes based on alternative tests, such as visual inspection following acetic acid application (VIA), are currently being investigated.

> Testing for HPV DNA is an alternative means of primary screening. Its accuracy and cost-effectiveness for the detection of precursor lesions (cervical intraepithelial neoplasia) are currently being investigated.

be reduced worldwide by applying current knowledge [1]. Cancer of the cervix is related to sexual activity, and infection with human papillomavirus (HPV) is central to the etiology (*Chronic infections*, p56). While it has been established that HPV is responsible for 82% of cervical cancers occurring in developed countries and 91% in developing countries [2], cervical cancer is, like all other cancers of known infectious origin, a rare response to the relevant infection. Efforts are underway to develop and test vaccines against HPV infection (*Human papillomavirus vaccination*, p148). However, variation in sexual behaviour and HPV infection may not entirely account for the very high rate of cervical cancer in many countries and its declining trend over time in some others. This applies both in developing countries and in developed countries, where the disease is predominant in women of lower socioeconomic status. Accordingly, screening is the main strategy for prevention. Cervical intraepithelial neoplasia grades II and III represent a “preclinical” stage of squamous cell carcinoma that has high prevalence and is detectable in the course of population-based screening. The most commonly used screening test, the cytological smear, is acceptable to a substantial proportion of the population at risk, but the test has recognized limitations.

The efficacy of cytological screening

By far the best established screening method for cervical cancer is the Papanicolaou (“Pap”) smear (Fig. 4.44). Population-based screening programmes using the Pap smear were initiated in British Columbia in 1949 and in regions of Norway in 1959 and Scotland in 1960. Since then, programmes based on the Pap smear have been introduced in many developed countries. The programmes vary in their organization, differing in the balance between public and private health care, whether the programme is systematic and population-based or opportunistic (based upon self-presentation), 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. Pap smear programmes which have been implemented in developing countries are limited to offering the test to women attending primary health care, antenatal, gynaecology and family planning clinics in urban areas, with no organized efforts either to encourage testing for high-risk women, or to ensure that those found to have abnormal smears receive follow-up and treatment [3].

The main evidence for efficacy of screening based on the Pap smear is indirect,

In many developed countries a decline in incidence and mortality of cervical cancer has been observed in the past 30 years (Fig. 4.43, 4.45). This shift suggests that the burden due to this form of cancer could

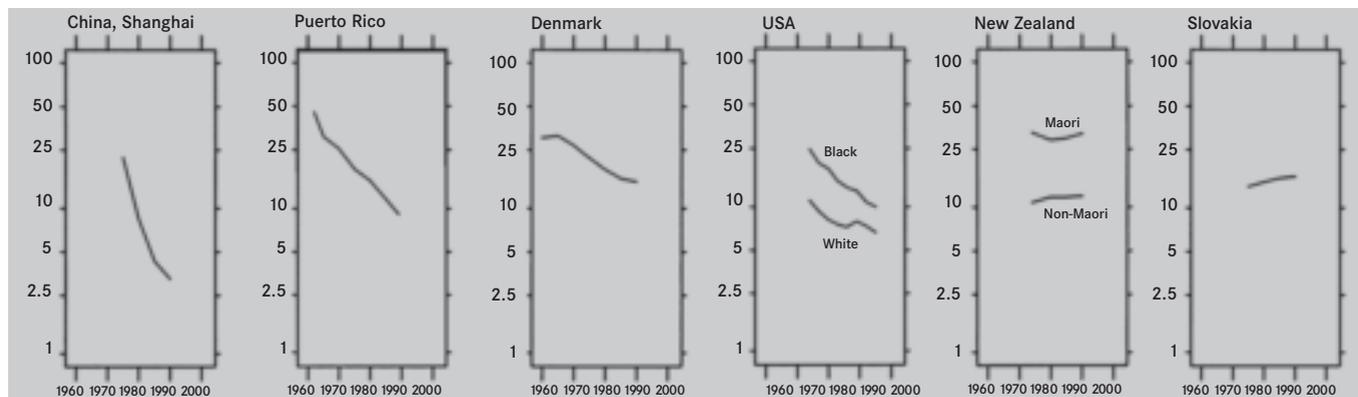


Fig. 4.43 Trends in the incidence of cervical cancer. In many regions, early detection has led to a marked decrease of invasive cancer. D.M. Parkin et al. (2001) *Eur J Cancer* 37, suppl. 8: S4-66.

Time since last negative smear (months)	Relative protection (no. of cases in brackets)	95% confidence interval
0-11	15.3 (25)	10.0-22.6
12-23	11.9 (23)	7.5-18.3
24-35	8.0 (25)	5.2-11.8
36-47	5.3 (30)	3.6-7.6
48-59	2.8 (30)	1.9-4.0
60-71	3.6 (16)	2.1-5.8
72-119	1.6 (6)	0.6-3.5
120+	0.8 (7)	0.3-1.6
Never screened	1.0	

Table 4.18 Screening offers protection against cervical cancer: combined analyses of cohort and case-control studies suggest that the shorter the time since the last negative smear result, the greater the protection a woman has against invasive cervical cancer.

