4

Acting for Prevention

4.1 Tobacco Control

Summary

> The main benefit from quitting smoking arises from avoiding the more pronounced increase in risk that would result from continuing to smoke

> Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers

> The WHO Framework Convention on Tobacco Control (WHO FCTC), the first-ever public health treaty with widespread support worldwide, encompasses a series of stipulations designed to control tobacco use and supply

> Comprehensive smoke-free and tobacco pricing policies, two of the WHO FCTC-endorsed policies, have been effective in reducing exposure to secondhand smoke, diminishing cigarette consumption and increasing quitting smoking

> There are pharmacologic and non-pharmacologic tobacco dependence treatments options, varying in effectiveness, available to aid those who want to quit smoking

Risk reduction

For smoking-induced morbidity and mortality to disappear, smoking initiation in the young must cease. Ironically, it would take many decades for morbidity and mortality trends to reflect the effects of such intervention, mainly due to the lag time of expected health consequences in prevalent smokers who will continue to do so. However, if current smokers quit, the risks of developing or dying from cancer as compared to continuing counterparts would diminish even if stopping after decades of smoking. An assessment of changes in cancer risk and of other diseases caused by smoking with smoking cessation was conducted by an international Working Group of experts convened at IARC in Lyon on March 13-19, 2006 [1,2]. The assessment addressed three questions:

- is the risk of developing cancer, for each of the 13 tobacco-associated cancers considered, lower in former smokers than in otherwise similar current smokers?
- Among otherwise similar former smokers, is the risk of disease lower with more prolonged abstinence?
- Does the risk return to that of never smokers after a long period of abstinence?

Conclusions by the Working Group on the effects of smoking cessation on the risk of developing and dying from lung, laryngeal, oral and oesophageal cancers are shown in Tables 4.1.1 and 4.1.2, indicating a lower risk of cancer at these sites in those who quit as compared to those who continue to smoke [2].

Tobacco control interventions

To arrest the global tobacco epidemic, initiation must be prevented and cessation pursued and maintained actively in the population. Interventions addressing these primary and secondary prevention strategies, for the purposes of this chapter, will be described in two major groups: policy and non-policy approaches—the former directed at the population level (e.g. smoking restriction in public places) and the latter often adopted by individual choice within the framework of recommended guidelines by healthcare professionals and/or regional or national health systems (e.g. pharmacologic and non-pharmacologic alternatives). Given the potential reach of interventions designed to affect an entire population or at a minimum the group of smokers in a geographic unit, policy interventions, in particular those that are WHO-backed, will be covered here in greater depth.

Policy-based interventions

Achieving prevention of initiation and increased cessation of tobacco use are two cardinal public health goals of the World Health Organization (WHO). Accordingly, the WHO and member states were proponents and overwhelmingly supported the first public health treaty conceived to reduce tobacco use worldwide.

The WHO Framework Convention on Tobacco Control (WHO FCTC) encompasses a series of measures, in their totality representing a comprehensive approach, designed to control tobacco use and supply. The body of policies stipulated in the treaty became binding international law on 27 February 2005. Of the 38 articles, articles 6 to 14 cover policy interventions directed at preventing tobacco use, decreasing consumption, reducing toxicity, protecting non-smokers and diminishing tobacco use initiation. Articles 15 to 17 relate to measures controlling the availability of tobacco (Table 4.1.3) [3]. The concerted adherence of countries to the treaty around the world will make it a global response to the tobacco epidemic. However, the reach of the policy interventions included in the WHO FCTC will depend on how effectively countries formulate and implement these policies. As of November 2008, 160 countries have subscribed to the treaty (Figure 4.1.1)[3]. IARC convened a group of international tobacco control policy experts in March 2007 to propose a framework for guiding the evaluation of tobacco control policies expected to be formulated worldwide in response to WHO-FCTC. This framework and its scientific and policy bases will aid tobacco control policy authorities to assess if intended targets are fulfilled [4].

Comprehensive tobacco control programs are more likely to be successful in reducing tobacco use than programs relying in few interventions. Joossens and Raw [5] have proposed a scale to quantify the implementation of tobacco control interventions at country level. Their work is based on a baseline survey conducted in 2005 in 30 European countries. Tobacco control policies taken into account in the scale included price of cigarettes and other tobacco products, smoke-free work and other public places on July 1, 2005, spending on public information campaigns in 2004, comprehensive bans on advertisement and promotion on July 2005, large health warning labels, on 1 July 2005, and cessation services in place. Tobacco control performance varied greatly within Europe, from countries accruing ≥70 points (Great Britain, Ireland, Norway and Iceland) to countries accumulating <30, with results by type of intervention indicating areas where future efforts could be concentrated.

Protection from exposure to SHS. Countries enacting laws banning smoking in public places have shown high compliance and significant decrease in SHS exposure. The banning of smoking in pubs and restaurants in Scotland started in 26 March 2006, with pre-ban concentration levels of particulate matter ($PM_{2.5}$) aver-

Benefits of quitting smoking on risk of developing and/or dying from lung cancer

These conclusions are based on epidemiologic studies comparing lung cancer risk in persons who stop smoking with the risk of those who continue, showing lower lung cancer risk in former than in current smokers.

The main benefit from quitting arises from avoiding the more pronounced increase in risk that would result from continuing to smoke.

Within five to nine years after quitting, the lower lung cancer risk in former compared with otherwise similar current smokers becomes apparent and widens increasingly with longer time since cessation.

Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers

The absolute annual risk of developing or dying from lung cancer does not decrease after quitting smoking. An individual who has smoked will always have a greater risk of developing lung cancer in comparison with an otherwise similar individual who has never used tobacco.

There is a lasting increased risk of lung cancer in former smokers compared to never smokers of the same age, even after a long duration of abstinence.

Table 4.1.1 *Benefits of quitting smoking on risk of developing and/or dying from lung cancer*
Adapted from Reversal of Risk After Quitting Smoking [2]

Cancer site	Is the risk lower in former smokers than in otherwise similar current smokers?	Does the difference in risk between former smokers and otherwise similar current smokers become larger with time since cessation?	Does the risk return to that of never smokers after long period of abstinence?
Laryngeal	Yes. The risk is lower in former smokers than in those who continue to smoke	Yes. The benefits of cessation relative to continued smoking increase with longer time since cessation	No. The risk does not return to that of never smokers after a long duration of abstinence. It remains higher for at least two decades
Oral	Yes. The risk of oral and pharyngeal cancer is lower in former smokers than in current smokers	Yes. The reduction in risk for former smokers compared with current smokers increases with longer time since cessation	Yes. The relative risk for former smokers who have stopped for at least twenty years is not increased over that of never smokers
Oesophageal (squamous-cell)	Yes. The risk is lower in former smokers than in those who continue to smoke	Yes. The reduction in risk for former smokers compared with current smokers increases with longer time since cessation	No. The relative risk does not return to that of never smokers; it remains elevated for at least two decades after cessation

Table 4.1.2 *Benefits of quitting smoking on risk of developing and/or dying from laryngeal, oral or oesophageal cancers*
Adapted from Reversal of Risk After Quitting Smoking [2]

aging 246 µg/m^3 (range 8-902 µg/m^3) and post-ban levels 20 µg/m^3 (range 6-140 µg/m^3) equivalent to an average reduction of 86% [6].

A meta-analysis of 26 studies conducted in Australia, Canada, Germany and the USA on the effects of total smoke-free work places documented smoking cessation in adults and younger smokers as well as protection from SHS [7]. This systematic review found an overall reduction in smoking prevalence (3.8%; 95% CI=2.8–4.7%) and number of cigarettes smoked daily in continuing smokers (3.1 cigarettes; 95% CI= 2.4–3.8) with total smoking bans.

One year after the Scottish ban a significant 39% decrease (95% CI=29–47%) in exposure to SHS using biomarkers of exposure (salivary cotinine concentrations) in non-smoking adults has been reported [8]. The drop in exposure was higher for individuals living in households with no smokers (a 49% decline; 95% CI=40–56%). Nonetheless, non-smokers living with smokers experienced a 16% drop in cotinine concentration that was, however, not statistically significant. Findings from the evaluation assessing exposure in primary school students found significant reductions in exposure, as revealed by salivary cotinine concentrations, only in children living in households with no smokers (a 51% drop) or in those where only the father smoked (44%) [9]. These results from the Scotland evaluation pinpoint the importance of the household (and cars) as a source of exposure to SHS.

Price and tax measures to reduce demand. Policies prohibiting smoking in public places are intended to protect the health of all but in particular that of non-smokers. Tax policies on tobacco products also affect a substantial portion of the population and are intended to discourage tobacco use in established and in potential users, in addition to generating revenues. The WHO FCTC contemplates the use of taxes on tobacco products as an effective intervention to control tobacco use by increasing prices and impacting product demand. Chaloupka and colleagues have extensively documented the role of fiscal policies in reducing tobacco consumption and increasing cessation in users and sustaining abstinence in non-smokers [10,11]. Studies from high-resource countries show that a 10% increase in the price of cigarettes, following elevation of taxes, produce a decline in use that varies between 2.5% and 5%, affecting both the prevalence of smoking and the amount consumed [10]. Gallus and colleagues have also studied the effect of price on cigarette consumption in Europe reporting for each 10% increase in the price of cigarettes a drop in consumption of 5–7% [12].

The impact of similar price increments (10%) on tobacco use in low/medium-resource countries appears to be greater, depending on the population studied and the income level referred to (5.4–6.6% in China; 13.3% and 5.2% in lower and higher income groups respectively in Bulgaria) [11]. Long-term reduction in tobacco use as a result of increases in price tend to be higher than short-term effects, reflecting the progressive overcoming of addiction among those who are successful in quitting or in reducing consumption (up to 2% and 8% reduction in consumption in the short and long-term respectively in Brazil) [11]. Income is also a significant variable explaining tobacco demand (i.e. increments in income leading to greater consumption). Changes in smoking behaviour in response to increments in cigarette prices tend to be more pronounced in the young and in less affluent groups in the population.

Cigarette price affects smoking initiation, too, based on studies conducted in both more and less developed countries. Ross and Chaloupka cite results from a study conducted in Vietnam using survey data from different periods and concluding that a 10% increase in cigarette price would decrease smoking initiation by 11.8% [11]. Slater and colleagues [13] have conducted a more sophisticated analysis of US data taking into account cigarette price, point-of-sale advertising and promotion. Their results indicate that for each dollar increase in price the odds that an adolescent moves upward in the smoking uptake ladder will decrease by 24% (never smoker, puffer, non recent experimenter, former established smoker, recent experimenter and current established smoker) [13].

Article 6	Price and tax measures to reduce demand
Article 8	Protection from exposure to tobacco smoke
Article 9	Regulation of the contents of tobacco products
Article 10	Regulation of tobacco product disclosures
Article 11	Packaging and labelling of tobacco products
Article 12	Education, communication, training and public awareness
Article 13	Tobacco advertising, promotion and sponsorship
Article 14	Demand reduction measures concerning tobacco dependence and cessation
Article 15	Illicit trade in tobacco products
Article 16	Sales to and by minors
Article 17	Provision of support for economically viable alternative activities

Table 4.1.3 *WHO FCTC Articles addressing key interventions to reduce tobacco demand and supply (Adapted from WHO, 2003[3])*

Non-policy interventions

The majority of smokers desire to quit smoking, but the path from intention to actual cessation is long in the greater part of smokers. There are pharmacologic (i.e. nicotine replacement therapy, NRT, Table 4.1.4) and non-pharmacologic approaches (i.e. counselling, Table 4.1.5) available to aid smokers quit their dependence on nicotine, the addictive component of tobacco, and both types are often prescribed jointly. There are three pharmacologic therapies that have proven efficacious: nicotine replacement therapy (odds ratio of quitting of 1.5 to 2-fold over placebo), bupropion, an antidepression medication (odds ratio of quitting of 2 over placebo), and varenicline, a nicotine receptor partial agonist that reduces nicotine withdrawal symptoms (odds ratio of quitting of 3-fold over placebo)[14,15]. The characteristics of these therapies are compared in Table 4.1.4. These products have been tested in clinical trials where psychological, behavioural and emotional supports have been available to trial participants. Since approximately 70% of smokers want to stop smoking, it is imperative that smokers become aware of the existence of these pharmacologic approaches and that healthcare providers use every opportunity possible to assess patient's desire to quit, provide information on quitting aids, advise additional support of non-pharmacologic interventions for the treatment of tobacco dependence and if possible follow smokers in their quitting attempts (Table 4.1.5).

More recently, vaccine technology has been used to produce antibodies against nicotine as an approach to prevent relapse in former smokers and to allow quitting smoking. Several vaccines have been formulated and tested in animals and humans with cessation success been observed in those mounting strong antibody responses [16]. At present, 3 vaccines have been tested in Phase II clinical trials, each using a different antigen (nicotine) presentation approach: Ta-NCI (Celtic Pharma, Hamilton, Bermuda) binds nicotine to recombinant

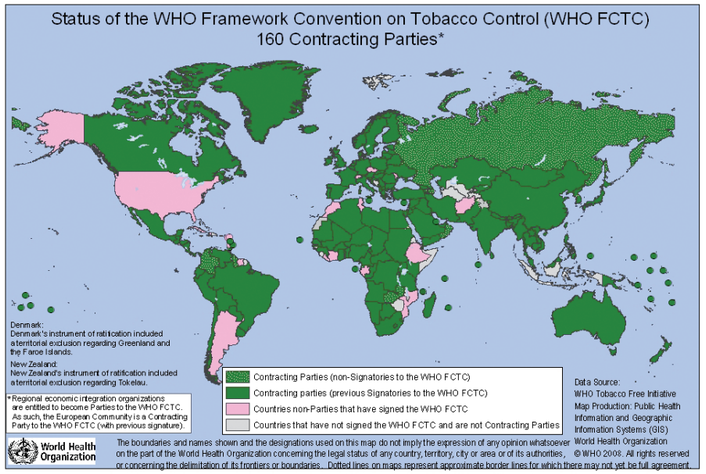

Fig. 4.1.1 *Status of the WHO FCTC 160 Contracting Parties*

cholera toxin B; NicQb (Cytos Biotechnology, Zurich, Switzerland) employs virus-like particles from the bacteriophag Qb; and NicVax® (Nabi Pharmaceuticals, Boca Raton, Florida, USA) uses recombinant exoprotein A [15]. The nicotine vaccine can also bring about a reduction in the amount smoked by making the metabolism of nicotine slower and inducing its effect to last longer, hence reducing craving.

The duration of the vaccine immunity is, however, unknown at present. Dosing and administration schemes are being formulated in order to carry on Phase III clinical trials that will reveal vaccine efficacy. The potential use of this secondary prevention approach is very promising given the number of smokers who wish to quit and the number of former smokers who desire to remain abstinent.

Discussion

Two WHO FCTC-endorsed policies with impact at the population level and several approaches to treat tobacco dependence have been presented in this chapter. The success of these policies in achieving reductions in tobacco use and protection in non-smokers will depend on a more complex array of factors than those included in this chapter, such as total or partial ban of smoking restrictions in work and public places, enforcement of restrictions, tax avoidance, smuggling of tobacco produces and/or proliferation of grey markets to name few. Still, these are policies that have been shown to decrease the use of tobacco products and that are receiving global attention in response to the activation of the WHO FCTC legislative clock. These are not the only policy interventions effective in curbing tobacco use. Suppression of tobacco advertising, promotion and sponsorship, education and communication campaigns to raise awareness and product labelling, for example, have been shown to modulate tobacco use in adolescents and adults.

Lung cancer rates are influenced by smoking initiation and smoking cessation in the population. At present, there are many countries showing increasing trends in lung cancer mortality in younger age groups where there are no evident trends in decreasing smoking initiation and/or

increasing smoking cessation. If these smoking trends remain unaltered, projected lung cancer incidence and mortality will grow rather than decrease. Policies leading to smoking cessation and preventing smoking initiation must be fostered and maintained. Also important, smokers and former smokers can and should be assisted in their attempts to quit and remain abstinent by receiving pharmacologic and nonpharmacologic intervention treatments within the healthcare system or as advised by the principal healthcare provider. However, smokers tend to avoid clinic-based smoking cessation programmes but on the other hand respond to environmental prescriptions such as smoking bans. Hence the importance of policy-based interventions designed to deter tobacco use and eventually leading to the denormalisation of this behaviour.