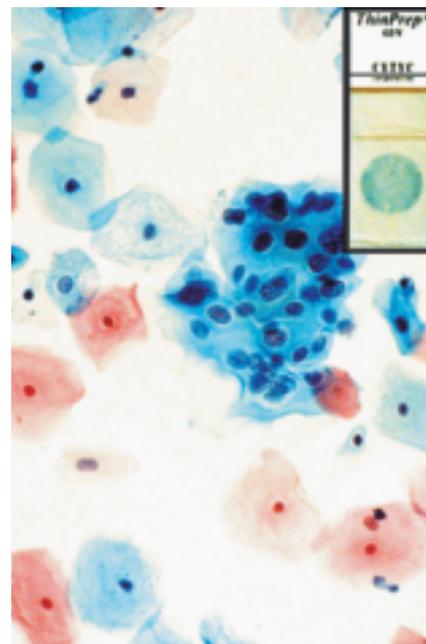


Fig. 4.44 Papanicolaou-stained cervical smear preparation showing a cluster of abnormal cells.

being based on (i) time trends in the incidence of, or mortality due to, cervical cancer in relation to screening intensity; (ii) risk of cervical cancer in individuals in relation to their screening history [1,4]. Nationwide programmes were established in Finland, Iceland and Sweden; in Denmark, programmes covered only 40% of the female population and in Norway only 5% [5]. In Iceland, cervical cancer mortality fell by 80% between 1965 and

1982, compared with 50% in Finland, 34% in Sweden, 25% in Denmark and 10% in Norway. More recently, the effect of cytologic screening on the incidence of cervical cancer has been examined in 17 populations covered by cancer registries between the early 1960s and late 1980s [6]. Compared with the time before the introduction of screening, the age standardized incidence rates decreased by at least 25% in 11 of the 17 populations, with

the largest effect occurring in the 45-55 year age groups. The reduced efficacy of screening in older women is attributable to a lower screening coverage and possibly by lower test sensitivity. Where evident, apparently reduced efficacy in younger women may be the result of transfer of cases to younger ages, as a result of earlier detection in the women's lifetime due to cytological screening. This phenomenon in turn may obscure ineffec-

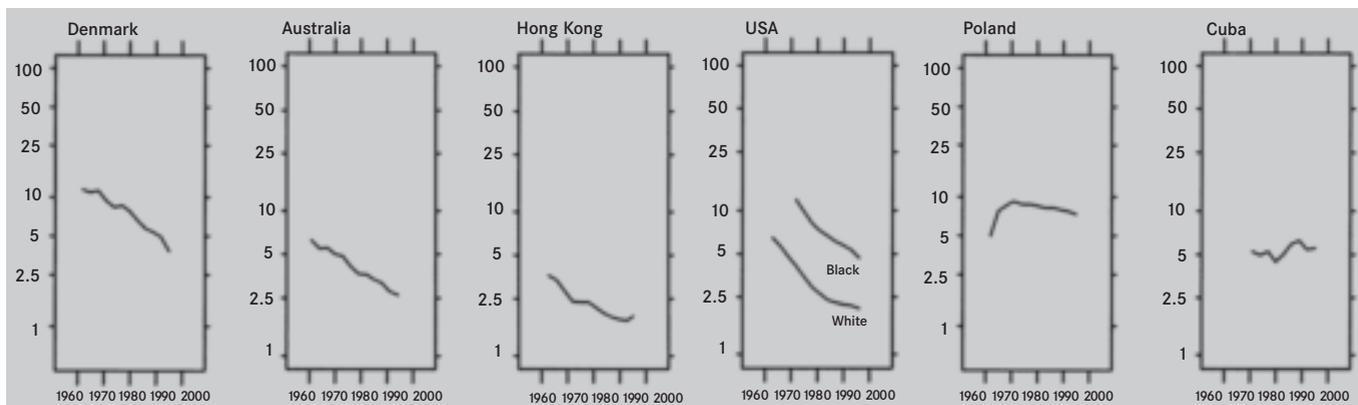


Fig. 4.45 Trends in mortality from cervical cancer. D.M. Parkin et al. (2001) *Eur J Cancer* 37, suppl. 8: S4-66.

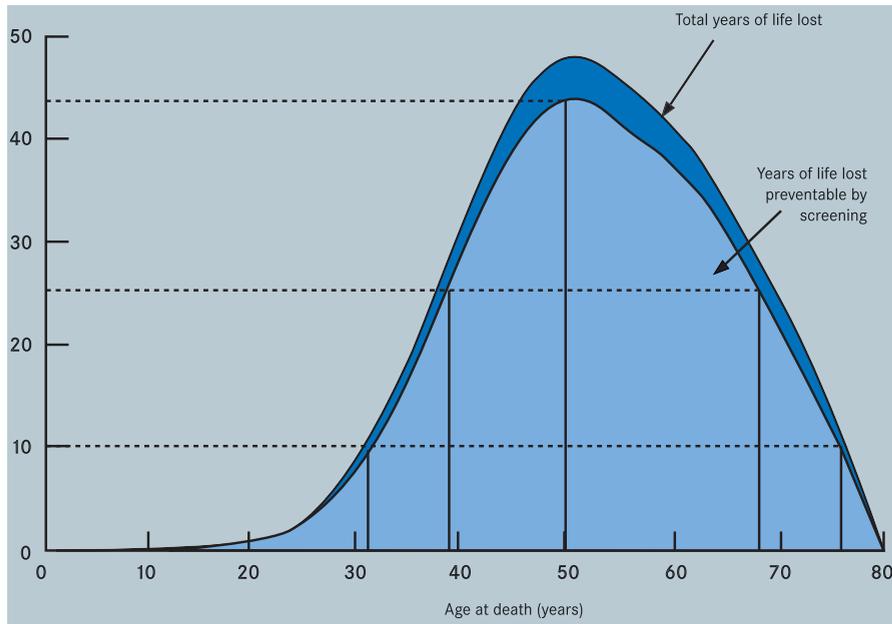


Fig. 4.46 Annual numbers of years of life lost as a result of deaths from cervical cancer per 10,000 women, at each year of age, up to age 80, in the absence of screening (dark blue plus light blue). If screening is implemented, many of these deaths can be prevented; at the peak (age 50), 44 years of life may be gained per 10,000 women screened (light blue).

tive screening at younger ages or, more controversially, the possibility that invasive cancers in young women might be a rapidly progressing subset of neoplasia [7].