Drug	Dose	Duration of treatment	Contraindications	Adverse effects*
Nicotine replacement therapy	Dose is adjusted to level of nicotine dependence and is decreased progressively over treatment period Patch: 21–42 mg/d initially Gum: 8–10 pieces (2 or 4 mg each) per day Inhaler: 4–6 puffs per day Lozenge: 9–20 lozenges per day	8–12 weeks; can be longer (up to 1 year) for the prevention of relapse	Patch: allergy to constituent of nicotine patch	Patch: skin irritation, sleep disturbance Gum or lozenge: mouth irritation, sore jaw, dyspepsia, hiccups Inhaler: mouth and throat irritation, cough
Bupropion, sustained release (Zyban)	150 mg/d for first 3 days, then 300 mg/d	8 weeks; can be longer (up to 1 year) for the prevention of relapse	Seizure, central nervous system tumour, bipolar disorder, alcohol withdrawal, benzodiazepine withdrawal, use of monoamine oxidase inhibitor, anorexia, bulimia, liver disease	Insomnia, seizure, gastrointestinal disturbance, jitteriness
Varenicline (Champix)	0.5 mg/d for first 3 days, then 0.5 mg twice daily for the next 4 days and 1 mg twice daily thereafter	12 weeks; can be longer (up to 24 weeks) for the prevention of relapse	None	Nausea, vomiting, constipation, flatulence, bad taste in the mouth, abnormal dreams, sleep disturbance

Table 4.1.4 *Pharmacologic treatment of tobacco dependence. Adapted from Le Foll and George, 2007[14]*
**Most frequent adverse events*

Intervention	Description	Estimated efficacy odds ratio (95% CI)
Advice from physician to quit smoking	Even a short intervention (3 minutes or less) can increase a person's motivation to quit and can significantly increase abstinence rates. Since an estimated 70% of smokers visit a physician each year, physicians have a substantial opportunity to influence smoking behaviour	1.3 (1.1–1.6)
Self-help materials	Self-help materials come in the form of pamphlets, videotapes, audiotapes, hotlines/helplines and information on websites. Such materials may be more effective than no intervention in motivating people to quit, but they are not as effective as materials tailored for individual smokers	1.1 (0.9–1.3)
Proactive telephone counselling	Telephone counselling is efficacious in assisting people interested in quitting smoking. However, the effects are not additive when it is combined with nicotine replacement therapy	1.3 (1.1–1.4)
Group counselling	Group therapy offers individuals the opportunity to learn behavioural techniques for smoking cessation and to provide each other with mutual support. There is limited evidence that the combination of group therapy with other forms of treatment (e.g., advice from a health professional or nicotine replacement therapy) produces extra benefit	1.3 (1.1–1.6)
Individual counselling	Face-to-face individual counselling with a health care worker not involved in the patient's routine clinical care is efficacious. However, there is no significant additive effect when it is combined with nicotine replacement therapy. Brief counselling may be as effective as intensive counselling	1.6 (1.3–1.8)
Intra-treatment social support	Support is provided during a smoker's direct contact with a clinician	1.3 (1.1–1.6)
Extra-treatment social support	Interventions that increase social support in the smokers' environment are efficacious. The clinician should help the patient in requesting social support from family, friends and coworkers and in establishing a smoke-free home	1.5 (1.1–2.1)

Table 4.1.5 *Nonpharmacologic interventions for the treatment of tobacco dependence and their estimated efficacy. Adapted from Le Foll and George, 2007[14]*
Note: CI = confidence interval

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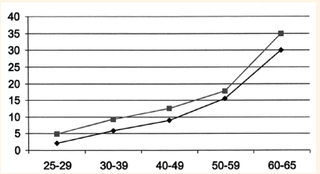
CANCER INSTITUTE PROFILE: Centre Regional Francophone de Formation a la Prevention des Cancers Gynecologiques (CERFFO pcg)

The French-speaking Regional Centre for Training in Gynaecologic Cancer Prevention (known by its French acronym CERFFO), located in Conakry, Guinea, provides information, training and technical assistance based on practical solutions that insure the implementation and continuation of gynaecologic cancer prevention strategies fitted to social, cultural and environmental settings of our region.

The centre has three missions: Training, Research and Services Management.

At the centre, reproductive health providers may further new assessment approaches for screening and treating major gynaecological cancers, improve healthcare systems in diagnosis and health management, and contribute to the implementation of gynaecologic cancer prevention programs with respect to national policies and programs for fighting against cancer.

Through their wide range of multidisciplinary skills, the staff of CERFFO also collaborates with specialised agencies in the implementation of regional research projects, assisting in innovative studies of the impact and evolution of national programmes aimed at reducing gynaecologic cancer incidence and mortality. The Centre also contributes to the education and training of healthcare professionals and researchers via its short-term training schedule for enhancing the managerial and pedagogical skills of project leaders and programme officers.



4.2 Prevention of Occupational Cancer

Summary

> In high-resource countries, prevention of occupational cancer is likely to have occurred during the last decades thanks to regulation and improvement of working conditions. However, quantifying the effect of this change is difficult

> Regulation (e.g. setting of standards) often has to rely on experimental data, as evidence from epidemiological studies is often lacking

> Measures aimed to prevent occupational cancer should be implemented in low-resource countries as well

Over the past 50 years, the number of occupationally-induced cancers has likely decreased in high-resource countries [1]. This is the result of several different trends. The decline in blue-collar heavy industry and the corresponding growth of white-collar knowledge industries has served to decrease the number of workers in particularly "dirty" occupations. At the same time, many industries have instituted procedures and processes that provide much cleaner work sites than in the past [2]. The motivations for this are complex and multi-dimensional. In part, this is a by-product of epidemiologic research carried out in the past [3,4]. In many countries the identification and characterisation of occupational carcinogens triggers regulatory actions intended to reduce the permissible exposure levels. Such actions may range from substitution of one substance in an industrial process for another, modification of industrial procedures or ventilation/emission control procedures, or the use of protective equipment by workers. But the real benefits of such regulations may be quite non-specific. That is, while regulations concerning a particular carcinogen may serve to reduce the risk of cancer in relation to that carcinogen, cleaning up an industrial process induces reduction in exposure to many substances, some of which may be in the hidden part of the iceberg of occupational carcinogens.

It is impossible to estimate how many occupational cancer cases have been prevented, but it is certainly a partial success story. In addition, there has been a growing realisation on the part of many industries that good industrial hygiene makes good business sense. The cautionary tales of companies that have suffered from regulatory or legal opprobrium, as well as compensation costs, as a result of being identified as a "cancer-causing company" might have served as an incentive for other companies to clean up.

Setting standards for regulatory purposes is a difficult task that relies on epidemiologic, toxicologic and other data [5,6]. Historically, these standards have usually been based on considerations of acute toxicity; increasingly, however, cancer has become a key endpoint. The main problem with setting standards aimed at reducing carcinogen exposure is the lack of reliable epidemiologic data on dose-response relationships. For the most part, the regulators must rely on animal data, with complex mathematical models used to translate the animal experience into terms that are relevant for human risk assessment.

One approach, which can only be implemented if a known carcinogen has not yet been introduced into industrial practice, is to ban its introduction. On occasions when an agent has been used and shown to be carcinogenic in one country, that information can then be used by other countries. For example, following reports from the United States on the increased bladder cancer risk among workers exposed to 4-aminobiphenyl, its introduction was banned in the United Kingdom [7]. Substitution of products known to be carcinogenic has been used successfully, as in the example of asbestos and man-made mineral fibres. More common have been attempts to reduce exposure levels to known or suspect carcinogens. Successful examples include: the virtual elimination of radiation-related cancer risk among nuclear

Fig. 4.2.1 *Clothing to prevent contamination*

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 4.2.1 *Percent decrease in air concentrations of six key air pollutants, USA (1986-1995)*

Country	Year	Butadiene concentration (mg/m3)	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)°	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). ° Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

Table 4.2.2 *International occupational exposure limits and guidelines for butadiene (which is classed by IARC as an established human carcinogen, Group 1)*

industry workers [8], the significant decrease in liver cancer risk among workers in the vinyl chloride industry following recognition of its carcinogenicity in the 1970s [9], the significant decrease in lung cancer risk among American workers exposed to chloromethyl ethers following recognition of its carcinogenicity in the 1950s [10], and the significant decrease in lung cancer risk among Norwegian nickel refinery workers following recognition of cancer risks in the 1930s [11].

The decrease in exposure to occupational carcinogens may be due to reduced emissions, improved ventilation or use of personal protection by the workers. As a general rule, the first two approaches are more efficient in achieving a durable reduction in exposure than is the use of protective equipment. Reduction of emissions can be easily achieved for chemicals produced under controlled conditions, such as intermediates formed during chemical manufacturing processes. However, reduction of exposure at the sources might be difficult to achieve for substances that are use under less controlled conditions, such as motor exhausts.

Screening of occupationally exposed workers has been proposed as an additional measure to prevent cancer deaths. However, for none of the cancers for which it has been proposed is there evidence of efficacy. This is the case in particular of lung cancer and mesothelioma among asbestos-exposed workers, and bladder cancer among workers exposed to aromatic amines [12,13].

Operative measure	Examples
Preventing exposure	
Use of gloves and face mask	Pharmacists handling cytotoxic drugs
Full respirator	Specified emergency procedure for spillage of hazardous material
Controlling exposure	
Environmental monitoring	Measurement of asbestos fibre level in breathing zone
	Film badge to assess radiation exposure
Assessing uptake and excretion	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

Table 4.2.3 *Means to either prevent or determine the level of exposure to occupational carcinogens*

There has been significant improvement in occupational hygiene conditions in large industries in high-resource countries [2]. The challenge is to extend this improvement to smaller enterprises and to medium- and low-resource countries, where there remain significant problems of exposure to such agents as asbestos, crystalline silica and pesticides [14].

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

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4.3 Vaccination

Summary

> Hepatitis B virus (HBV) vaccine has proven to be safe and effective in preventing chronic hepatitis and hepatocellular carcinoma

> Twenty-five years after having been licensed, HBV vaccination programs are now carried out in at least 158 countries. However, they have yet to obtain high penetration in many high-risk areas, such as in sub-Saharan Africa

> Two human papillomavirus (HPV) vaccines were licensed in 2007 and show high efficacy in the prevention of precancerous lesions of the cervix uteri in young women who have not already been infected by the HPV types included in the vaccine

> The duration of the efficacy of the HPV vaccine and the need for a booster are not yet known, and the vaccine price is currently unaffordable in medium- and low-income countries

> The development of vaccines against infections other than HBV and HPV has been very difficult. A more realistic goal for vaccines against hepatitis C virus (HCV), *Helicobacter pylori* (Hp) or human immunodeficiency virus (HIV) may be in the prevention of chronic infection and disease as opposed to inducing complete protection against primary infection

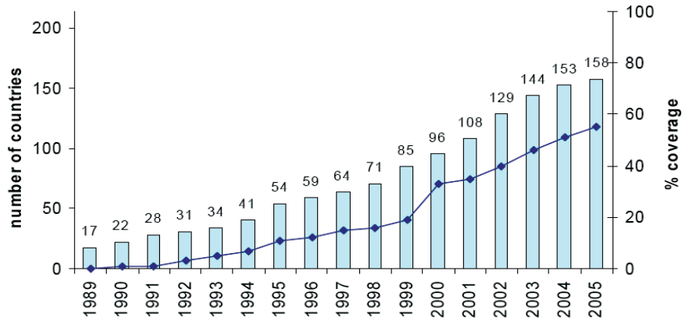

Fig. 4.3.1 *Number of countries that introduced hepatitis B virus (HBV) vaccine in children and global infant HBV vaccine coverage, 1989-2005.*
Source: WHO/UNICEF estimates 1980-2005, as of August 2006 and WHO/IVB database, 2006 192 WHO Member States.

The most important implication of our understanding that a high fraction of cancer may be caused by chronic infections (18% worldwide [1]) is the possibility of preventing the onset of these cancers through vaccination. Mass immunisation, when it has proved feasible, has resulted in some of the greatest medical successes in human history. Vaccination programmes have been implemented even in the poorest countries of the world and in fact can lead to substantial cost-saving, something that is rarely expected of healthcare interventions.

The renewed interest in vaccines that has been seen in the past few years, including those meant to prevent certain cancers, is greatly encouraging. However, there are also some major limitations in vaccine research, development and distribution in different parts of the world, which will be explored briefly in this chapter.

Cancer-causing chronic infectious agents include DNA viruses, RNA viruses, bacteria and parasites. Two vaccines against two DNA viruses, HBV and HPV, have shown efficacy in preventing the corresponding chronic infection, as well as precancerous lesions of the affected sites (liver and cervix). Progress in the design of vaccines against RNA viruses that are associated with increased cancer risk (HIV and HCV) have been hampered by the enormous genetic diversity of these agents. With respect to the bacterium (Hp) strongly associated with gastric cancer, the main obstacles to vaccine development have been insufficient understanding of the role of immunity in Hp infection. The state of the art in developing vaccines against HIV, HCV and Hp will also be briefly reviewed in this chapter.

HBV vaccine

An epidemic of jaundice due to HBV infection was reported for the first time in 1883 and was an adverse effect of a smallpox vaccination campaign in Germany (see [2] for a review). The etiology of what was formerly called "serum hepatitis" was identified in the 1960s and became better understood in the two subsequent decades following the development of laboratory markers of exposure (antibodies against hepatitis C core antigen, anti-HBc) and chronic infection (hepatitis B surface antigen, HBsAg).

HBsAg seroprevalence has marked geographic variation. Countries with high endemicity are defined as those where HBsAg seroprevalence is ≥8%. They include all of sub-Saharan Africa, the Middle East, Southeast Asia, Indonesia, China, Korea, Mongolia and, in the Americas, the northern parts of Brazil and Peru. The other extreme is embodied by low-endemicity countries (where HBsAg seroprevalence is <2%), i.e. Northern Europe, Australia, North America and the majority of South American countries. The degree of HBV endemicity often correlates with the predominant mode of transmission. In highly endemic settings, perinatal and horizontal routes, such as exposure to chronically infected household members, are responsible for most HBV transmission. Healthcare-related transmission is also common. In countries with low HBV endemicity, most new infections occur among young adults and are acquired sexually or through intravenous drug use.

The likelihood that newly infected persons will develop chronic HBV infection depends on their age at the time of infection. More than 90% of infected infants, 25–50% of children infected between 1 and 5 years of age, and 6–10% of older children and adults develop chronic infection. Immunosupressed individuals are also at higher risk of developing chronic infection [3]. Therefore, affected individuals in high-endemicity countries, where infection early in life predominates, have a disproportionally high burden of severe HBV sequelae including hepatocellular carcinoma. It has been estimated that adults who have had chronic HBV infection since childhood have a 5% incidence of hepatocellular carcinoma per decade.

HBV vaccines were first licensed in the United States in 1981. Formerly, they were plasma-derived and composed of purified HBsAg. Nowadays, HBV vaccines are predominantly produced by recombinant DNA technology. The vaccine is administered in a three-dose series and has resulted in high immunogenicity and efficacy, which to date has been monitored using short-term measures (i.e. reduction in acute HBV infection and serial seroprevalence studies in vaccinated populations). Declines in incidence and mortality rates from hepatocellular carcinoma have been reported only in children and adolescents in Taiwan, which established the first HBV immunisation program in 1984 [4].

A better estimate of the decrease in the cancer burden will be possible in approximately a decade in the two large randomised trials of HBV started in 1986 in The Gambia [5] and in 1990 in Qidong, China [6]. Despite decreases in anti-HBsAg titres to relatively low levels, immunocompetent immunised individuals have not developed chronic hepatitis infection in 10–22-year follow up. HBV vaccine injection within 12–24 hours after birth, followed by a 3-dose vaccine series, is effective in preventing vertical transmission, and the safety of the vaccine has been demonstrated in large studies. Concerns were expressed about the possibility of the vaccine having caused some cases of multiple sclerosis, diabetes mellitus and demyelinating diseases, but an expert panel dismissed these for lack of an association [7]. In addition, breakthrough infections by HBV mutant escapes among successfully vaccinated persons have been excluded.

In 1992, the World Health Organization (WHO) recommended the integration of the HBV vaccine into national immunisation campaigns. As shown in Figure 4.3.1, the number of countries that introduced the vaccine and implemented global infant coverage grew steadily from 17 in 1989 to 96 in 2000. By 2005, 158 of the 192 WHO Member States had infant HBV vaccination programs in place, with over half of these countries (62%) reporting ≥80% coverage by their programs (Figure 4.3.2). The 34 countries that have not yet introduced infant HBV vaccination notably include several highly endemic countries in sub-Saharan Africa. Several high-resource countries with low HBV endemicity, including the United Kingdom, Scandinavian countries and Japan, do not routinely vaccinate children, but have instead chosen to target high-risk groups (e.g., immigrants from high-endemicity areas, adolescents, and adults with risk factors for HBV infection).

Priorities for the future are clearly to expand the number of high-endemicity countries that

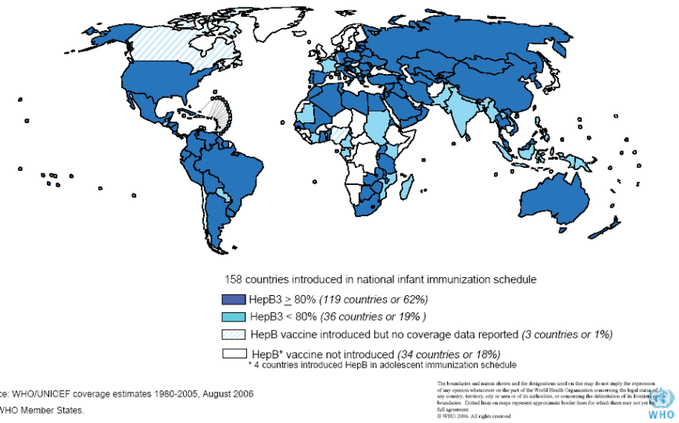

Fig. 4.3.2 *Countries having introduced hepatitis B virus (HBV) vaccine in children and infant HBV Vaccine coverage, 2005*
From WHO slide presentation Progress Toward Global Immunization Goals 2005
Summary presentation of key indicators Last update of set: 10 October 2006

include HBV vaccination in infant immunisation schedules (Figure 4.3.1) and to improve coverage in countries that have already opted to do so (Figure 4.3.2). The drop in the price of the HBV vaccine and the efforts of vaccine-donating organisations should help to make these targets possible. In addition, as policies of selective immunisation of high-risk individuals are seldom effective, routine HBV vaccination is now also advocated in low-endemicity countries on the grounds that whenever a potentially devastating disease like hepatocellular carcinoma is easily preventable, steps should be taken to achieve this outcome.

	Per protocol	By intention to treat	
	HPV-negative	Against HPV 16/18 % (CI)	Against any HPV type % (CI)
CIN2/3 or AIS	99 (93–100)	44 (31–55)	18 (7–29)
By lesion:			
CIN2	100 (93–100)	50 (34–62)	21 (7–33)
CIN3	98 (89–100)	39 (21–53)	17 (-0.1–31)
AIS	100 (31–100)	54 (-30–86)	57 (-19–87)

Table 4.3.1 *Efficacy of quadrivalent vaccine against human papillomavirus (HPV) 16/18*
Adapted from [9]. Confidence interval (CI); cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS)

	Vaccine / Control	Efficacy % (CI)
HPV16/18		
CIN2 or more severe	2 / 21	90 (53–99)
CIN1 or more severe	3 / 28	89 (59–99)
Persistent infections (12 months)		
HPV16/18	11 / 46	76 (48–90)
Other high-risk types	100 / 137	27 (0.5–47)
All high-risk types	112 / 180	38 (18–54)

Table 4.3.2 *Endpoints and efficacy of bivalent vaccine against human papillomavirus (HPV) 16/18 (15,626 women, 15 months follow-up)*
Adapted from [10]. Confidence interval (CI), cervical intraepithelial neoplasia (CIN)

HPV vaccine

HPVs are DNA viruses that infect epithelial (skin or mucosal) cells. There are more than 100 known mucosal HPV types, and at least 13 of them, called high-risk types, can cause cancer of the cervix [8]. HPV16 and 18 are found in over 70% of cervical cancer worldwide and also predominate in cancer sites other than the cervix (i.e. anus, vulva, vagina, penis, and a small fraction of cancers of the head and neck). The discovery that cervical cancer was associated with sexual contact paved the way to an understanding of the role of HPV infection, which is predominantly sexually transmitted [8].

The two currently available HPV vaccines [9,10] include HPV16 and 18 and are based on L1 virus-like particles (VLPs), i.e. empty viral capsids. They were therefore expected, as has been subsequently confirmed, to be very safe, as they include neither viral oncogenes nor live or attenuated viruses. They have been licensed since 2007 for use in women aged 9–26 years in the United States, European Union and in a number of other countries. In clinical trials that included approximately 40 000 women, both vaccines were at least 90% effective in preventing persistent HPV infection and 95% effective in preventing type-specific precancerous lesions (i.e. cervical intraepithelial neoplasias (CIN) grade 2 and 3 and in situ adenocarcinoma of the cervix). One of the two vaccines also includes low-risk HPV types 6 and 11, and is therefore able to prevent genital warts, in addition to cervical HPV infections.

Available vaccines did not, however, prevent development of CIN2 and 3 in women who had been infected by HPV16 and 18 before immunisation, or CIN2 and 3 caused by other HPV types in clinical trials. [9]. Therefore, in the analyses by intention to treat, the efficacy diminished from 99% to 18% (95% confidence interval: 7–29%) when all CIN2 and 3 lesions were considered (Table 4.3.1). This efficacy profile obliges us to: 1) concentrate on the vaccination of girls before they become sexually active; 2) try to increase the number of high-risk HPV types present in the vaccine; and 3) make every possible effort to match immunisation with high-quality organised screening programs [11]. Although data on all high-risk types present in CIN2 and 3 have not yet become available, some cross-protection against persistent infection from high-risk types other than HPV16 and 18 has been reported (Table 4.3.2) [10].

However, successful prevention of cervical cancer through immunisation presents enormous challenges. The greatest of these are the lack of information on the duration of vaccine efficacy, which at this point has been evaluated for no more than five years, and by the vaccine price that is unaffordable in many medium- and low-income countries. In addition, reaching girls before puberty or in their early teens may be more difficult than delivering vaccines to newborn and infants, especially in low-resource countries. Cultural barriers and misinformation may also burden HPV vaccine acceptance.

For the moment, no plan exists to expand the use of HPV vaccine to boys, as 1) efficacy of the vaccine in the prevention of HPV infection in men is not yet proven, and 2) if good coverage is achieved, a sexually transmitted infection like HPV should be greatly reduced even by vaccinating one gender only.

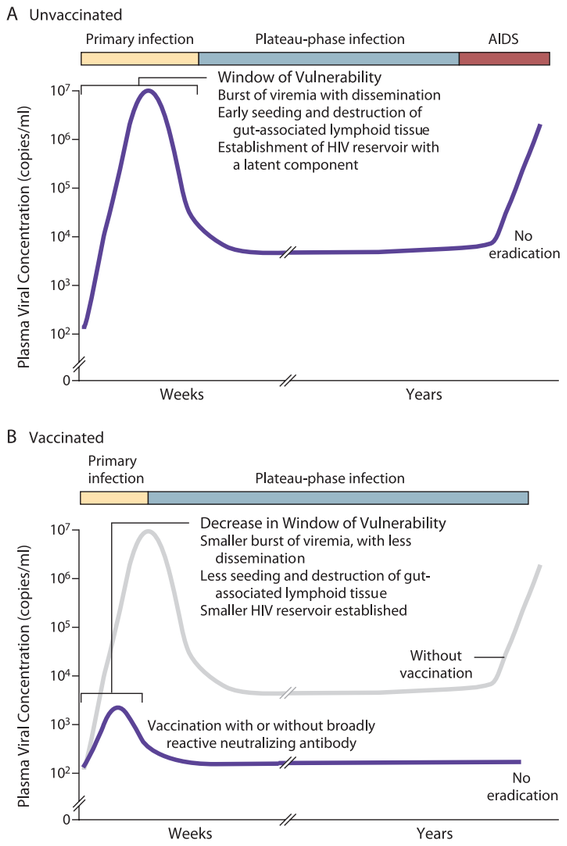

Fig. 4.3.3 Course of human immunodeficiency virus infection in unvaccinated persons and the hypothetical course of infection in vaccinated persons

Panel A shows the course of infection in unvaccinated persons. The primary stage of HIV infection (yellow) starts with a burst of viremia, dissemination of the virus, early seeding and destruction of gut-associated lymphoid tissue, and establishment of a viral reservoir with a latent component (window of vulnerability). HIV levels in plasma then decline to a set point that lasts from months to years. Eventually, in the absence of effective therapy, the virus escapes immune control and AIDS results (red). Panel B shows the hypothetical course of infection in vaccinated persons. A T-cell vaccine might decrease the burst of viremia and dissemination that occurs in primary infection (yellow), preserving gut-associated lymphoid tissue, diminishing the viral reservoir, decreasing virus levels at the set point, and increasing the length of time that viral levels are controlled (blue). From Johnston and Fauci, 2007

Vaccines against other cancer-causing chronic infections

Research into new prophylactic and therapeutic vaccines is also ongoing for at least three additional infections that are responsible for a large portion of the cancer burden worldwide: HCV, HIV and Hp. Although the first two agents are RNA viruses and the third is a bacterium, they all have in common some characteristics that have greatly undermined past efforts to produce efficacious vaccines: 1) they display high genetic and antigenic diversity and mutate very rapidly in the host; 2) they induce, after natural infection, strong humoral and cellular responses that seem, however, unable to eliminate the infection or prevent reinfection; and 3) no small animal model or cell culture systems were available until recently to help vaccine developments.

Several candidate vaccines (e.g. virus-like particle vaccines) against HCV, an increasingly important cause of liver cancer, were tested in chimpanzees [12], and induced a strong cellular-immune response. Vaccination did not prevent the chimpanzees from becoming infected, but the course of the infection was apparently attenuated.

Hp, a Gram-negative flagellate bacterium that is present in the stomach of more than half of the global population, is the leading cause of chronic gastritis, peptic ulcer disease and gastric adenocarcinoma and lymphoma (see

[13] for a review). A few vaccination studies involving between 6 and 42 infected or uninfected humans and based on various Hp formulations such as recombinant urease, killed whole cells, or live Salmonella vector presenting the subunit antigens, have not provided satisfactory results. One trial that used recombinant Hp urease coadministered with native Escherichia coli enterotoxin demonstrated a reduction of Hp load in infected participants [14].

HIV is not a carcinogenic virus *per se*, but it greatly increases the risk of many types of cancer (Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and cancer of the cervix and anogenital tract) via immunosuppression [3,15]. On account of the magnitude and severity of the HIV epidemic, enormous investment has gone into the design of HIV vaccines, but development of a vaccine has thus far proven unsuccessful (see [16] for a review).

A unique feature of HIV is that a pool of latently infected lymphocytes (resting CD4+ T cells) is

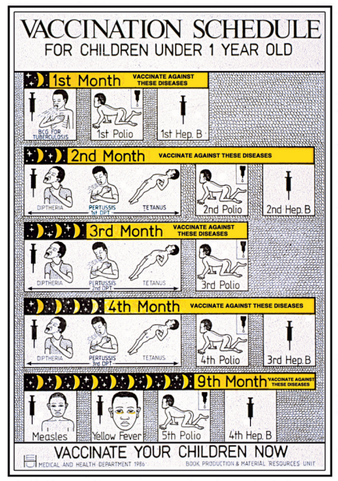

Fig. 4.3.4 *Public health poster publicizing vaccination against HBV for children under one year old in the Gambia*

Product profile of prophylactic HPV vaccine	
Cervarix, GSK	**Gardasil, Merck**
16/18 High Risk HPV types	16/18 high risk plus 6/11 low risk HPV types.
Pure Cervical Cancer Vaccine	Cervical cancer&genital warts
Women only (10-55 yrs)	Women and Men (9-45 yrs).
3 i.m. injections, 20 microg VLP	3 i.m. injections, 40 microg for HPV 11/16
Innovative AS04 adjuvant (MPL+Aluminium)	Conventional aluminium

Fig. 4.3.5 *Prophylactic HPV vaccines*

8 most common HPV types in 14,097 cases of invasive cervical cancer by region (Smith et al, 2007)

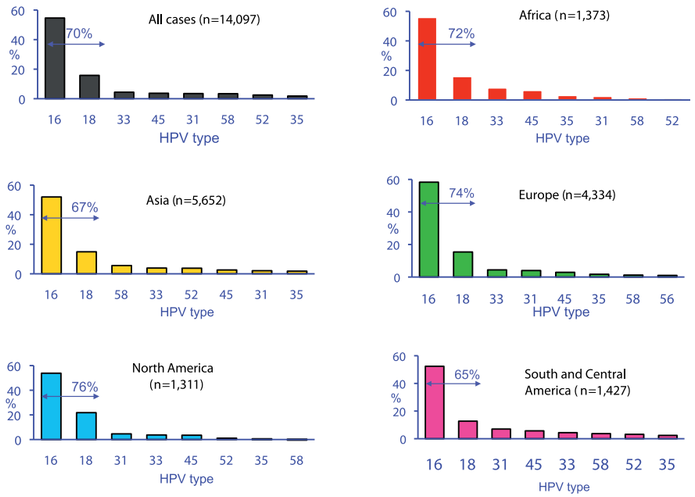

Fig. 4.3.6 *Most common types of HPV in different regions of the world*

established very early during primary infection (Figure 4.3.3). Thus, the window of opportunity for a prophylactic vaccine to clear HIV and prevent chronic infection is very small. On a positive note, HIV has some highly conserved epitopes. Initially, vaccine developers focused on recombinant forms of the viral envelope, which is the target of the virus, but later their attention moved to vaccines able to enhance T-cell immunity. However, T-cell mediated control of infection may not prove to be complete. Deciding whether the level and durability of moderated protection observed in clinical trials are sufficient to seek or grant vaccine licensing will challenge vaccine developers and regulators alike. At the moment, at least a dozen trials of candidate vaccines against HIV are under way, including a few phase II and III trials [16].

In conclusion, the development of a vaccine against infections other than HBV and HPV has been very difficult. A more realistic goal for vaccines against HCV, Hp or HIV may be preventing chronic infection and disease as opposed to inducing complete protection against primary infection. Disease-modifying vaccines represent unchartered territory, as vaccines would not be a stand-alone preventive measure, as are most classic preventive vaccines. Instead, they would need to be delivered in the context of global preventive strategies, as will be the case for HPV vaccines and cervical cancer screening [17].

Finally, it is worth bearing in mind that the private pharmaceutical sector has less incentive to invest in research and development of vaccines against cancer than anti-cancer medications [18]. The development of new cancer-preventive vaccines, as well as their accessibility to low-resource countries, is therefore crucially dependent upon the support of public and private donors such as the Bill & Melinda Gates Foundation, and those included in the Global Alliance for Vaccines and Immunization. Combined public and private research expenditures will therefore be necessary to develop important new vaccines.

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4.4 Cancer Chemoprevention

Summary

> In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer

> There is evidence that use of some anti-oxidant supplements may increase mortality

> Folic acid supplements are suspected to increase the risk of colorectal cancer

> In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing breast cancer

> Randomised trials using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence on cancer risk, although these ordinary doses seem to reduce mortality

Chemoprevention is the reduction of cancer risk through the use of pharmaceuticals or other agents such as micronutrients. Chemoprevention is an appealing low-cost and easy cancer control method, mainly for subject having an inherited predisposition to certain cancers.

Laboratory data and observational studies have suggested that higher intake of some micronutrients was associated with reduced cancer risk. Micronutrients are defined as nutrients present in the body in amounts less than 0.005% of body weight. Micronutrients usually encompass the vitamins, minerals and trace elements (e.g. selenium, zinc). Research on vitamins and cancer in humans has focused mainly on carotenoids, retinoids, vitamin A (retinol) and retinoid, vitamin E (which includes alpha-tocopherol), vitamin C and some of the group of B vitamins (folic acid). The biological basis of the interest in these vitamins is their involvement in two metabolic mechanisms commonly called an antioxidant effect through free-radical scavenger properties (carotenoids, vitamin A, C and E, retinoids) and methyl donation (folic acid).

Laboratory data and observational studies have also suggested that several commonly used pharmaceuticals could have anti-cancer activity, and could be candidates for chemoprevention of cancer of the digestive tract, such as the anti-inflammatory drugs.

Chemopreventive agents are to be considered as pharmacological compounds, that is, substances that will interact with several biological receptors which may reduce cancer risk, and also, cause other effects due to impact on other physiological activities. This notion also applies to apparently "natural" substances that can be found in usual foodstuffs, as chemoprevention will generally use doses (much) higher than those in typical dietary intakes. Also, a putative chemoprevention compound may be selected, while the average diet represents a composite mixture of hundreds of compounds. Therefore, a number of randomised trials have been mounted to verify the reality of anti-cancer activity suggested by basic research and observational studies.

Many trials tested composite intervention, mixing vitamins and trace elements, which renders it difficult, if not impossible, to disentangle the effects of individual compounds. In the remainder of the text, we have selected results from trials that provide information on effects specific to each supplement.

Anti-Oxidants

Beta-carotene

Observational epidemiological studies have consistently shown that beta-carotene is associated with decreased cancer risk, particularly of lung cancer. In contrast, randomised trials testing the effect of beta-carotene supplementation on cancer incidence and mortality generally have not been supportive [1-3]. Randomised trials did not show a change in prostate cancer risk with beta-carotene supplementation [1,4,5].

Two of these trials, the ATBC [6] and the CARET [5], yielded results suggesting the possibility of serious harmful effects of beta-carotene used as a supplement: total mortality was significantly increased in intervention groups mainly because beta-carotene given to smokers or past asbestos workers increased lung cancer incidence by 18% and 28% respectively. A meta-analysis of randomised trials concluded that beta-carotene supplementation significantly increased by 24% the risk of lung cancer among current smokers [7].

Randomised trials that tested beta-carotene for prevention of basal and squamous-cell carcinoma of the skin were negative [8,9].

Vitamin A and retinoids

Compounds related to vitamin A comprise preformed vitamin A compounds, essentially retinol and retinyl esters. These compounds were initially shown to modulate differentiation in many experimental systems [10,11]. No significant effects on mortality rates were observed for supplementation with combination of retinol and zinc [12], beta-carotene and vitamin A [5]. One large randomised trial of a vitamin A analogue, fenretinide, showed no impact on occurrence of secondary breast cancer in breast cancer survivors [13]. Vitamin A and retinols may antagonise the physiological action of Vitamin D, mainly on bone. Two studies have reported doubling of hip fracture rates among women with high retinol intakes from food or supplements (>1.5 mg per day) [14,15].

In 1998, a systematic review by a IARC Expert Group concluded that there was evidence suggesting lack of anti-cancer activity of preformed vitamin A compounds, and thus also of vitamin A (Table 4.4.1) [10].

Agent	Humans	Animals
Non-steroidal anti-inflammatory drugs		
Aspirin	Limited	Sufficient
Sulindac	Limited	Sufficient
Piroxicam	Inadequate	Sufficient
Indomethacin	Inadequate	Sufficient
Carotenoids		
beta-Carotene (high dose supplements)	Lack of activity	Sufficient
beta-Carotene (usual dietary levels)	Inadequate	Sufficient
Canthaxanthin	Inadequate	Sufficient
alpha-Carotene	Inadequate	Limited
Lycopene	Inadequate	Limited
Lutein	Inadequate	Limited
Fucoxanthin	Inadequate	Limited
Retinoids		
all-trans-Retinoic acid	Inadequate	Inadequate
13-cis-Retinoic acid	Limited	Limited
9-cis-Retinoic acid	Inadequate	Limited
Fenretinide (4-HPR)	Inadequate	Sufficient
Etretinate	Inadequate	Limited
Acitretin	Inadequate	Inadequate
N-Ethylretinamide	Inadequate	Lack of activity
Targretin	Inadequate	Inadequate
LGD 1550	Inadequate	Inadequate
Preformed vitamin A	Lack of activity	Limited

Table 4.4.1 *Evidence of cancer preventive activity: evaluations from the IARC Handbooks of Cancer Prevention series*

Retinoids are a class of compounds structurally related to vitamin A. In 1999, a systematic review by an IARC Expert Group concluded that there was inadequate or limited evidence for anti-cancer activity of nine different retinoid acid compounds, and some of them are teratogenic in humans or in animals (Table 4.4.1) [11].