In contrast to squamous cell carcinoma, adenocarcinoma of the cervix has no readily detectable pre-invasive stage. Therefore, cytological screening would not be expected to be effective in the control of this type of cervical cancer [7].

The application of cohort and case-control studies to the evaluation of screening effectiveness is complex. Self-selection

for screening by individuals at lower risk of disease or mortality has been observed frequently. It is possible that signs or symptoms led to a cytological smear being performed, but this may have been misclassified as a screening test. If differential, this misclassification would bias the estimated effect of screening.

Implementation

The major barrier to prevention of cervical cancer is failure to be screened at all (Table 4.18). Organized screening is generally considered to be substantially more

efficient than opportunistic screening. However, there have been few direct comparisons and the results of these have been inconsistent. Some reduction in incidence may be achieved by opportunistic screening [8].

An estimate of the years of life potentially saved as a result of screening on the basis of data has indicated that three-yearly cytological screening reduces mortality by 91% [9]. This may be an overestimate because of selection bias. At the age of 50, 44 years of life can be gained per 10,000 women screened. At the ages of 68 and 39, 25 years of life are gained per 10,000 women screened, and at ages 31 and 76, 10 years of life are gained (Fig. 4.46).

Selective screening has been considered. However, asking women about their sexual habits is at best difficult, and may be unacceptable in many societies. Moreover, it may be difficult to reduce screening coverage once a programme aimed at total population coverage is in place. Another proposal is to cease the offer of screening to women aged 50 or more who have had regular negative smears [10]. It has been suggested that if a combination of HPV and cytological testing were introduced in primary screening, screening could then be stopped at an earlier age in women negative on both tests [11].

Considerable variation in the sensitivity and specificity of cervical cytology smear tests has been reported [12]. A number of suggestions for methods to improve cervical specimen cytology have been made, with liquid-based cytology techniques currently receiving most attention. Overall,

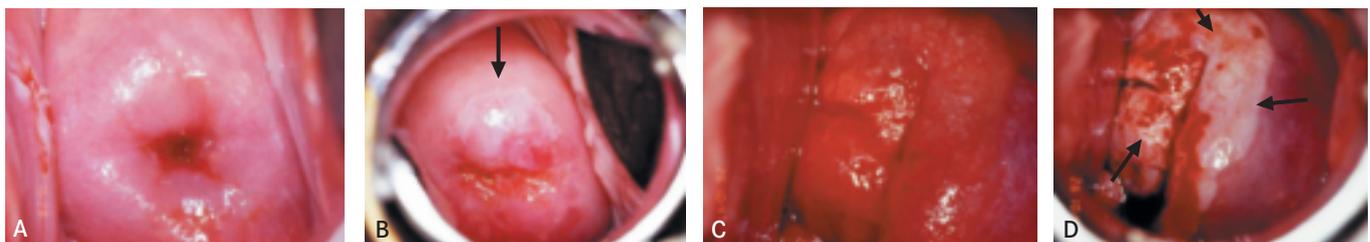


Fig. 4.47 Visual inspection of the cervix with 4% acetic acid. In the normal cervix, after the application of acetic acid, no definite acetowhite areas are seen (A). The visual inspection is declared positive (B) when, after the application of acetic acid, thick, dense, well-defined acetowhite areas develop (arrows). An invasive cancer is shown before (C) and after (D) the application of acetic acid.



Fig. 4.48 Women at a clinic in India participating in a study of early detection of cervical cancer.

the liquid-based method seems to result in more slides being classified as having low-grade squamous epithelial lesions or higher, which were classified as having less severe disease by conventional smears, than the reverse situation. The difference in cost between liquid-based and conventional cytology is unclear because of substantial uncertainty about the relative effectiveness of these two approaches [13].

It has been suggested that improvements in the detection of dyskaryosis (abnormal changes in cell nuclei) using extended tip plastic spatulas instead of the traditional wooden Ayre's spatula would be of approximately similar magnitude to the improvements which might result from replacing conventional cytology with liquid-based methods [14]. Automated cytology reading systems are under development and some health economic evaluation has been carried out.

In view of the importance of HPV in the etiology of cervical cancer, HPV testing to allow women to be classified as high-risk HPV-positive (displaying HPV types associated with an increased risk of cervical neoplasia) or negative (otherwise) could be used as an adjunct to cytological smear tests. However, the possible value of HPV testing in the triage of women with low-grade abnormalities is uncertain.