Vitamin C

Vitamin C is deemed to be a free-radical scavenger, and high intakes of foodstuffs rich in vitamin C (e.g. citrus fruits) could play a role in decreasing gastric cancer incidence. Double-blind randomised trials of supplementation with ascorbic acid (1g twice per day) combined with other anti-oxidants (usually vitamin E, selenium, beta-carotene) of populations at high risk for gastric cancer in China and Venezuela did not result in higher rates of regression of dysplastic lesions in the stomach [16,17].

Vitamin E

Vitamin E exists in eight different isomers, and alpha-tocopherol is the most biologically active. Vitamin E has anti-oxidant properties that were deemed to play a role in control of cellular oxidative damage.

In the ATBC study [6], the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However, deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women's Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk [18].

A meta-analysis of vitamin E supplementation including 16 randomised trials suggests that high doses of vitamin E supplementation

above 200 IU per day may increase all-cause mortality [19].

Selenium

Selenium is involved in defence mechanisms against oxidative stress through the selenoproteins. Selenium at high doses is known to be toxic. Selenium supplementation with doses around 200µg per day was thought to prevent non-melanoma skin cancer, and colorectal and prostate cancer. Selenium has been part of several trials, but often mixed with vitamins, making it difficult to isolate an effect specific to this compound.

The Nutritional Prevention of Cancer (NPC) Trial [20] was a placebo-controlled randomized trial to test whether selenium supplements could reduce the incidence of non-melanoma skin cancer. The incidence of non-melanoma skin cancer remained the same in the intervention and in the placebo groups. However the group that received the supplement had statistically significant reductions of approximately 40% and 50% in overall cancer incidence and cancer mortality, respectively. Main reductions in incidence were observed for prostate, colorectal and lung cancer. Separate follow-up of lung cancer and prostate cancer showed a reduction of the incidence of these two cancers in subjects who had low serum selenium levels at baseline, and not in subjects with higher levels at baseline [21,22]. A re-analysis of trial data showed that all the protective effect was confined to males, and that selenium supplements decreased cancer risk in subjects with low serum selenium levels at baseline, whereas these supplements seemed to increase cancer risk in subjects with high selenium levels at baseline [21].

A randomised trial organised within the NPC Trial failed to show reduction of colonic polyps with selenium supplementation [23], but again a significant decrease was noticeable among subjects with low serum selenium levels at baseline, while in subjects with high serum selenium level at baseline, the frequency of polyps was greater, although statistically non significant.

Recent results of the Third National Health and Nutrition Examination Survey (NHANES III) cohort study in the USA call for caution with use of this compound, as the study suggests a U-shaped curve in associated risk with serum selenium levels and all-cause and cancer mortality, with higher mortality in subjects with low or with high serum levels of selenium, and lower mortality around optimal serum levels [24].

Hence, supplementation with selenium has little influence on cancer risk, and instead can be detrimental for subjects who have high levels of serum selenium.

Micronutrients in subjects with poor nutritional conditions

One large trial tested a combination of beta-carotene, vitamin E, selenium and trace elements (e.g. zinc) in a poorly nourished Chinese population [12]. After 5 years, the treated group experienced a statistically significant 9% reduction in total mortality, primarily as a result of a statistically significant 21% lower stomach cancer mortality rate. There was no significant reduction in oesophageal cancer, the primary endpoint of the study. Indirect evidence that beta-carotene may protect from stomach cancer in high-risk subjects comes from the randomised, controlled double-blinded chemoprevention trial in subjects with gastric dysplasia in the area with a very high gastric cancer incidence in Colombia. Gastric biopsies taken at baseline were compared with those taken after 72 months; daily use of 30mg beta-carotene (combined with vitamin C) resulted in a statistically significant increase in the frequency of rate of regression of preneoplastic lesions of the stomach [25].

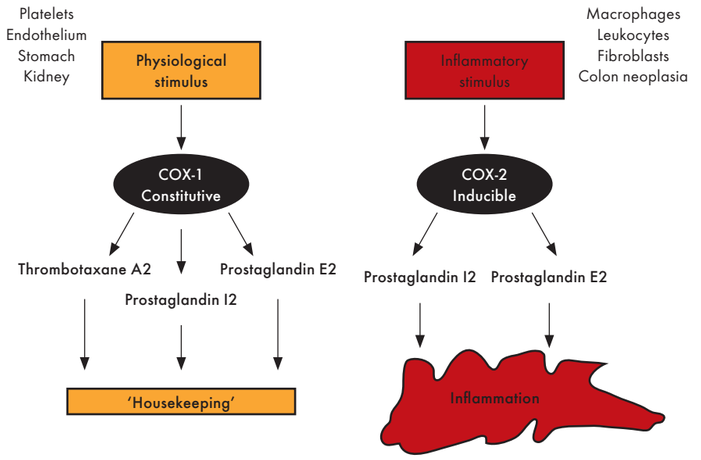

Fig. 4.4.1 *COX-1 and COX-2 cyclooxygenases: COX-1 is constitutively expressed and regulates the homeostasis of various tissues, including the generation of cytoprotective prostaglandins. Inflammatory stimuli induce COX-2, which is also highly expressed in colorectal neoplasia in the absence of stimulation*

Multivitamin preparations

A systematic review conducted under the auspices of the US National Institute for Health found no evidence that multivitamin preparations could reduce cancer risk (or the risk of other chronic diseases) [26].

Meta-analyses

A meta-analysis of randomised trials on supplementation with anti-oxidant supplements (alone or in combination) in well-nourished populations found no impact on gastro-intestinal cancer risk, but found a significantly increased risk for all-cause mortality of 6% associated with the taking of these supplements, mainly for beta-carotene (7% increase), vitamin A (16% increase), and vitamin E (4% increase) [27].

Methyl donation: Folic acid

Folic acid plays an important role in DNA repair, synthesis and methylation reactions. Two randomised placebo-controlled trials indicate that folic acid supplements may in reality increase the risk of colorectal and prostate cancer, and of adenomatous polyps [28,29].

Other micronutrients

Lycopene (from tomato), flavonoids and green tea are some examples of compounds for which anti-cancer activity is suggested by observational studies. No recommendation about the value of these substances in cancer prevention can be issued before publication of randomised trials testing their efficacy.

Vitamin D

Vitamin D is to be considered more as a hormone than as a vitamin. Furthermore, Vitamin D is not strictly speaking a vitamin, as its synthesis takes place in skin exposed to ultraviolet B radiation. Ecological studies have suggested that cancer burden increased with increasing latitude. Increasing latitude has been equated with a decrease in vitamin D status because of supposedly less sun exposure and thus less endogenous synthesis of vitamin D in the skin. Cohort studies that examined the association between serum 25-hydroxyvitamin D and cancer found weak or no association with breast and prostate cancer [30], while an inverse relationships with pancreas cancer was reported in Finish smokers [31,32]. A possible role of vitamin D in colorectal cancer is suggested by cohort studies [30]. But two randomised trials found no impact at all of ordinary doses of vitamin D supplements [33, 34] on colorectal and all-cancer risk. The trial by Trivedi et al [33] had as its primary objective the reduction of fracture risk and used 830 IU vitamin D alone per day; the WHI trial [34] used 400 IU vitamin D per day and 1g of elementary calcium.

A small 3-arm randomised trial found decreased cancer occurrence in subjects receiving vitamin D (1000 IU per day) and calcium [35]. The methodology and statistical analysis of this trial have been much criticised. For instance, subjects that received calcium supplements alone had a decrease in cancer risk of similar magnitude than subjects receiving calcium and vitamin D supplements, and thus a correct intent-to-treat analysis would have shown no significant decrease in cancer risk [36]. Also, artefacts in the placebo group severely undermined the trial's findings [37].

A meta-analysis of randomised trials on intake of vitamin D and calcium supplements found that 500–600 IU per day of vitamin D (i.e., doses similar to those tested in the WHI and in the trial by Trivedi et al. [33]) decreased all-cause mortality [38]. This result is in sharp contrast with trials on anti-oxidants showing increasing all-cause mortality. The biological mechanisms underlying the gain in life expectancy remains obscure but is probably not mediated by a reduction in cancer risk.

The question remains whether higher doses of vitamin D supplements would have more beneficial effects than ordinary doses, on cancer risk, on the risk of other non-cancerous diseases, and on mortality. The associations between high intakes or high baseline serum levels of several compounds and higher disease or mortality rate is a call for caution. It could well be that ordinary doses of vitamin D supplements may have beneficial impact on health status, as reflected by the lower all-cause mortality found by the aforementioned meta-analysis by Autier & Gandini [38]. But no data exist on the health effects of intakes of high doses of vitamin D (≥1500 IU per day) over the long term (i.e. >1 year). Therefore, before any recommendation can be made on supplementation with high doses of vitamin D, such a schedule should first be tested by large-scale double-blind placebo-controlled randomised study [32].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Numerous observational epidemiological studies have found that long-term users of aspirin or other NSAIDs have a lower risk of colorectal adenomatous polyps and colorectal cancer than nonusers [39, 40], and biological mechanisms stem from anti-cancerous properties of NSAID, in the digestive tract and also in other organs [41]. The cyclooxygenase pathway is a major target for prevention by non-steroidal anti-inflammatory drugs, primarily because the cyclooxygenase-2 (COX-2) plays a role in inflammation, apoptosis and angiogenesis, and an early potential indication of COX-2 inhibitors was the prevention of colorectal cancer.

In 1997, a systematic review by an IARC Expert Group largely based on observational studies concluded that there was limited or inadequate evidence for cancer prevention properties of aspirin, sulindac, piroxicam and indomethacin [39].

Randomised clinical trials have shown that in patients with familial adenomatous polyposis (FAP), the prodrug sulindac and the selective

Fig. 4.4.2 *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*

cyclooxygenese (COX)-2 inhibitor celecoxib effectively inhibit the growth of familial adenomatous polyps and cause regression of existing polyps [44, 45]. However, randomised trials in patients with sporadic adenomatous polyps reduced the possibility of using this class of drug for cancer prevention because of significant cardiovascular toxicity despite effectiveness in preventing sporadic polyps [43,44]. Administration of sulindac did not result in regression of adenomas [46] or high doses required to achieve the effect may cause toxicity, which outweigh benefits of treatment [47].

Results of a large-scale, placebo-controlled long-term trial organised within the Women's Health Initiative suggested that alternate day use of low-dose aspirin (100mg) for an average 10 years of treatment did not lower risk of total, breast, colorectal or other site-specific cancers [48].

Estrogen receptor modulators

Since 1990, tamoxifen has become widely used for breast cancer treatment. Tamoxifen use has been rapidly known to increase thromboembolic events and cancer of the corpus uteri. In spite of these side effects, and tamoxifen being classified as an IARC Group I carcinogenic agent [49], it has been tested for preventing contralateral breast cancer in women with a first breast cancer. Trials started in women without a uterus, and there is conclusive evidence that tamoxifen reduces the risk for contralateral breast cancer by 38% in women with a previous diagnosis of breast cancer [50]. There was no effect for breast cancers negative for oestrogen receptors (ER-negative), but ER-positive cancers were decreased by 48% (95% CI 36-58%). Rates of endometrial cancer were increased in all tamoxifen prevention trials.

Raloxifene is a non-steroidal selective estrogen receptor modulator (SERM). One trial (the MORE trial) on treatment of osteoporosis found a reduction 72% in the incidence of breast cancer among raloxifen users [51]. A further trial (the RUTH trial) with breast cancer as a primary endpoint found a 44% decrease in breast cancer incidence among raloxifene users, but also a 49% increase of fatal stroke and 44% increase of venous thromembolism [52]. The preventive effect of raloxifene was confined to ER-positive breast tumours.

In order to better evaluate the respective properties of tamoxifen and raloxifene, a randomised trial was mounted in the USA by the National Surgical Adjuvant Breast and Bowel Project [53]. This trial showed that raloxifene and tamoxifen had a similar ability to reduce breast cancer incidence. Raloxifene induced fewer thromboembolitic events, but seemed to increase the incidence of in situ breast cancer. Death rates among women taking tamoxifen or raloxifene were similar.

Omega-3 fatty acids

Omega-3 fatty acids are mainly found in oily fish, and were deemed to protect against oxidative reactions involved in cancer and cardiovascular diseases. Systematic reviews of prospective cohort studies and of randomised trials found no evidence for a protective effect of these fatty acids on either cancer (including colorectal and breast cancer) or cardiovascular diseases [54, 55].

Dietary fibre (see also chapter on diet and cancer)

A systematic review of 13 prospective cohort studies found no effect of dietary fibre intakes on colorectal cancer incidence [56].

In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas [57-61]. The randomised trial by Bonithon-Kopp et al. [58] found that subject assigned in the intervention arm (ispaghula husk 3.5g per day) had in fact a significant increased risk of adenoma recurrence.

Calcium

One double-blind, placebo-controlled randomised trial [62] found that calcium supplementation (1.2 g elementary calcium per day) reduced by 15% the risk of recurrence of adenomatous polyps of the large bowel. The effect of calcium was independent of initial dietary fat and calcium intake. The same trial also found that calcium supplement seemed more likely to decrease the risk for more advanced polyps, suggesting that such supplements could decrease the incidence of colorectal cancer [63].

Another double-blind, placebo controlled randomised trial concluded that a moderate reduction of adenomatous colonic polyps with calcium supplements 1.2 g elementary calcium per day was only seen in subjects with above average serum 25-hydoxyvitamin D levels [64]. The randomised trial of Bonithon-Kopp et al [58] found a decrease of colorectal polyp recurrence in subjects assigned to calcium 2g per day, but the difference with the placebo group was statistically non-significant.

Calcium supplements (1g elementary calcium per day) were associated with a 17% increase in kidney stone formation in the WHI trial [34].

Conclusions

Most of these trials testing chemopreventive properties of many compounds found to possibly have anti-cancer properties in observational studies turned out to be negative or to show serious adverse events. Therefore no recommendation for use of a compound (even "natural substances" found in the diet) for cancer chemoprevention should be made before a large randomised trial (preferably double-blind and placebo-controlled) has evaluated both the efficacy as well as adverse effects of ingestion of the compound.

In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer, and there is evidence that use of antioxidant supplements may increase mortality (beta-carotene, vitamin E), or increase mortality in subject with high baseline serum levels of the compound (selenium), or may increase the risk of fracture (Vitamin A). Folic acid supplements are suspected to increase the risk of colorectal cancer. In communities with sub-optimal nutritional status, supplements with anti-oxidants may reduce mortality and stomach cancer risk.

In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing a second breast cancer (e.g. contralateral other breast). In subjects with familial adenomatous polyposis, the non steroidal anti-inflammatory drug sulindac may eventually be considered for prevention of adenoma recurrence although gastrointestinal and cardiovascular toxicity may be limiting. In the future, low-dose combinations of effective agents may serve to mitigate toxicity.

Randomised trials conducted so far using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence of vitamin D supplements on colorectal cancer risk. However, these ordinary doses seem to reduce all-cause mortality. The effects of intakes of high doses of vitamin D (≥1500 IU per day) over the long term are unknown, and such schedule should be first tested by a placebo-controlled randomised study [32].

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4.5 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, particularly in countries that have implemented population-based screening programmes. In countries with lower participation compliance and a less developed healthcare system, screening has been much less effective in reducing mortality

> In developing countries, the cost of infrastructure and initial investments for organised cytological screening may be prohibitive. Alternative methods such as visual inspection with acetic acid (VIA) or with Lugol's iodine solution (VILI) are effective in preventing cervical cancer in low-resource countries

> HPV testing is an alternative but currently expensive method for screening and preventing cervical cancer. There is a need to develop simple, affordable and accurate methods of HPV testing with comprehensive guidelines for its use in screening programmes

> Screening should be implemented in the context of an organised programme following comprehensive quality assurance guidelines, with adequate attention paid to planning and training, resources for management of detected lesions, and coordination, monitoring and evaluation of performance and effectiveness

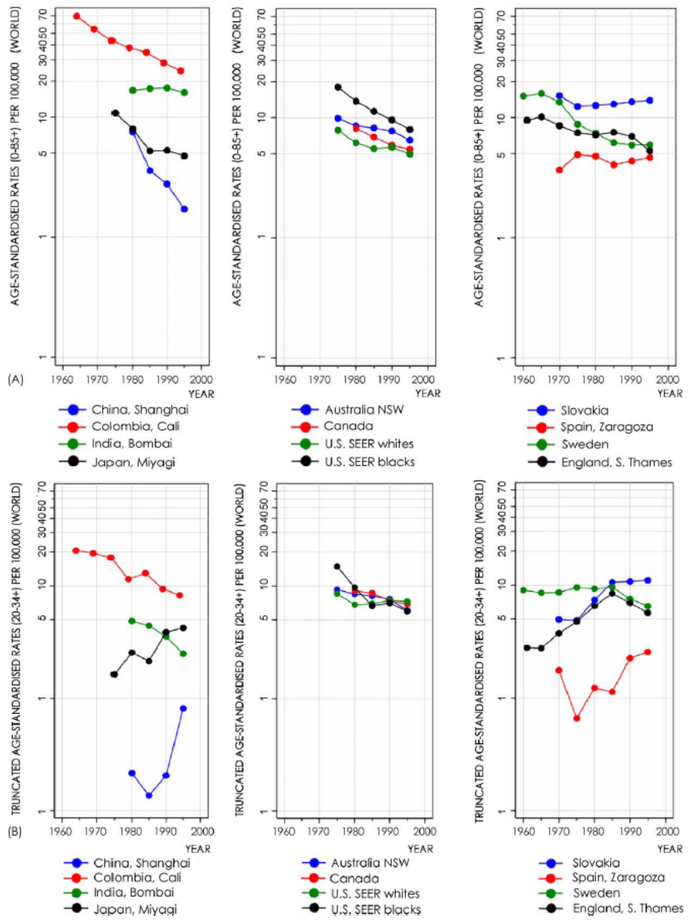

Fig. 4.5.1 *(A) Time trends in age-standardised (World) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive Volumes of Cancer Incidence in Five Continents [Parkin DM, Whelan S, Ferlay J, Storm H. Cancer Incidence in Five Continents, vol. I–VIII. Lyon: IARC CancerBase No. 7; 2005.]. (B) Time trends in age-truncated (World, ages 20–34) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive volumes of Cancer Incidence in Five Continents [Parkin DM, Whelan S, Ferlay J, Storm H. Cancer incidence in five continents, vol. I–VIII. Lyon: IARC CancerBase No. 7; 2005.]*
(Parkin et al. (2006): [28])

Invasive cervical cancer is preceded for several years by asymptomatic and slowly progressing precancerous lesions such as high-grade cervical intraepithelial lesions (CIN grade 2 and 3) or adenocarcinoma ***in situ***. The early detection of CIN by screening and their effective treatment leads to prevention of invasive cervical cancer. Following the introduction of cervical screening programmes in many developed countries a decline in incidence of and mortality from cervical cancer has been observed in the past 5 decades (Figure 4.5.1).

Persistent infection with one or more of the oncogenic types of human papillomaviruses (HPV) is the cause for cervical neoplasia [1], and cervical cancer is a rare long-term outcome of a common viral infection of the cervical epithelium. This knowledge has opened up new avenues of prevention such as HPV vaccination and HPV testing for cervical screening. While HPV vaccination is an exciting and emerging preventive option in the long run, currently screening remains the principal strategy to prevent cervical cancer globally. CIN 2–3 lesions represent a "preclinical" stage of cervical squamous-cell carcinoma that has high prevalence and is detectable in the course of population-based screening. On the other hand, screening is often not effective in detecting the pre-invasive glandular lesions of the cervical canal; thus screening has limited impact in preventing adenocarcinoma of the cervix.

Conventional cervical cytology (Pap smear, Figure 4.5.2), the most commonly and widely used cervical screening test, has been largely responsible for the early detection of cervical precancerous lesions and subsequent decline of invasive cervical cancer incidence and mortality in many developed regions of the world where successful screening programmes have been introduced. However, certain limitations of the Pap smear, in terms of the subjective nature of the test, resources required and low sensitivity in most routine settings, have led to the development and evaluation of alternative screening tests such as liquid based cytology, HPV testing and visual screening tests.

The efficacy of Pap smear screening

Cytology screening involves collection of cervical cells from the cervical epithelium using a wooden spatula or a brush, preparation and fixation of the smear by a doctor or a nurse followed by staining and reading and reporting of the results by a cytotechnician and a cytopathologist. Cytology requires a laboratory infrastructure, with internal and external quality control measures to process slides and microscopy, and a system to communicate the results to the women. High-quality training, continuing education and proficiency testing of personnel are essential to ensure reliable and efficient testing. Population-based Pap smear screening programmes were initiated in British Columbia in 1949 and in regions of Norway in 1959 and Scotland in 1960. Since then, programmes have been introduced in many developed countries. These programmes vary in their organisation, differing in the balance between public and private health care, whether the programme is systematic and population-based or opportunistic (based upon self-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.

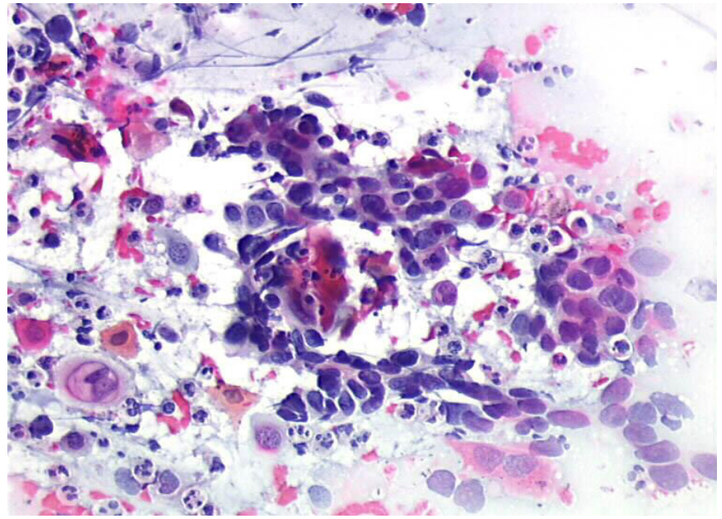

Fig. 4.5.2 *Pap smear suggestive of invasive squamous-cell carcinoma*

In most routine settings, Pap smear has a wide range in sensitivity in detecting cervical neoplasia. The sensitivity to detect CIN 2 and 3 lesions ranged from 47–62% and the specificity from 60–95% in reviews of several studies [2,3]. The sensitivity of Pap smear ranged from 31–78% and the specificity from 91–96% in studies in developing countries [4].

Large-scale population-based cytology screening programmes have resulted in a marked reduction in the incidence of and mortality from cervical cancer in the past five decades in the developed countries of Europe, North America, Japan, Australia and New Zealand [4]. Organised screening with systematic call, recall, follow-up and surveillance systems have shown the greatest effect (e.g. Finland, Iceland), while using fewer resources than the less organized programmes (e.g. USA, France). In the UK,

	Control group	Intervention group (VIA)
Eligible individuals	30,958	49,311
Cervical cancer incidence		
Cancer cases	158	167
	Hazard ratio (95% CI)	
Overall	1.00	0.75 (0.59 -0.95)
30-39 years	1.00	0.62 (0.40-0.96)
40-49 years	1.00	0.82 (0.55-1.24)
50-59 years	1.00	0.76 (0.50-1.16)
Cervical cancer mortality		
Cancer deaths	92	83
	Hazard ratio (95% CI)	
Overall	1.00	0.65 (0.47-0.89)
30-39 years	1.00	0.34 (0.18-0.66)
40-49 years	1.00	0.55 (0.31-1.00)
50-59 years	1.00	0.99 (0.58-1.66)

Table 4.5.1 *Cervical cancer incidence and mortality in the cluster randomized controlled trial in Tamil Nadu, India. R. Sankaranarayanan et al. (2007) [24]*

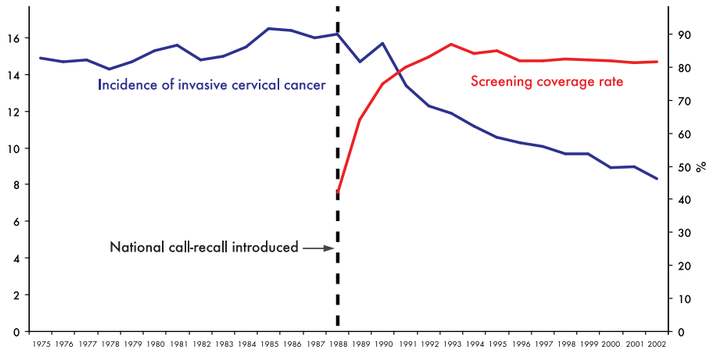

Fig. 4.5.3 *Age-standardised incidence of invasive cervical cancer and screening coverage rate England, 1975-2002. M. Quinn et al. (1999) [29], B.J. Willoughby et al. (2006) [30] Cancer Research UK (http://info.cancerresearchuk.org/)*

cervical cancer incidence rates started declining after coverage for screening was improved (Figure 4.5.3) Cervical cancer incidence has been reduced by as much as 80% where the cytology screening quality, coverage and follow-up of women are high. The highest reduction in cervical cancer incidence was in the 30–49 age group, where the focus of screening was the most intense.

Pap smear screening has been very sparsely implemented in most developing countries. Establishing quality-assured cytology screening programmes with national coverage is a challenging task in many developing countries, in view of the infrastructure for testing, trained personnel for reading, quality assurance and the resources and organisation required. Cytology screening programmes in Latin American countries such as Cuba, Brazil, Mexico, Peru and Colombia, among others, have not resulted in a significant reduction in the cervical cancer burden in these countries [5]. Possible reasons for the lack of success in these countries include a combination of sub-optimal cytology testing, lack of quality assurance, poor coverage of women at risk and inadequate follow-up of screen-positive women with diagnosis and treatment.

A critical appraisal of reasons for the sub-optimal performance of cytology screening in low- and medium-resourced countries has prompted the reorganisation of programmes in many Latin American countries and the evaluation of alternative screening tests, such as HPV DNA testing, visual screening with 3–5% acetic acid or Lugol's iodine, and paradigms that require one or two visits to complete the screening and diagnosis/treatment processes [4,6]. Following the reorganisation of the Pap smear programme in Chile, incidence and mortality started to decline [7].

Alternatives to the Pap smear

Liquid-based cytology

Liquid-based cytology (LBC) relies on a uniform thin layer of cervical cells (Figure 4.5.4) without debris prepared from processing a fluid medium containing the cervical cells, leading to improved sample adequacy and microscopic readability of the smear. It is a more expensive test than conventional cytology, and requires additional instrumentation to prepare the smears. Although earlier reviews claimed improved sensitivity to detect high-grade CIN [3,8], results from a recent review [9] and a randomised trial [10] do not support claims of better performance by LBC.

HPV testing

The fact that cervical neoplasia are caused by persistent infection with oncogenic types of HPV has led to the evaluation of HPV testing as a primary screening test for cervical neoplasia.

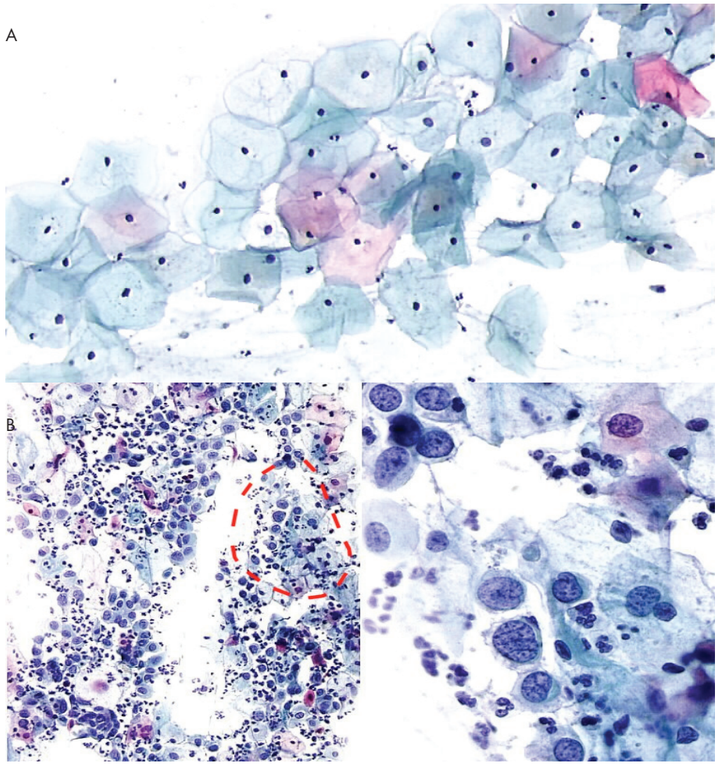

Fig. 4.5.4 *Liquid-based cytology smears showing A. normal cervical cytology B. high-grade squamous intraepithelial lesion (HSIL)*

HPV testing is the most objective and reproducible of all currently available cervical screening tests. In several cross-sectional studies the sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66–100% and the specificity varied from 62–96% [4,11,12]. The sensitivity of HPV testing reported by studies in developing countries has been somewhat lower than that reported by studies in developed countries. Recently reported randomised trials indicate that HPV testing has higher sensitivity for the detection of CIN as compared with Pap smear [13-15].

Although self-sampling for HPV DNA testing seems to be a viable screening option, and potentially promising for use in under-resourced areas or for women who are reluctant to participate in screening programmes, further definitive research is needed to provide a solid evidence base to inform on the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened [16].

In low-resource settings, where repeated screening of women is not feasible, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease [4]. However, it is currently more expensive (US$20–30) than other screening tests and requires sophisticated laboratory infrastructure including testing equipment, storage facilities for samples and trained technicians. Further developments in terms of less expensive testing and less sophisticated infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings. Efforts are now under way to develop simple, affordable, rapid and accurate HPV testing methods for use in low- and medium-resource settings.

In summary, compared to cytology, HPV testing is substantially more sensitive for prevalent CIN 2 or worse lesions, but significantly less specific. Whether this gain represents overdiagnosis or protection against future high-grade CIN or cervical cancer is not clear. Reduced incidence

of or mortality from invasive cervical cancer among HPV-screened subjects compared with cytologically-screened subjects has not yet been demonstrated; this issue is being addressed in a randomised trial in India [17]. Interim results from this trial show similar detection rates of CIN 2 and 3 lesions per 1000 screened women among those screened by cytology, HPV testing or visual screening with 4% acetic acid. HPV testing reportedly does not add significant psychological distress when combined with cytology in routine primary cervical screening [18].

Visual inspection

Visual screening is carried out after application of dilute acetic acid or Lugol's iodine solution. Visual inspection with acetic acid (VIA) involves naked-eye inspection of the cervix using a bright torch light or a halogen focus lamp, 1–2 minutes after the application of 3–5% acetic acid using a cotton swab or a spray. A positive test is characterised by well-defined acetowhite areas close to the squamo-columnar junction (SCJ), to the external os, on the entire cervix or a cervical growth turning acetowhite (Figure 4.4.5) [19]. Immediate results following VIA allow diagnostic investigations and/or treatment in the same session as screening. However, VIA is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for VIA are yet to be standardised and assuring consistent high performance can be challenging under field conditions, requiring constant monitoring and frequent re-training of test providers.

The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37–95% and the specificity varied from 49–97% in several cross-sectional studies in developing countries [4]. The wide range in the accuracy of VIA underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used to establish the true positive disease. When Pap smear was concurrently evaluated, the sensitivity of VIA was found to be higher than or similar to that of Pap smear, but had lower specificity. It appears that a good quality VIA has an average sensitivity of around 50% and specificity of around 85% to detect high-grade CIN in experimental study settings.

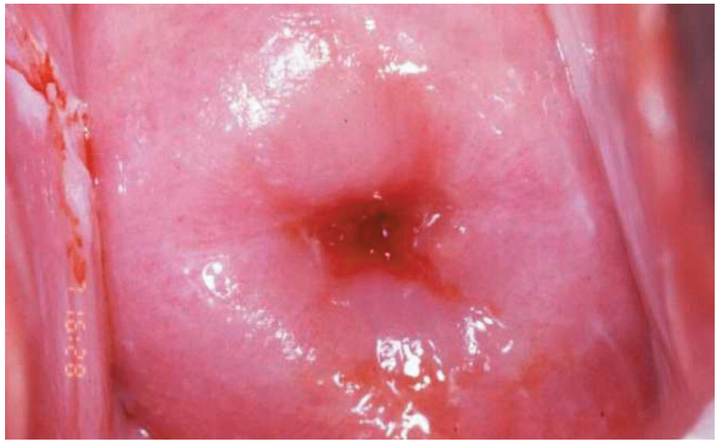

Fig. 4.5.5 *Visual inspection of the cervix with 4% acetic acid. In the normal cervix, after the application of acetic acid, no definite acetowhite areas are seen*

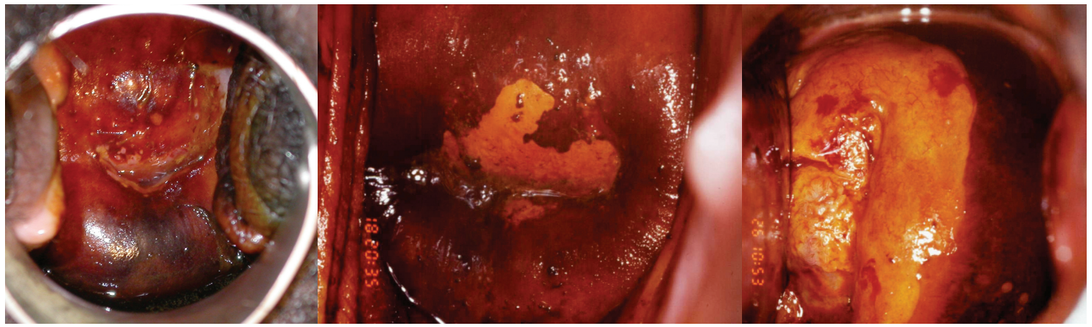

Fig. 4.5.6 *Visual inspection of the cervix with Lugol's iodine (VILI) A. VILI negative B. VILI positive C. VILI positive, invasive cancer*

The immediate availability of test results following visual testing has opened up the option of "screen and treat" or "single-visit" approach to ensure a high compliance to the treatment of screen-positive women, in which those women, with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. The safety, acceptability and feasibility of combining VIA and cryotherapy in a single-visit approach have been demonstrated in rural Thailand [20], Ghana [21], Guatemala [22] and South Africa [23]. In a randomised controlled trial in South Africa, VIA followed by cryotherapy resulted in 37% and 46% lower prevalences of CIN 2–3 lesions at 6 and 12 months follow-up compared with a control group [23]. Cryotherapy for HPV test-positive women resulted in much higher declines in the prevalence of CIN 2–3 at 6 and 12 months (77% and 74% respectively) in this study.