Alternatives to the Pap smear

HPV testing

HPV testing may be used for primary screening. In developed countries, most attention has been focused on HPV testing as an adjunct to cytological screening

(see above), in part because of ethical and medico-legal problems which might ensue in conducting a randomized trial which would involve withdrawal of the offer of cytological screening from the group assigned to be offered HPV testing. This would not be the case for populations in which Pap testing has not been introduced, notably in developing countries. The major issues in relation to such use of HPV testing have been the cost of the test itself and its relatively poor specificity [15,16]. Poor specificity results in follow-up for women without cervical disease, incurring costs which may be more than the society can afford. In both developed and developing countries, the development of primary screening based on HPV tests might be rendered obsolete by mass HPV vaccination (*Human papillomavirus vaccination*, p148).

Visual inspection

Unaided visual inspection of the cervix by nurses and other non-medical health workers, also known as "down-staging", has been proposed for developing countries which lack the laboratory facilities or resources to implement cytological screening [17]. Women with abnormal findings require further investigation, which entails a cytological test if appropriate facilities are available, or specialist medical examination if no cytology services are available.

In view of the unsatisfactory performance of unaided visual inspection, consideration has been given to aiding naked-eye visual inspection by impregnating the cervix with 3-4% freshly prepared acetic acid to detect acetowhite areas (Fig. 4.47). This screening approach is known as visual inspection with acetic acid (VIA) (synonyms are cervicoscopy and direct visual inspection). In studies in China, India, South Africa and Zimbabwe, visual inspection with acetic acid has emerged as a satisfactory screening test to detect cervical cancer precursor lesions, with a sensitivity ranging from 67 to 90% [14, 18-20]. This is similar to (or higher than) the sensitivity of cytological screening, but specificity is generally lower (range is 64-92%). Therefore, if screening based on

visual inspection with acetic acid is instituted, a potential consequence would be high rates of referral for further investigation. Currently, randomized intervention trials are in progress in India to evaluate the cost-effectiveness of visual inspection with acetic acid in cervical cancer screening [21].

Addition of magnification to visual inspection with acetic acid has not further improved the test performance [14, 22]. Cervicography involves the taking of a photograph of the acetic acid-impregnated cervix to be reviewed by trained cervicographic interpreters. Cervicography has been found to have a lower sensitivity than cervical cytology [14, 23], and also reportedly suffers from high false positive rates [24].

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WEBSITES

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<http://www.cdc.gov/cancer/nbcccdep/about.htm>
- The NHS cervical screening programme (UK):
<http://www.cancerscreening.nhs.uk/cervical/>
- National Cervical Cancer Coalition (Australia):
<http://www.nccc-online.org>

SCREENING FOR ORAL CANCER

SUMMARY

- > Oral cancer and its precancerous lesions, including leukoplakia, can be readily detected by visual inspection of the oral cavity by trained health workers and doctors.
- > Population screening for oral cancer results in the diagnosis of large numbers of oral precancers and an increased proportion of early stage tumours. However, a reduction in incidence of and mortality from oral cancer resulting from such interventions remains to be demonstrated.

Oral lesions such as leukoplakia, erythroplakia and oral submucous fibrosis are precancerous. A high risk of malignant transformation of such lesions has been established in follow-up studies. The proportion of oral cancers that arise from pre-existing precancerous lesions is variably reported in the range of 30-80%. The natural history of these lesions is not as extensively documented as that of the precursors to cervical cancer. Thus, for example, it is not known whether the different types of leukoplakia and erythroplakia constitute a continuum similar to the different stages evident during the development of cervical intraepithelial neoplasia.

Oral leukoplakia refers to uniform, flat, predominantly white lesions in the lining of the mouth that cannot be characterized as any other disease. White lesions with a smooth, corrugated or wrinkled surface are referred to as homogeneous leukoplakia, and those with irregularly flat or nodular or exophytic white or red and white lesions are referred to as non-homogeneous leukoplakia. Erythroplakia refers to velvety red, non-removable lesions in the oral mucosa. Oral submucous fibrosis is characterized by recur-

rent inflammation and stiffness of the oral mucosa with progressive limitation in opening the mouth and protrusion of the tongue. In hospital-based studies, a malignant transformation rate of 44-17.5% for leukoplakia, and in population-based studies rates of 0.13-2.2% over several years have been reported [1]. The risk of malignant transformation varies with sex (higher in females), type and location of leukoplakia (higher with 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 leukoplakias which regress has been reported to vary between 5 and 20% per year. In a subset of 159 individuals with oral leukoplakia in one oral cancer screening trial, after three years of follow-up the lesions could no longer be detected in 104 cases (71.2%). 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.

Nature of the intervention

Early oral cancers mostly present as asymptomatic, small indurated nodules or thickening or ulceroproliferative growth (*Head and neck cancer*, p232). Auxiliary health care workers can identify the above early lesions after adequate training [2]. There are four methods available for the early detection of oral cancer: visual examination of the oral cavity by health professionals, visual examination after application of toluidine blue, mouth self-examination and oral cytology.

Visual inspection of the oral cavity by trained health workers and doctors is the most widely-evaluated early detection procedure for oral cancer. Except for an ongoing randomized intervention trial in India and the oral cancer screening programme in Cuba, all other studies are cross-sectional, mostly in selected clinical or industrial settings, with the exception of a few studies in specified general

populations. Very limited information is available on intermediate and long-term end-points such as sensitivity and specificity, stage distribution, fatality rates, reduction in incidence and mortality.