Currently, the efficacy and effectiveness of VIA screening in reducing cervical cancer incidence and mortality are being addressed in randomised controlled trials in India [17,24]. A 25% reduction in cervical cancer incidence and a 35% reduction in mortality have been observed 7 years from the beginning of VIA screening in one of the trials (Table 1)[24].

Visual inspection with Lugol's iodine

Visual inspection with Lugol's iodine (VILI) involves naked-eye examination of the cervix to identify mustard-yellow lesions in the transformation zone after application of Lugol's iodine (Figure 4.5.6) [19]. The sensitivity of VILI varied from 44–92% and specificity from 75–85% in cross-sectional studies [25-27].

Fig. 4.5.7 *Training materials and technical reports*

Fig. 4.5.8 *Women at a clinic in India participating in a study of early detection of cervical cancer*

Conclusions

Cervical cancer reflects striking global health inequities, resulting in deaths of women in their most productive years, resulting in devastating effects on the society at large. It is the largest single cause of years of life lost to cancer in the developing world. The major barrier to prevention of cervical cancer is failure to be screened at all.

Organised screening is generally considered to be substantially more effective and efficient than opportunistic screening. The long natural history of cervical cancer presents several opportunities in terms of prevention, screening, early detection and treatment of CIN to prevent invasive cancer. Both screening and vaccination have the potential to save many lives. At the public health level, health care infrastructure, affordability and capacity to initiate and sustain vaccination and screening programmes are critical factors in cervical cancer control. Substantial evidence now exists on implementation of screening programs based on cytology, visual screening tests or HPV testing, and such action has the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

To screen successfully in low-resource settings the following requirements must be met:

- Adequate and timely investments to assure sufficient infrastructure for screening, diagnosis and treatment and to train screening staff;
- Screening, diagnosis and treatment provided on-site in clinics that are accessible to the majority of eligible, target women;
- An affordable, low-cost/low-technology screening test that can lead to immediate treatment of abnormalities;
- High coverage of at-risk women;
- Appropriate educational efforts directed towards health workers and women to ensure correct implementation and high participation; and
- A built-in mechanism for monitoring and evaluation of the program and adequate coordination and quality assurance.

Delaying investments in screening in low-resource countries means that many women will continue to miss opportunities for preventing cervical cancer for several decades to come. While HPV vaccination provides the hope for the future, screening provides the means for the present.

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4.6 Screening for Breast Cancer

Summary

> Breast cancer is the most frequent cancer in women and accounts for over one in five new cancer cases in women worldwide. Due to an overall aging of the world population, the number of cases is expected to increase in the coming years

> The large randomised trials performed from 1976–1990 have shown that an invitation to breast cancer screening based on mammography can reduce mortality from breast cancer averaging 25% in women aged 50–69 years. More recently, analysis of population-based service screening programmes in women aged 40–69 years has demonstrated that regular mammography screening attendance can provide 40–45% reduction in breast cancer mortality

> There is only indirect evidence that screening by clinical breast examination will reduce the number of breast cancer deaths

> Screening should be implemented in the context of an organised, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation.

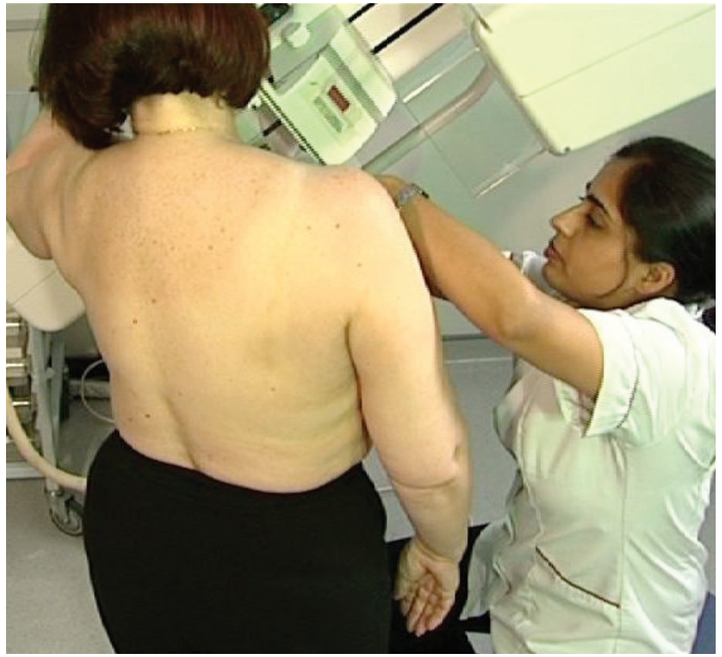

Fig. 4.6.1 *Positioning of the breast for screening mammography. Image provided by Dr ARM Wilson, Dept of Academic Oncology, Guy's Hospital, London, United Kingdom.*

Cancer of the breast is the most common cancer in women worldwide, and in many regions it is the most common cause of death from cancer in women. Breast cancer is characterised by a preclinical detectable phase lasting from 1–7 years, depending on the specific disease subtype. Mammography (X-ray examination of the breasts) can detect preclinical cancer, that is, detect the tumour before it is palpable and before it causes symptoms. Tumours detected and treated at an early stage are 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 therapy and decrease complications related to intensive treatment and recurrence [1-5].

The impact of screening

The incidence of breast cancer worldwide has been on the rise for at least the past half century. Factors such as diminished and delayed childbearing are partly responsible for this increase. Improved diagnostic methods are also generally considered to influence the increase. However, the introduction of screening mammography occurred several decades after the documented increase in incidence and can account for only a minor part of the increase. On the other hand, the marked increase in the incidence of *in situ* breast carcinoma appears to be directly related to the availability of mammography, as this form of breast cancer is difficult to detect by clinical methods [4-6].

In many developed countries mortality rates have been rather stable despite the steady increase in incidence. No clear overall decline in mortality was observed in any place before the late 1980s, when a gradual downturn occurred in Europe, North America and Australia. These decreases in breast cancer mortality have been attributed to a combination of earlier detection and improved treatment, but the relative contribution of each has not been determined [3,4,7,8].

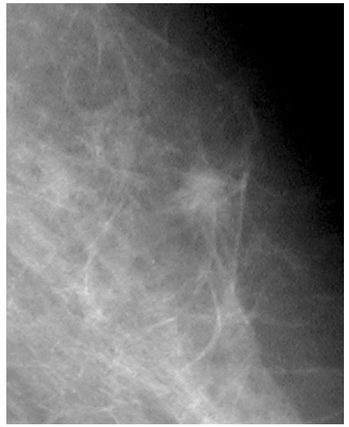

Fig. 4.6.2 *Detailed view of a mammogram from a patient revealing a small breast cancer. Image provided by Dr Margrit Reichel, Screening Reference Team, Koenigstein and Meinhard, Germany*

Protocols for screening

Breast cancer screening is delivered in a variety of ways, including organised programmes and "opportunistic" activities which involve referral to mammography facilities by clinicians and self-referral by women themselves. Organised programmes are recommended because they include an administrative structure responsible for implementation, quality assurance and evaluation. The screening process begins with information and invitation of the eligible women to attend screening and extends from performance of the screening test (in most cases mammography) to the diagnostic assessment of women with suspicious test results and, if necessary, treatment of women with screen-detected lesions. Overall screening outcome and quality depend on the performance at each step in the screening process. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each woman in the eligible target population. The population-based approach to programme implementation is recommended because it provides an organisational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimisation of invitation to screening and for evaluation of screening performance and impact.

Fig. 4.6.3 *The evaluation of mammograms requires appropriate expertise and performance standardisation. Image provided by Prof Peter B Dean, Dept of Diagnostic Radiology, University of Turku, Turku, Finland*

By the mid-1990s at least 22 countries had established national, sub-national or pilot population breast cancer screening programmes [9]. Currently, most of the 27 member states of the European Union are running or establishing population-based breast cancer screening programmes based on mammography [10]. Many programmes target the age group 50–69 years for mammography screening. The youngest age targeted for screening is generally 40 years. Some opportunistic programmes do not set an upper age limit for eligibility, whereas some population-based screening programmes target women up to age 74 or, in at least one case (The Netherlands) age 75. The upper age limit for three-yearly population-based invitation to attend the NHS Breast Screening Programme in the United Kingdom is 70 years; older women can also request to attend screening. Most screening programmes have adopted a two-year screening interval; shorter intervals of 12 or 18 months have been adopted by programmes targeting women under age 50 which is consistent with the shorter mean sojourn time of breast tumours in younger women [11].

Mammography screening is performed on large numbers of predominantly asymptomatic women. The potential harm caused by mammography includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost and the use of ionizing radiation. The strongest possible emphasis on quality assur-

Fig. 4.6.4 *A positive mammogram requires comprehensive follow-up, often including percutaneous core needle biopsy under ultrasound or stereotactic guidance. Image provided by Dr ARM Wilson, Dept of Academic Oncology, Guy's Hospital, London, United Kingdom.*

ance and physico-technical quality control is required to maintain an appropriate balance between harm and benefit of screening. The evaluation of individual mammograms requires appropriate expertise and performance standardisation (Figure 4.6.3). Independent double reading of mammograms with a protocol for resolution of discrepant interpretations, and use of two views (mediolateral oblique and craniocaudal) is recommended to increase accuracy in detection of lesions [12-14]. It is also essential to adhere to adequate standards of diagnostic assessment of women with abnormal results of the initial screening evaluation, as well as standards of multidisciplinary management of lesions detected in screening. Failsafe mechanisms should be established to ensure that all women with abnormalities are contacted and recalled or referred for diagnostic assessment, which may involve repeat and/or more comprehensive mammography, clinical breast examination, ultrasonography and biopsy, if suspicion of malignancy cannot otherwise be ruled out (Figure 4.6.4). Women with a diagnosis of breast cancer should be offered an appointment for treatment within a reasonably short period of time.

Numerous countries have adopted regulations and guidelines on quality assurance of mammography screening [13]. In the United States, the Mammography Quality Standards Act (MQSA) has made certification of mammography facilities mandatory [15].

Comprehensive multidisciplinary guidelines for quality assurance in breast cancer screening and diagnosis have been developed by experts and published by the European Commission [14]. The Council of the European Union has recommended implementation of population-based breast cancer screening programmes according to the EU guidelines to all EU member states [16].

There is currently insufficient evidence from studies in high-resource countries to support the efficacy of clinical breast examination or the teaching of self-examination of the breast as a public health strategy to lower the number of breast cancer deaths in the population. These methods are being evaluated for screening in low-resource countries in which most patients currently present for treatment at very late stages [17]. A study aiming to reduce the proportion of newly diagnosed advanced stage breast cancer from 80% to 60% using breast awareness, breast self-examination, clinical breast examination and centralised assessment of abnormalities is currently underway in India.

Cancers diagnosed in the interval between two routine screening examinations, or within the time period corresponding to the regular screening interval after a negative screening examination, are known as "interval" cancers. Mammographic breast density appears to be a major risk factor for interval cancer, with the highest risk being associated with extremely dense breasts [18]. Clinical examination and self-examination, whilst not proven to show a benefit in terms of reduction in breast cancer mortality [19], may aid in the detection of interval cancers in mammography-based screening programmes.

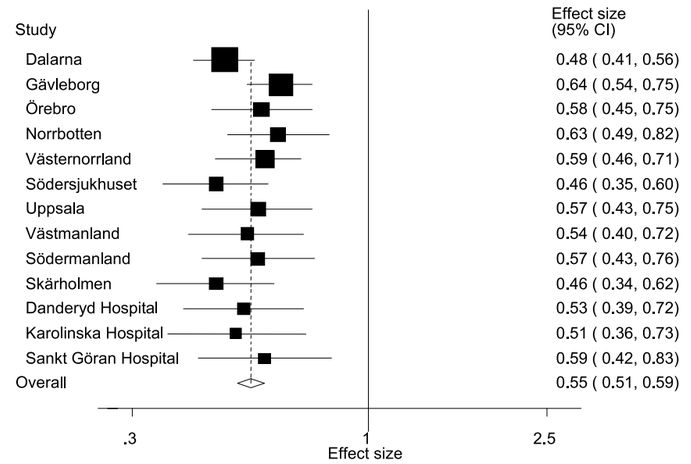

Fig. 4.6.5 *Relative risk of incidence-based breast cancer mortality for screened women in the screening epoch compared with the prescreening epoch, adjusted for self-selection bias [29]. Figure reproduced from Cancer Epidemiol Biomarkers Prev 15: 45-51 with permission of the American Association for Cancer Research, Inc.*

Evaluation of screening

Screening by mammography began to be widely adopted in the late 1980s following the demonstration of its effectiveness in two major randomised trials [20,21].

Inconclusive results were found in two trials in Canada in which annual mammography and breast physical examination were compared with single breast physical examination and subsequent care in 40–49-year-old women [22], and with annual breast physical examination in women aged 50–59 years [23]. Additional randomised controlled trials have also demonstrated a significant decrease in breast cancer mortality in the invited populations compared to the non-invited control populations. The principal factors influencing the magnitude of this decrease include the participation rates of the invited women, the performance of mammography in the control population, and the diagnostic accuracy of mammography in each particular trial [19].

Most of the existing randomised controlled trials have been criticized for putative methodological weaknesses by critics who also argued that breast cancer mortality is not a valid endpoint for screening trials [24,25]. These critics dismissal of all the positive randomized trials is generally considered to be inappropriate because, essentially, it is based on a mechanistic evaluation of technical criteria that are of questionable relevance to the results [26].

A re-appraisal of the randomised controlled trials, conducted by a working group of experts convened by the International Agency for Research on Cancer, concluded that the exclusion of the positive randomised controlled trials was unjustified and that there is sufficient evidence for the efficacy of screening women aged 50–69 years by mammography as the sole screening modality in reducing mortality from breast cancer. Women who were invited to be screened showed a reduction in breast cancer mortality averaging 25%, with the degree of benefit depending on the particular trial. Since not all women accepted the invitation, the reduction among those who chose to participate in screening is somewhat higher, being estimated at 35% [19].

None of the population screening trials had sufficient statistical power to evaluate the results by 10-year age cohorts, and attempts to determine the efficacy of mammography screening in the 40–49 year age cohort have yielded less promising results [19]. The lower incidence of breast cancer, and a somewhat greater radiopacity of the premenopausal breast at mammography, combined with a more rapid progression of breast cancer in premenopausal women may be contributing factors, but the current evidence is far from complete [1,5,27].

The effect of up to seven years of annual mammographic screening is under investigation in a randomised controlled trial in the UK which recruited women 39–41 years of age at study entry. The recently reported results at 10-year follow-up are not statistically significant but are consistent with other findings showing a significant but lesser impact of screening in women aged 40–49 years than in older women. The authors pointed out that the non-significant effect was much larger (ca. 24% mortality reduction) in the women actually exposed to screening (participants) than in the entire group of women invited to attend screening (ca. 15%). Due to the study protocol, sensitivity was reduced after the initial screening examination, which may have reduced the observed effect of screening [28].

Organized service mammography screening has been evaluated in Sweden by combining individual breast cancer patient data with screening invitation data to document the impact upon the individual woman of actually receiving the screening mammography examination. In this large study involving women in the age range 40–69 years in nearly half of the country, data were collected on 542 187 women in the pre-screening era and 566 423 women in the screening era. Approximately two thirds of the study population was from regions with invitation to screening in the age-

range 40-69 and approximately one third was from regions with invitation to screening in the age range 50-69. Some counties also offered screening to women in the age range 70-74, but the analysis was restricted to women <70. In an average follow-up period of 13 years, the observed mortality reduction to the population of 27% (screened and non-screened women combined) corresponded to a mortality reduction of 40–45% in the women actually screened (Figure 4.6.5).

Approximately 472 women (95% CI 418–554) needed to be screened by mammography to save one life from breast cancer. The number needed to screen to save one life ranged from 188 to 862 in the various regions covered by the study and was inversely related to the respective length of follow-up, which varied between 22 and 11 years due to uneven rollout of screening across the country [29].

For effective quality management, screening should be implemented in the context of an organized, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation. Due to the favourable prognosis of breast cancer in high-resource countries, long-term follow-up is required to assess the full impact of service screening programmes [29,30].