Evidence of outcome

Oral visual inspection has been shown to be a sensitive and specific test to detect oral precancerous lesions and early asymptomatic oral cancers in several studies [1-7]. In the population-based studies, between 1.3 and 7.3% of screened subjects were referred for fur-



Fig. 4.49 The ingredients of betel-quin include betel leaf, slaked lime, areca nut and tobacco, with or without other condiments. Betel chewing is one of the major causative factors of oral cancer (together with bidi smoking and alcohol drinking) in the Indian subcontinent.

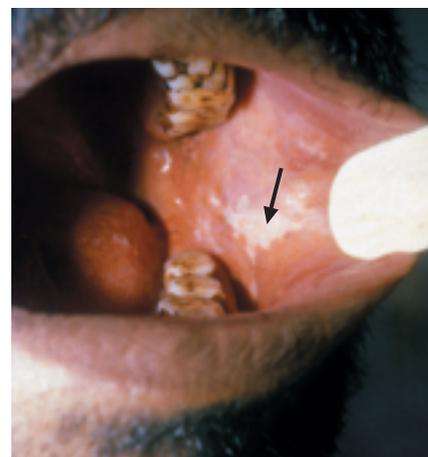


Fig. 4.50 Homogeneous oral leukoplakia. This precancerous lesion can be detected by visual inspection.

Stage	Intervention	Control
I (<2 cm)	24 (37.5%)	2 (6.9%)
II (2 - 4 cm)	14 (21.9%)	3 (10.3%)
III (>4 cm)	11 (17.2%)	7 (24.1%)
IV (adjacent structures involved)	8 (12.5%)	13 (44.8%)
Not known	7 (10.9%)	4 (13.9%)
Total	64 (100%)	29 (100%)

Table 4.19 Oral cancer cases according to stage (and percentage distribution), detected during an Indian screening trial (1995-1999), compared with an unscreened control population.

ther investigations although the compliance rates for referral were sub-optimal, ranging from 54 to 72%. The sensitivity of visual examination for detecting oral lesions varied from 58 to 94% and the specificity from 76 to 98%. In an on-going randomized controlled oral cancer

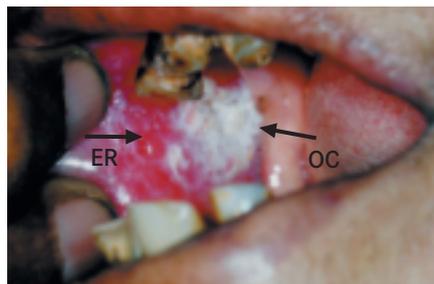


Fig. 4.51 Oral cancer (OC) arising from a pre-existing erythroplakia (ER).



Fig. 4.52 Confirmatory examination by a dentist in a woman referred as "screen positive" after oral cancer screening in Trivandrum District, Kerala, India.

screening intervention trial during 1995-1999 in Trivandrum, South India, involving 115,000 subjects, 60% of oral cancers in the intervention group were detected in early stages as opposed to 17% in the control group (Table 4.19) [7].

An oral cancer screening programme in Cuba, which has been running since 1984, involves annual oral examination of subjects aged 15 and above by dentists. A descriptive evaluation in 1994 revealed that participation and compliance were sub-optimal [8]. There has been no decline in oral cancer incidence and mortality in Cuba since the initiation of the programme, though there is limited evidence for a shift in the stage of cancers detected, from advanced to early, after the introduction of screening. In summary, there is no evidence as yet to establish that screening with oral visual inspection can reduce incidence of and mortality from oral cancer.

Toluidine blue

Toluidine blue dye has been mostly used as an adjunct for early detection of oral cancer in selected subjects with precancerous lesions, in order to provide better demarcation of malignant and dysplastic changes so as to help select sites for biopsies [9]. This test has been evaluated only in a few specified clinical settings where the reported false negative and false positive rates ranged from 20 to

30%. There are no studies investigating its use in the context of screening. Thus, the value of visual examination after toluidine blue application in the early detection of oral cancer is not known.

Self-screening

There is very little information on self-screening for oral cancer or on health education to promote mouth self-examination, especially in high-risk population groups. In a study to evaluate the feasibility of mouth self-examination in India, 36% of 22,000 subjects who were taught mouth self-examination reportedly practised the test and in the 247 subjects visiting the clinic within two weeks of a promotion campaign, 89 precancers were detected and 7 oral cancers [10]. There is no information available on long-term feasibility of and detection rates with self-screening in oral cancer detection.

Oral cytology

Screening by oral cytology has never achieved the same recognition or efficacy as cervical cytology screening. There are major limitations for oral exfoliative cytology as a screening modality for oral cancer. Firstly, the lesion needs to be seen before a sample can be collected, to ensure adequate numbers of abnormal cells. Secondly, only a small number of cells are identifiable in a smear. Furthermore, interpretation is of a subjective nature and there are high false negative diagnosis rates with leukoplakia [11,12]. If a lesion can be seen, it may prove preferable to biopsy it rather than to take a cytological sample. Thus oral cytology has received only limited attention and no adequate information is available on the utility of this approach for oral cancer screening.

Implementation

Organization of oral cancer screening programmes based on visual inspection of the oral cavity is currently not recommended as a public health policy for high-risk countries due to lack of information on reduction in incidence and mortality, as well as cost-effectiveness of such an approach [13]. It is likely that the trial in

India will provide useful information in this regard in the future [7]. Meanwhile, in high-incidence regions, health education messages and information on self-exami-

nation may be regularly provided by mass media and by posters in health centres, dispensaries and other establishments, in order to prompt subjects at high risk and

those who suspect that they may have an oral precancer to avail themselves of early detection services.