WEBSITES

Information from the US NCI on testing for various cancers, including breast:
http://www.cancer.gov/cancerinfo/screening

FDA's Mammography Programme:
http://www.fda.gov/cdrh/mammography/mqsa-rev.html

European Cancer Network
(breast, cervical and colorectal cancer screening, diagnosis and management)
See: IARC Screening Quality Control Group (ECN)

European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis (pdf version):
http://bookshop.eu.int/eGetRecords?Template=Test_EUB/en_publication_details&CATNBR=ND7306954ENC

IARC Screening Quality Control Group (ECN):
http://www.iarc.fr/en/Research-Groups/Clusters-Groups/Pathogenesis-and-Prevention-Cluster/Screening-Quality-Control-Group

International Cancer Screening Network:
http://appliedresearch.cancer.gov/icsn/

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4.7 Screening for Colorectal Cancer

Summary

> Early detection of colorectal cancer increases surgical curability. Several screening modalities exist, including the faecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy and virtual colonoscopy

> Population-based FOBT screening may reduce CRC mortality by 16%, but cannot much reduce CRC incidence. The use of rehydrated FOBT in one trial did decrease CRC incidence by about 20% after 18 years, but this could be due to the high rate of colonoscopies induced by the low specificity of rehydrated FOBT

> Observational non-randomised studies suggest that endoscopic methods would decrease both CRC incidence and mortality, with much larger gains in mortality reduction than with FOBT

> Offering FOBT screening to a population must take into consideration the logistics of screening and the burden CRC screening will represent in terms of colonoscopy

In 2002, the worldwide burden of colorectal cancer (CRC) was estimated as 550 000 new cases and 278 000 deaths for men and 472 600 new cases and 255 000 deaths for women [1]. Colorectal cancer is most frequent in North America, Australia, New Zealand and parts of Europe. Benign or malignant neoplastic lesions of the large bowel are termed superficial when their depth is limited to the mucosa or the submucosa. These superficial CRCs are assumed to be completely curable by surgical means (laparotomy, laparoscopy) or by endoscopic removal. These superficial CRCs and advanced adenomas typically defined as adenomas 1cm or greater, or with villous components (tubulovillous or villous), or with high-grade or severe dysplasia, are the targets of screening.

Most CRCs arise from adenomatous polyps, and their removal is likely to decrease both CRC incidence and mortality. The likelihood that a polyp will evolve into CRC is correlated to its size. Adenomatous polyps less than 0.5 or 1cm are unlikely to give rise to a CRC. Hence, adenomatous polyps 1cm in size or larger are an important target for screening. Autopsy and colonoscopy studies confirm a prevalence of adenomatous polyps in the range of 30% in the adult populations above 50 years old in various Western countries. This means that the majority of polypoid precursors will never progress to cancer.

The faecal occult blood test (FOBT)

Screening with the Guaiac or Immunochemical Fecal Occult Blood Test is proposed for organised mass screening to men and women from the age of 50 years, and repeated in successive campaigns. There is no benefit in prolonging screening above age 70 years for persons who have always tested negative [2]. Persons with positive FOBT tests are referred to colonoscopy. Meta-analysis by a Cochrane Review Group of combined results from randomised controlled trials [3-8] shows that participants allocated to screening had a 16% reduction in the relative risk of colorectal cancer mortality (RR 0.84, CI: 0.78–0.90) [9]. In the three studies that used biennial screening there was a 15% relative risk reduction (CI: 0.78–0.92) in colorectal cancer mortality. When adjusted for screening attendance in the individual studies, there was a 25% relative risk reduction (RR 0.75, CI: 0.66–0.84) for those attending at least one round of screening using the faecal occult blood test.

The real efficacy of FOBT as assessed in randomised trials has been debated [10,11]. Also, sensitivity of FOBT for CRC detection is low, in the order of 40–50%, and with FOBT, most CRC are still clinically detected. Usually, non-rehydrated FOBT is used. Rehydrated FOBT leads to numerous false positive results, and in the Minnesota trial, after 18 years of follow-up, 38% of subjects in the screening group had undergone colonoscopy. This high rate of colonoscopy also led to a 20% reduction in CRC incidence [12]. When the false-positive rate is lower (as when non-rehydrated FOBT is used), FOBT screening does not lower CRC incidence because this test rarely detects the presence of adenomatous polyps.

Flexible sigmoidoscopy

Rigid rectosigmoidoscopy is now abandoned in screening protocols, while flexible sigmoidoscopy is often proposed because of a better acceptance than colonoscopy. Most guidelines recommend flexible sigmoidoscopy every 5 years. A major advantage of the procedure is that it can also be performed by trained nurses. The efficacy of rigid or flexible sigmoidoscopy has been evaluated in case–control or observational studies. The Kaiser study [13] compared exposure to rigid sigmoidoscopy during the previous 10 years in cases (distal CR cancer) and in controls (no cancer); sigmoidoscopy reduced the incidence of distal colorectal cancer by 59%. In the USA, a cohort study conducted in 24 744 health professionals [14] has shown that screening with flexible sigmoidoscopy reduces mortality from colorectal cancer by 50% and incidence by 44%.

Several studies have shown that subjects with adenomatous polyps in the descending (left) colon and rectum had a greater chance of having adenomatous polyps or CRC in the transverse and ascending (right) colon [15]. Therefore, flexible sigmoidoscopy may serve as a first-line screening procedure, followed by colonoscopy when adenomatous polyps are found.

Evaluation of the efficacy of flexible sigmoidoscopy is underway: this method is included in the PLCO (Prostate, Lung, Colorectal & Ovarian cancer) randomised screening trial in the USA [16]. Trials in the UK [17] and Italy [18] are evaluating the efficacy of a once-in-a-lifetime flexible sigmoidoscopy offered at age 55–64 years.

Colonoscopy

Colonoscopy is a total endoscopic evaluation of the colon, up to the caecum. This procedure also allows removal of polyps. The chance of finding a cancer during the 5 years following a negative colonoscopy is very small [19]. Colonoscopy is less adapted to a mass screening strategy because compliance is limited, cost is high and the possibility of complications (e.g., intestinal perforation) is present. There is indirect evidence from non-randomised studies that colonoscopy and polypectomy may reduce CRC incidence and mortality. In the prospective National Polyp Study in the USA, a 75% reduction in the CRC incidence attributable to colonoscopy was observed [20].

Other screening modalities

Numerous new tests for detection of CRC biomarkers in stools are proposed, including detection of abnormal DNA in stools. Searching for abnormal DNA seems 3 to 4 times more sensitive and has similar specificity as the least sensitive non-rehydrated Guaiac-based FOBT (Hemoccult II). However, an early version of a stool DNA-based test still failed to detect three fifths of colorectal cancers detected by colonoscopy [21].

Virtual colonoscopy (computed tomographic colonography or CTC) comprises an evaluation of the colon by CT scanning and reconstruction of the colon anatomy using computer software. While appealing, virtual colonoscopy is expensive, involves low-dose radiation, requires a similar bowel preparation as colonoscopy, and requires further colonoscopy for removal of significant polyps eventually detected. Several software packages are commercially available or have been developed by academic researchers, and detailed evaluation of their respective merits is still needed. A recent multicenter trial in the USA of 2600 asymptomatic men and women aged 50 years or older confirmed the sensitivity of CTC to be equivalent (90% accurate) to optical colonoscopy for the detection of large adenomas and cancers over 1 cm in diameter [22].

Implementation of screening measures

Implementation of screening measures depends on health authorities, reimbursement policies, and compliance of the target population. Often, several CRC screening modalities coexist in the same country. Mass screening with the FOBT is proposed and reimbursed in Japan, Germany, France, Czech Republic, and the UK. Germany and Italy have organised screening protocols based on endoscopic methods. Screening with primary sigmoidoscopy is encouraged in Scandinavian countries and in the UK. In the USA, annual FOBT or sigmoidoscopy every 5 years or colonoscopy every 10 years is recommended. New guidelines in the USA also include the use of virtual colonoscopy every 5 years.

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4.8 Screening for Oral Cancer

Summary

> Oral cancer and its precancerous lesions can be readily detected by visual inspection of the oral cavity by health care providers.

> Oral cancer screening leads to the diagnosis of an increased proportion of early stage oral cancers and improves 5-year survival.

> A statistically significant 33% reduction in oral cancer mortality following oral visual screening has been demonstrated in a large population-based randomised controlled trial.

> The assessment of the oral cavity during routine health care interactions and improved awareness among health care providers and seekers provide excellent opportunities for implementing oral cancer screening.

Oral cancer is a major health problem worldwide, accounting for 274 000 new cases and 145 000 deaths annually, of which two thirds occur in developing countries. [1] Oral cancer is often preceded by precancerous lesions such as leukoplakia, erythroplakia, lichen planus and submucous fibrosis. Oral leukoplakia refers to the presence of flat, predominantly white lesions in the lining of the mouth that cannot be characterised as any other disease. White lesions with a uniform smooth, corrugated or wrinkled surface are referred to as homogeneous leukoplakia (Figure 4.8.1), and those with irregularly flat, nodular, white or red exophytic and white lesions are referred to as non-homogeneous leukoplakia (Figure 4.8.2). Erythroplakia refers to velvety red, non-removable lesions in the oral mucosa (Figure 4.8.3) and they often harbour early invasive cancers. Oral submucous fibrosis (Figure 4.8.4) is characterised by recurrent inflammation and stiffness of the oral mucosa with progressive limitation in opening the mouth and protrusion of the tongue.

The natural history of oral precancerous 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. Although only a small fraction of subjects with these lesions may progress to invasive cancer, around 30-80% of invasive cancers are associated with pre-existing oral precancerous lesions (Figure 4.8.5). In hospital-based studies, a malignant transformation rate of 4.4–17.5% for leukoplakia, and in population based studies transformation rates of 0.13–2.2% over several years have been reported [2]. The risk of malignant transformation varies with sex (higher in women), 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. It is difficult to determine to what extent the above findings are due to variations in case selection or are a true reflection of the natural history.

Early detection of oral cancer

Early oral cancers clinically present as small indurated ulcers, surface thickenings, nodules (Figure 4.8.6), reddish velvety areas (Figure 4.8.7) or ulceroproliferative growths (Figure 4.8.8), often with no symptoms. Pain is usually absent with these early lesions. Careful assessment of oral precancerous lesions for any suspicious areas, and directed biopsies, is important in the early detection of underlying invasive oral cancers. Both oral precancerous and early suspicious cancerous lesions can be readily detected by trained clinicians, nurses and auxiliary health workers, by a systematic visual oral inspection and by palpation [3]. A high level of awareness among health care providers can lead to a high degree of clinical suspicion and appropriate diagnostic follow-up (such as referral), directed biopsies and histopathological examination. It is possible to diagnose such lesions in subjects during routine healthcare interactions, particularly at the primary healthcare level. Although other methods of early detection such as mouth self examination, adjunctive tests like toludine blue application, oral cytology and fluorescence imaging exist, systematic naked eye visual inspection of the oral cavity and neck coupled with palpation of oral mucosa and neck are the most useful and readily applicable early detection procedures.

Oral visual inspection

The evidence supporting the routine use of oral visual inspection in the early detection of oral cancer is based on the performance characteristics of the test in cross-sectional studies, evaluation of routine screening programmes in health services and from a randomised controlled trial.

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; the sensitivity of visual examination for detecting oral lesions varied from 58 to 94% and the specificity from 76 to 98% [3-10].The frequency of positive screening tests ranged between 1.3 and 7.3% of screened subjects and the frequency of adherence to referral among screen-positive subjects was sub-optimal, ranging from 54% to 72%.

An oral cancer screening programme in Cuba, initiated 1984, involved annual oral examination of subjects aged 15 and above by dentists. Although the proportion of stage I cancers increased from 24% in 1983 to 49% in 1989, no reduction in oral cancer mortality has been observed since the introduction of screening, due to sub-optimal coverage of target populations both for participation and treatment. [11]. A case-control study in the context of the programme revealed a 33% reduction (odds ratio 0.67 [95% CI: 0.46-0.95]) in the risk of advanced oral cancer [12]. The programme has been reorganised to cover subjects aged 30 years and above with oral visual inspection once in 3-years and with an improved referral pathway for diagnosis and treatment.

In a community-based cluster randomised controlled oral cancer screening intervention trial involving three rounds of oral visual inspection at 3-year intervals provided by trained health workers during 1995–2004 in Trivandrum, South India, a shift towards early stage at diagnosis (41% vs. 23%) and a higher 5-year survival frequency (50% vs. 34%) were observed

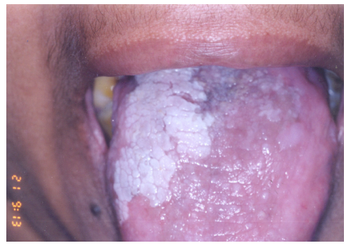

Fig. 4.8.1 *Homogenous leukoplakia on the right side of dorsum tongue*

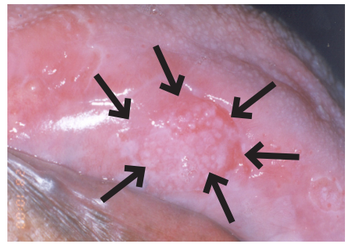

Fig. 4.8.2 *Nodular leukoplakia right lateral margin of the tongue: note the small nodules (yellow arrows) on an erythematous base (red arrows)*

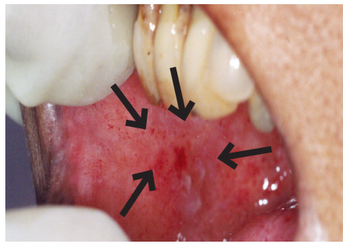

Fig. 4.8.3 *Erythroplakia with petechiae in the right buccal mucosa*

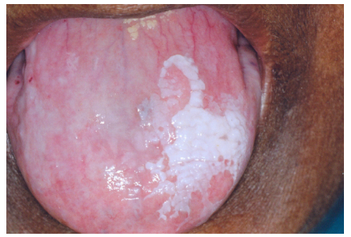

Fig. 4.8.4 *Oral submucous fibrosis, with a co-existing homogenous leukoplakia on the left side of dorsum tongue*

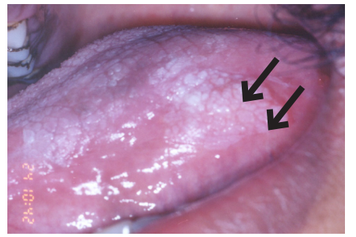

Fig. 4.8.5 *Homogenous leukoplakia on the dorsum and left lateral margin of the tongue, showing malignant transformation. Directed biopsy from the white plaques with erythematous margin posteriorly (arrows) revealed well differentiated squamous-cell carcinoma*

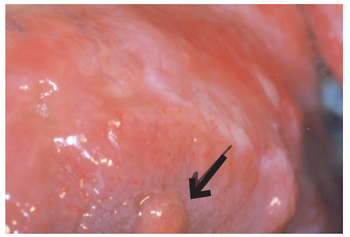

Fig. 4.8.6 *Early invasive cancer presenting as a nodule arising in a non-homogeneous, nodular leukoplakia in the left lateral margin of the tongue*

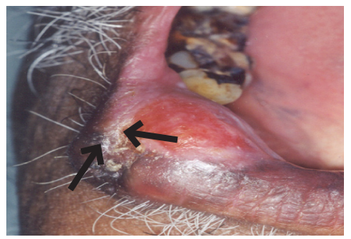

Fig. 4.8.7 *Directed biopsy from ulcerated and crusted area (thick arrow) in the red, velvety erythroplakia of the lower lip (thin arrow) revealed well differentiated squamous-cell carcinoma*

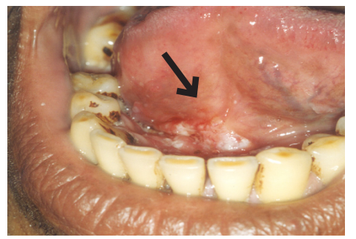

Fig. 4.8.8 *Early invasive oral cancer in the floor of mouth presenting as an ulceroproliferative growth and erythematous area around the Wharton's duct (arrow)*

in the screened population (Table 4.8.1) [8]. A 21% reduction in oral cancer mortality was observed in the intervention group compared to the control group 9-years from the initiation of screening in this study, which did not reach statistical significance. However, a statistically significant 34% reduction in mortality was observed among tobacco and/or alcohol users as compared to similar control subjects (Table 4.8.2). In summary, evidence from the Indian study shows that oral visual screening can reduce mortality in high-risk individuals. The cost-effectiveness of oral visual inspection is currently being addressed in the context of this trial.

Stage	Intervention	Control
I (<2 cm)	51 (25%)	20 (13%)
II (2-4 cm)	34 (17%)	17 (11%)
III (>4 cm)	37 (18%)	35 (22%)
IV (adjacent structures involved)	67 (33%)	70 (44%)
Not known	16 (8%)	16 (10%)
Total	205 (100%)	158 (100%)

Table 4.8.1 *Oral cancer cases according to stage (and percentage distribution), detected during an Indian screening trial (1995-1999), compared with an unscreened control population*

	Intervention group	Control group	Rate ratio (95%CI)	
Overall				
Eligible individuals (number)	96,517	95,356		
Oral cancer cases (number)	205	158		
Stage I and II cancer cases (%)	41	23		
Oral cancer deaths (number)	77	87		
5-year survival (%)	50	34		
Oral cancer mortality rate (per 100 000)	16	21	0.79	(0.51 – 1.22)
Among tobacco or alcohol users, or both				
Oral cancer deaths (number)	70	85		
Oral cancer mortality rate (per 100 000)	30	45	0.66	(0.45 – 0.95)
People with no habits				
Oral cancer deaths (number)	7	2		
Oral cancer mortality rate (per 100 000)	3	1	3.47	(0.12 – 96.51)

Table 4.8.2 *Oral cancer incidence, stage distribution and mortality in a randomised control trial of oral cancer screening in Trivandrum District, India*
Ref: Sankaranarayanan et al., Lancet 2005; 365: 1927-33 [8]

Visual inspection after toluidine blue staining

Toluidine blue dye has been predominantly used as an adjunct for early detection of oral cancer in subjects with precancerous lesions, in order to provide better demarcation of possible malignant and dysplastic changes so as to help select sites for biopsies [13]. This test has been evaluated only in a few specified clinical settings where the reported false negative and false positive rates ranged from 20–30%. The value of visual examination after toluidine blue application as a primary screening test in the early detection of oral cancer is not known.

Mouth self examination

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 and 7 oral cancers were detected [14]. There is no information available on long-term feasibility and detection rates of oral cancer with self-screening.