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STOMACH CANCER PREVENTION AND SCREENING

SUMMARY

- >Prevention or eradication of *Helicobacter pylori* infection may contribute to reduced incidence of stomach cancer, in addition to other health benefits.
- >Reduced intake of salted food and increased consumption of fresh fruit and vegetables has decreased the risk of this malignancy worldwide.
- > Early detection of premalignant lesions by population-based screening, using photofluorography and/or endoscopy, improves the prognosis of stomach cancer patients.

Stomach cancer is a leading cause of cancer-related deaths worldwide that lends itself to primary and secondary prevention. Stomach cancer typically becomes clinically evident at an advanced stage and has a poor prognosis (*Stomach cancer*, p194). The natural history of gastric adenocarcinoma is characterized by the development of premalignant lesions that provide a basis for early detection and treatment which can improve the prognosis.

For decades, stomach cancer was known to be strongly associated with gastritis. The discovery that infection with a bacterium, *Helicobacter pylori* (*Chronic infections*, p56) causes gastritis and plays an

etiological role in stomach cancer [1, 2] suggested that it might be possible to markedly reduce the incidence of stomach cancer, or even to eliminate it, on this basis. However, incidence varies among countries and regions with similar prevalence of *H. pylori* infection and incidence has declined rapidly in many countries and among specific ethnic groups (Fig. 4.54). These considerations suggest a role for additional environmental factors, such as diet, in causation and hence, potentially, in prevention.

Helicobacter pylori infection

The proportion of stomach cancers that can be attributed to *H. pylori* infection may be determined. "Attributable risk" refers to the proportion of stomach cancer cases that would be theoretically eliminated if *H. pylori* were to disappear and is mathematically dependent on the prevalence of *H. pylori* and the risk ratio (or odds ratio) linking *H. pylori* to stomach cancer. Accordingly, the calculated attributable risk of *H. pylori* is 40-70%. This estimate is considered likely to underestimate the true attributable risk associated with *H. pylori* (a study in Japanese patients indicated that stomach cancer developed in persons infected with *H. pylori*, but not in uninfected persons [3]). Moreover, a drawback of using "attributable risk" in this context is that, while not ever having an *H. pylori* infection probably reduces the risk of subsequent stomach cancer to a marked degree, it remains

unclear whether curing an existing chronic *H. pylori* infection would have a similar effect.

Given the long lag period between acquisition of the infection and development of cancer in the small percentage of infected patients, it will be very difficult to demonstrate that cure of the infection prevents cancer. No study has yet accomplished this. In a small non-randomized Japanese study, patients underwent endoscopic resection for early stomach cancer followed by *H. pylori* treatment and cure. No new cancers developed after a follow-up of three years in those cured of infection (0/65) compared with a 9% rate of incidence of new intestinal-type stomach cancers in the (6/67) non-*H. pylori* treated group [4]. Small Japanese non-randomized trials have demonstrated reduced risk of malignant transformation of gastric adenomas after curing infection. Conversely, in other studies *H. pylori* eradication in patients with mild and moderate dysplasia did not result in a significant reduction in the progression of dysplasia into stomach cancer. Overall, neither dysplasia nor intestinal metaplasia is thought to regress significantly following cure of *H. pylori* infection and the problem of sampling error makes it unlikely that studies relying on endoscopic biopsies can ever answer this question.

There are other considerations relating to this issue. The major determinant of the cost-effectiveness of *H. pylori* screening and/or treatment is the reduction in can-



Fig. 4.53 Endoscopy showing early gastric carcinoma (superficial elevated type and superficial depressed type) in a 59-year-old male patient (A) and after methylene blue chromoendoscopy (B), obtained using a video gastroscope (C).

cer incidence following cure of infection; the higher the reduction, the more cost-effective screening becomes [5,6]. Factors that influence screening strategies are the prevalence of *H. pylori* in the population, and the need to focus upon older persons. The paradox is that the greatest benefit will be potentially gained by younger persons, in whom screening and treatment is less cost-effective. Due to associated comorbidity, the benefit in terms of life expectancy becomes negligible in older persons. Published analyses suggest favourable scenarios if screening and curing *H. pylori* among persons at a high risk of stomach cancer between the ages of 40 and 50 years were to reduce the risk of cancer by at least 30% [6]. However, in a high-risk population, most *H. pylori*-infected persons develop atrophic gastritis by age 40 and there is no evidence as to whether curing the infection at that stage will reduce the risk of cancer. Nonetheless, curing *H. pylori* infection gives the additional benefit of eliminating duodenal and gastric ulcer, a type of lymphoma associated with this condition, and up to 10% of cases of dyspepsia, as well as preventing transmission of the infection. There is considerable interest in the development of a vaccine to prevent *H. pylori* infection and possibly also to cure active infections [7,8]. Proof of concept has been obtained in animal experiments, candidate vaccines have been identified and clinical trials are poised to begin. An effective vaccine is the only practical method of eliminating *H. pylori* infection in developing countries where the incidence of the infection and the burden of disease are the greatest.

The role of dietary factors

Relevant dietary risk factors have been extensively investigated in observational epidemiological studies. Most studies of dietary factors in stomach cancer preceded the discovery of the role of *H. pylori*. Nevertheless, diet is thought to be a critical factor in the progression of superficial gastritis to chronic atrophic gastritis among persons infected with *H. pylori*. Several observations have been made that indicate a preventive role for

specific food items [9,10]. An inverse relationship between stomach cancer and regular dietary intake of fresh vegetables and fruits has been observed in many case-control studies as well as prospective studies conducted in several countries. Individuals eating 5-20 servings of fruits and 5-20 servings of raw vegetables every week reduce their risk of stomach cancer by almost half [11]. In addition, allium vegetables and onions have been negatively associated with stomach cancer in several countries. Fruits and vegetables are sources of many antioxidants, such as α -tocopherol, β -carotene, vitamin E, and vitamin C. However, a study in Finland found no impact of dietary supplementation with α -tocopherol and β -carotene for five years on the occurrence of neoplastic changes of the stomach in older male smokers with atrophic gastritis [12]. Intake of vitamin C is associated with an approximately 50% decrease in the risk of stomach cancer [11,13], although supplementation with vitamin C does not seem to reduce incidence among patients with pre-existing intestinal metaplasia. Prolonged consumption of foods rich in salted, pickled, and smoked products increases the risk of stomach cancer. These foods have high salt content and nitrates and low levels of antioxidants due to storage for a long time at room temperature before consumption. Excessive dietary salt has been associated with gastric atrophy in animals and probably accelerates gastric atrophy in humans. In Japan, the correlation between salt intake and stomach cancer follows the gradient of salt intake. Similar correlations between salt intake and stomach cancer have been observed in other countries. Increase in the per capita consumption of fruits and vegetables and a concomitant decrease in salted foods have paralleled the decline in stomach cancer mortality in Japan. Foods rich in carbohydrates have been associated with an increased risk of stomach cancer. However, consumption of carbohydrate-rich foods overlaps with high dietary salt intake and reduced intake of fruits and vegetables. Despite the implications of certain animal studies, foods rich in nitrates, nitrites and secondary

amines have not been shown to be independent significant risks. The spread of refrigeration has been associated with the decrease in stomach cancer, which probably relates to the replacement of more traditional methods of food preservation such as salting and pickling and making fresh fruits and vegetables more available all year round. However, there have been no intervention trials showing that a specific dietary modification reduces the incidence of stomach cancer.

Secondary prevention: screening

Screening for stomach cancer has been practised in Japan since 1963. Annual screening using seven-film photofluorography examination or endoscopy (Box: *Screening for stomach cancer in Japan*, p177) has been recommended for people of age 50 and above, although this is a matter of some controversy. The false negative rate has been reported to be up to 19% for gastroscopy and up to 40% for photofluorography. Screening in Japan has increased the proportion of tumours detected at an early stage to approximately 50%. Prognosis for stomach cancer patients identified by screening may be better than for those identified by other means [14]. Certainly, detection of the cancer at an early stage improves chances of survival; the five-year survival rate following surgical treatment for early stomach cancer is higher (99.2%) than for non-early stomach cancer (48.5%). The overall five-year survival increased from 20% in 1965 to 40% in 1992. The five-year survival rate for stomach cancer in the USA and other Western countries remained stable at 20% during the same time period. Screening is the most likely explanation for the improved survival but a reduction in incidence is not attributable to screening. The Ministry of Health and Welfare of Japan determined that a programme of population-based screening by barium meal included only 7-13% of the population over 40. Therefore, it may be concluded that the official mass screening programme in Japan detects only a small proportion of stomach cancers (10-15%). The remaining cases are identified symptomatically. Screening for stomach cancer

SCREENING FOR STOMACH CANCER IN JAPAN

There has been a long history of screening for stomach cancer in Japan. Screening by indirect X-ray examination started in around 1960 and has been part of the “Health and Medical Service Law for the Aged” since 1983. The Ministry of Health and Welfare in Japan reported that in 1997 4,273,000 residents participated in screening programmes provided by local governments based on this law. Moreover, the Japanese system of annual health check-ups in the workplace has provided an opportunity for screening; about 16.7% of an estimated 6,759,000 employees were screened for stomach cancer in 1997. In addition, screening for stomach cancer is also undertaken during the so-called “Human Dry Dock”, which incorporates multiple screening procedures, including measurement of blood pressure, urine analysis, blood tests, chest X-ray examination and stomach X-ray examination.

Consequently, at least 11,032,000 individuals (8.7% of the Japanese population) are estimated to have participated in screening for stomach cancer in 1997.

The main technique used to screen for stomach cancer in Japan is an indirect X-ray examination by the double contrast method, “double” referring to barium and air. When barium is swallowed, a small amount of air is also taken into the stomach. The barium makes the positive contrast and the air the negative contrast; this allows the detailed morphological patterns of the gastric surface to be visualized. This is usually conducted in a specially designed mobile unit equipped with a photofluorographic apparatus. This enables peo-

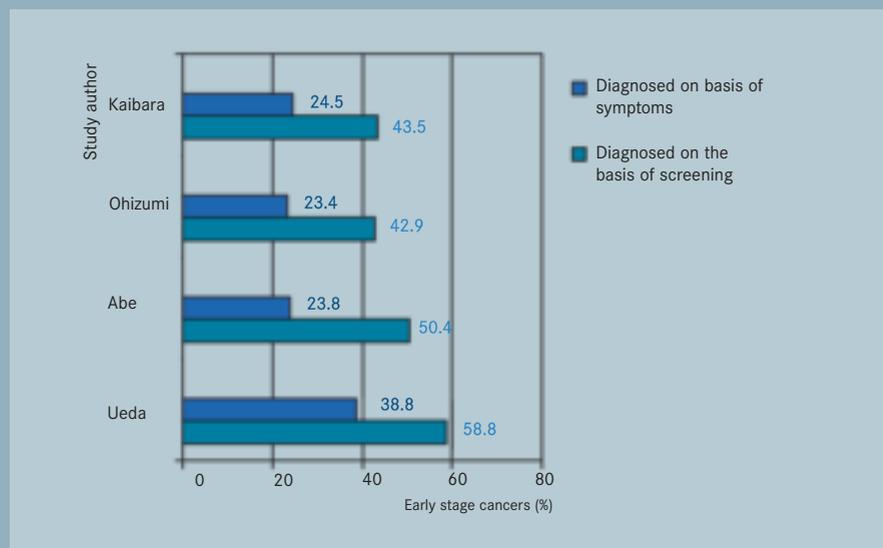


Fig. 4.55 Percentage of tumours detected at an early stage in Japanese patients diagnosed with stomach cancer, either during a screening programme or on the basis of presentation of symptoms.

ple to participate in screening near their homes or workplaces. Seven X-ray photographs are usually taken according to the standard method of the Japanese Society of Gastroenterology. Record linkage between participants in the screening and the lists of population-based cancer registry indicated that the sensitivity and the specificity of an indirect X-ray method by image intensifier were 88.5% and 92.0%, respectively (Murakami R et al., *Cancer* 65: 1255-1260, 1990).

Measurement of serum pepsinogen I and II levels has recently been introduced in Japan as a further method of screening for stomach cancer (Miki K, *Annual report 1997 of the research committee of studies on study of gastric cancer screening system using serum pepsinogen test*, 1998). However, a well-designed epidemiological evaluation of the efficacy of the pepsinogen method has not yet been conducted. Randomized controlled trials to evaluate the effectiveness of screening for stom-

ach cancer have not been undertaken in Japan. There have however been many other types of studies, such as case-control studies, cohort studies, and time trend analyses to evaluate the effectiveness of screening for stomach cancer (Hisamichi S et al., *Evaluation of mass screening programme for stomach cancer in Japan*, in *UICC Cancer Screening*, eds. Miller AB et al., Cambridge University Press, 1991; Inaba S et al., *Evaluation of a screening program on reduction of gastric cancer mortality in Japan: Preliminary results from a cohort study*. *Prev Med*, 29: 102-106, 1999). There is an absolute confidence among most Japanese people that screening provides benefit. This confidence might be a product of the success of screening programmes for tuberculosis during the decades following the Second World War.

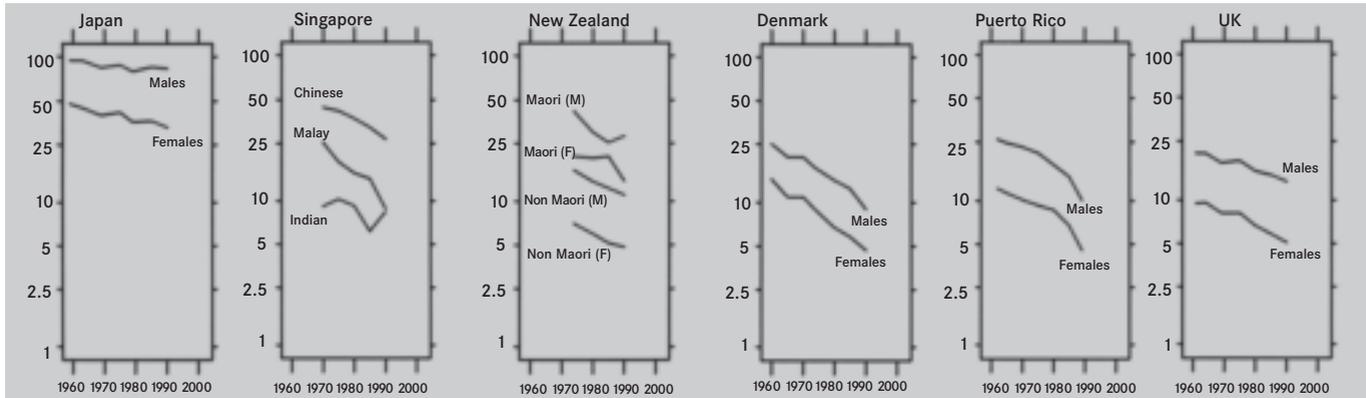


Fig. 4.54 The incidence of stomach cancer is decreasing worldwide. D.M. Parkin et al. (2001) *Eur J Cancer*, 37 Suppl. 8: S4-66.

has not been evaluated in a prospective, controlled study. Outside Japan, there are conflicting data about the efficacy of screening. In the North-East of Italy, an area with an intermediate incidence rate, surveillance was employed for patients with dysplastic gastric lesions. Three-quarters of cancers detected during a secondary prevention surveillance programme were considered

to be early stomach cancer. This contrasts with a case-control study in Venezuela which did not demonstrate a reduction in mortality among persons screened with radiography [15,16].

It is essential that in countries with a high incidence of stomach cancer, primary prevention should be promoted to reduce the disease burden. The pathogenesis of

stomach cancer is multi-factorial and even if the most powerful risk factor is eradicated, this does not guarantee an immediate or even rapid reduction in cancer risk. Testing and treatment for *H. pylori* in high-incidence areas should be complemented with dietary modifications. Population-based screening for stomach cancer is not appropriate in countries with low incidence rates.

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