Oral cytology

Screening by oral cytology has never achieved the same recognition or efficacy as cervical cytology screening, and its role as a primary oral screening test is not yet clear. Keratinization of the oral epithelium poses a major challenge in collecting an adequate number of cells and oral lesions need to be visible before a sample can be collected. Inadequate cellular smears and the subjective nature of interpretation leads to high false negative rates for oral lesions [6,15]. New collection techniques using brush biopsy have reportedly improved the sensitivity (92.3%) and specificity (94.3%) for detection of oral cancer or dysplasia when tested on visually identified lesions [16,17]. Recently, liquid-based oral cytology has also being investigated [18].

Fluorescence spectroscopy or imaging

Fluorescence spectroscopy evaluates the physical and chemical properties of tissue by analyzing the intensity and character of light emitted in the form of fluorescence. Autofluorescence, and 5-amino levulinic acid (5-ALA) induced protoporphyrin IX (PPIX) fluorescence can be recorded using a target integrating colour CCD camera [19]. Their usefulness as screening tools remains to be established.

Saliva-based tests

The value of using genomic targets in saliva as a early detection approach for oral cancer is currently being investigated [20].

Conclusions

Based on the findings from the large Indian cluster-randomised controlled trial, routine use of oral visual screening among tobacco and/or alcohol users is an effective method of reducing oral cancer mortality in addition to primary prevention efforts to reduce tobacco and alcohol use. The very low risk of oral neoplasia among non-users of tobacco or alcohol or both justifies the restricted use of screening among high-risk individuals. Health education messages and information on the usefulness of oral visual inspection through mass media and by posters in health centres, dispensaries and other health care establishments are conducive to improving awareness to prompt subjects at high risk to avail themselves of early detection services. Considering the fact that oral cavity assessment is an integral part of a general physical examination, awareness among health care providers of the effectiveness of oral visual inspection is critical in the early detection of oral neoplasia.

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4.9 Screening for Stomach Cancer

Summary

> Stomach cancer screening has been practiced in certain high-risk areas such as Japan and the Republic of Korea

> The efficacy and effectiveness of such screening has not been shown in a randomised trial

Stomach cancer screening has been practiced in Japan since 1963 and has been public health policy in The Republic of Korea since 1996. Screening is based on early detection of stomach cancer, with surgical resection of the stomach if a tumour is detected. The two techniques used for detection are X-ray examination, after the patient swallows a barium contrast medium, and endoscopic examination, with biopsies taken to confirm the presence of cancer. Gastric cancer screening is rare in less-developed countries, although pilot schemes based on the Japanese model have been conducted in Venezuela, Chile and Costa Rica.

It is difficult to judge the efficacy of stomach cancer screening in reducing mortality from stomach cancer. No randomised trial of stomach cancer screening has ever been conducted, though case–control studies with mortality from stomach cancer as an endpoint have been carried out. However, these studies were subject to several sources of bias that reduce the quality of the evidence they provide on screening efficacy. Recently, some prospective studies have shown important reductions in mortality from gastric cancer among participants in screening programmes in Japan and Costa Rica [1-3]. These studies are not subject to the recall bias that affects case–control studies. However, since these are observational studies, they still have the problem of self-selection: individuals who choose to participate in the screening programme may have a cancer risk that differs from that of non-participants. Therefore these studies cannot substitute for randomised trials.

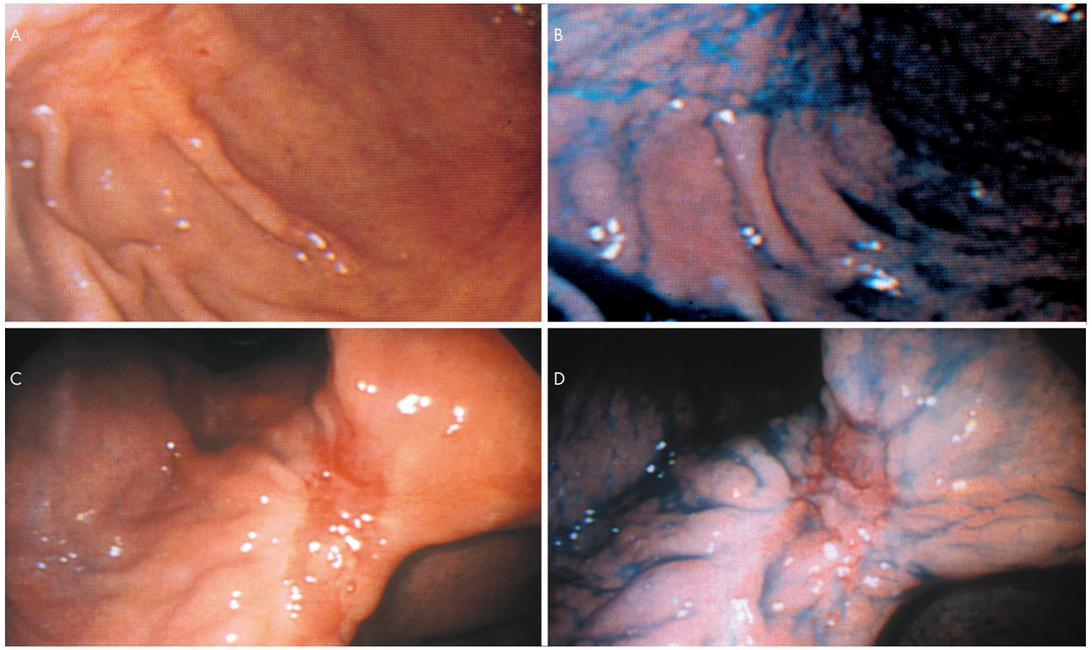

Fig. 4.9.1 *Endoscopic views of gastric cancer (A,C) and corresponding images with dye enhancement (B,D). A, B Depressed early gastric cancer. C,D Deep ulcer scar surrounded by superficial early gastric cancer infiltrating the mucosa and submucosa*

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4.10 Screening for Prostate Cancer

Summary

> Prostate cancer is now the leading incident form of cancer in men in many countries

> Evidence shows harms of screening, but no evidence from randomised trials shows efficacy of prostate cancer screening with PSA (or any other modality)

> Population screening for prostate cancer cannot be recommended at present

> Testing for PSA and integrated programmes of expert multidisciplinary diagnosis and treatment are effective at reducing mortality from prostate cancer

> The availability of a cheap and safe test such as PSA has thrown up new issues and challenges for epidemiology

Among several methods that have been proposed to screen for prostate cancer, case–control studies have found conflicting results for digital rectal examination. Prostate Specific Antigen (PSA) measurement, obtained from a simple blood sample, has been widely proposed as a screening tool for prostate cancer. The PSA test was first approved in 1986 for monitoring progression in patients with prostate cancer. In 1991, William Catalona [1] published results obtained from a large series of men in whom PSA was measured and concluded that the screening [*sic*] programme was able to identify patients at high risk. For the purposes of evaluating PSA as a screening tool, the absence of a parallel control group was a major handicap: the study simply involved testing levels of PSA in a large series of consecutive male patients.

Four randomised trials have investigated or are in the process of investigating the efficacy of prostate cancer screening, mainly using the PSA test. The Quebec study [2] was claimed to be the first randomised trial to show the efficacy of screening for prostate cancer. Fernand Labrie presented the data in the plenary session at the annual meeting of the American Society of Clinical Oncology (ASCO) in Los Angeles in 1998. He reported death rates of 48.7 per 100 000 in unscreened men and 15 per 100 000 in screened men, with a claimed odds ratio of 3.25 in favour of screening. Re-analysis of these data on an *intention-to-screen* basis found a 16% excess of deaths in the group invited to screening, suggesting that the comparison of compliers with non-compliers may have been affected by selection bias. The second randomised trial to be published came from Norrköping in Sweden [3] and reported a 47% higher rate of diagnosis in screened men than in controls. The intention-to-screen analysis on the data calculated the relative risk of death from prostate cancer to be 1.04: that is, a 4% increase in the risk of death from prostate cancer in the group offered screening. A recent Cochrane collaboration review concluded that both of these randomised trials had significant limitations in their methods, and a pooled analysis produced a relative risk of death of 1.01, with a non-significant confidence interval [4].

Results of two large randomised trials have been awaited for several years. The Prostate, Lung, Colorectal and Ovarian (PLCO) [5] cancer trial in the USA started in 1993. It recruited 37 000 men aged 55–74 years into a screening group and the same number into a parallel control group. The European randomised study of screening for prostate cancer [6] was started in 1991 and recruited 83 645 men aged 50–75 years into a screening group and 99 393 men into a control group. These trials have been ongoing for 14 and 17 years, respectively, without producing results on the efficacy of screening.

The PSA test itself is a simple blood test that involves minimal risk to study participants; the risk increases only when a patient is treated after receiving a diagnosis of prostate cancer. The availability of such a simple and cheap test has given rise to some very interesting and important consequences. The first is 'contamination' in randomised trials. The sample size for a clinical trial is calculated to give the number of events required to achieve an appropriate level of statistical power. Zelen and Parker [7] showed that the effective sample size is equal to $n(1-p)^2$, where p is the proportion of the control group who received the treatment and n is the original number of events required. In prostate screening trials, p would be the proportion of the control group who have their PSA measured outside the study. If the contamination rate is 10% then the effective sample size is 0.81 times the number of people in the study. The likely consequence of the high rate of PSA testing in the population is that contamination rates in clinical trials will be around 30–50%, and this is having a major impact on the effective sample size of studies. Since the sample size cannot be increased by entering new study subjects, more time will be required to have the (increased) number of events needed to obtain adequate statistical power. As recruitment has long since closed, considerable delays are being encountered in acquiring enough events (deaths from prostate cancer) to make comparisons between the screened and unscreened groups.

The side effects of radical therapy for all forms of prostate cancer have been well known for many years, so whether to recommend screening depends on whether any moderate reduction in mortality is offset by a decreased quality of life for the men treated [8]. In a random sample of patients in the USA, Potosky found a rate of serious adverse events (30-day postoperative mortality, incontinence, wearing pads at 6 months or a year, and an unchangeable loss of potency) of 28.6% in those treated radically [9]. Although a treatment needs to be in place for all men in the community, it could lead to a situation in which a huge loss in quality of life more than offsets a moderate reduction in mortality through screening.

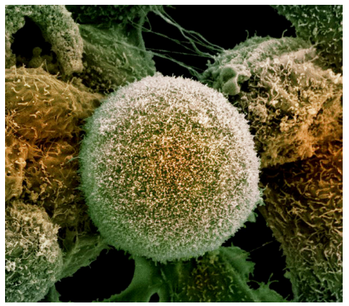

Fig. 4.10.1. *A cluster of prostate cancer cells. Scanning electron micrograph*

Even if the results of ongoing trials are null or inconclusive, however, it is clear that nothing can stop the inexorable rise in the use of PSA testing in the community. It would be helpful at this point, therefore, to introduce some method of evaluating the outcome of such an activity in a scientifically meaningful manner.

Nerve-sparing radical prostatectomy was introduced to the federal state of the Tyrol, Austria, in 1998. Unorganised cancer detection began in 1990, and PSA testing was made freely available to every man aged 45–75 years in 1993 [10]. By 2005, 86.6% of men who had passed through the age window had been screened at least once [11], and 14 000 had been screened 14 times. As this was a demonstration project in a community rather than a randomised trial, new ideas on how to treat and detect prostate cancer were incorporated into the algorithm and used throughout the state. Men in the rest of Austria were not offered PSA testing. Using the standardised mortality rate with the pre-screening era (1986–90) used as a baseline, the rate in 1991 was 113% of baseline, though this has gradually reduced to just 46% of baseline in 2005. In the rest of Austria, a gradual evolution in the uptake of PSA (as in most countries) has been accompanied by a 3% annual reduction in mortality since 1993 (similar to the reduction in the USA), while a 7.2% reduction was observed in the Tyrol [11].

Reassuringly, the screening did not result in a deferral of prostate cancers until after the age of 80 years, as there was a reduction of 64% in the number of cancer deaths expected in the Tyrol and 93% in the rest of Austria. When the age-standardised mortality was analysed with a different smoothing trend, a larger and more rapid reduction was seen in the Tyrol than in the rest of Austria. The entire state of the Tyrol has outstanding urological services for every patient, with free immediate access to many different types of treatment. Study of morbidity and mortality after radical prostatectomy in a series of 1663 patients in 1998–2004 showed no mortality at 30 days, no ureteral injury, and incidences of 0.6% for rectal injury (which has decreased to 0.1% since 2000), 0.7% for rectal bleeding that required intervention, 80.6% for continence at 3 months and 95.1% for continence at 12 months [11].

Since 2000 the potency status, defined as the ability of having intercourse 2 years after surgery with or without PDE5 inhibitors, of 512 men who were potent prior to the operation and younger than 65 years was assessed by an independent investigator; 78.9% preservation of erectile potency was observed. Continence was defined as no need for protective pads; 95.1 % urinary continence was recorded after 12 months in men under 65 years of age [11].

Randomised, controlled trials evaluating the effectiveness of PSA and digital rectal screening in reducing prostate cancer mortality are underway [5,6], but the results will not be available for several years. Furthermore, the randomised design of these trials may be compromised if non-adherence to the assigned intervention group is extensive, i.e. widespread contamination of the control group due to members seeking PSA testing. The consequences on the statistical power of these trials could be considerable.

Overall, these results from Tyrol confirm that, in the best of circumstances, a programme of PSA testing and rapid evaluation and specialised treatment can be effective. A paradox seen in many studies in the USA is that men diagnosed with prostate cancer live as long as, or longer than, men who have not been given such a diagnosis. Walsh and Thompson [12] sought an explanation for this paradox by studying a consecutive series of surgical patients treated at the Veterans Association Hospital in San Antonio. After surgery, 72% of men had a change of medical regimen, 61% had a change of drug treatment and 29% received a new medical diagnosis. Walsh and Thompson proposed that changes of such magnitude would be expected to affect survival outcomes of men recently diagnosed with prostate cancer. [12]

Since the introduction of PSA testing, the reported incidence of low-grade prostate cancer has declined [13]. A population-based cohort of 1858 prostate cancers diagnosed during 1990–92 was assembled at the Connecticut cancer registry. Histological slides were reread between 2002 and 2004 by an experienced prostate pathologist blinded to the original Gleason scores. Worryingly, the contemporary Gleason score readings were significantly higher than the original readings (the mean score increased from 5.95 to 6.8). The contemporary Gleason score-standardised mortality for prostate cancer (1.50 deaths per 100 person-years) seemed to be 28% lower than the standardised historical rate (2.08 deaths per 100 person-years), even though the overall outcome was unchanged. The authors concluded that the decline in reported incidence of low-grade prostate cancers seems to be the result of reclassification of Gleason scores over the past decade, which resulted in an apparent improvement in clinical outcome.

In a cohort of over half a million men aged ≥70 years assembled from 104 US Veterans Hospitals during 2002 and 2003, 56% of elderly men had a PSA test in 2003: 64% of men aged 70–74 years and 36% of men aged ≥85 years [14]. The US Preventive Services Task Force [15] claimed that men with a life expectancy of less than 10 years are unlikely to benefit from screening even under favourable assumptions, concluding that: "although potential harms of screening for prostate cancer can be established, the presence or magnitude of potential benefits cannot. Therefore, the net benefit of screening cannot be determined." They recommend that if physicians opt to perform screening for individual patients, they should first discuss uncertain benefits and possible harms.

The real impact and tragedy of widespread prostate cancer testing is the doubling of the lifetime risk of a diagnosis of prostate cancer without any effect on the risk of dying from this disease. In 1985, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% risk of dying from prostate cancer [16]. Twenty years later, in 2005, an American man had a 17% lifetime risk of being diagnosed with prostate cancer and a 3% risk of dying from prostate cancer [17]. Despite this, the increase in PSA testing will be impossible to stop.

Trial results for and against testing have always been contentious among supporters and opponents of screening. In the case of breast cancer, even with data available from nine randomized trials with reasonable methods, claims have been made that there is no evidence to support mammographic screening. With fewer trials available for evaluating prostate cancer screening and with contamination rates in the control group likely to be very high, questions will undoubtedly be posed about the reliability of the findings.

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4.11 Screening for Ovarian Cancer

Summary

> There is at present no established method for early detection of ovarian cancer

> Methods proposed to date yield many false-positive results requiring unnecessary laparatomy or are not sensitive enough for detection of ovarian cancer when in a early stage of development

> Randomised trials of potential screening methods are underway

Ovarian cancer is the fourth most common cancer in females, with annual incidence rates ranging between 8.5 and 21.5 per 100 000 in female populations of European countries. The International Agency for Research on Cancer estimated that in 2002 there were 204 499 ovarian cancer cases and 124 860 ovarian cancer deaths worldwide [1]. Ovarian cancer is a heterogeneous group of malignancies that can remain asymptomatic despite being at an advanced stage, or cause non-specific symptoms. In about 70% of patients, ovarian cancer is diagnosed at an advanced stage, leading to a poor prognosis: in Europe, the average 5-year survival of ovarian cancer patients is around 40% [2].

The ability to non-invasively distinguish between non-cancerous and cancerous ovarian process and to detect ovarian cancers at an earlier stage would be major benefit in the management of women with symptomatic pelvic conditions. Many methods, used alone or in combination, for distinguishing between non-cancerous and cancerous ovarian process have been investigated, including transvaginal sonography (TVS), Doppler ultrasonography, measurement of serum CA 125, computed tomography scan (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) and positron emission tomography (PET) scan (the FDG-PET scan) and radioimmunoscintigraphy [3-7]. However, for a number of reasons, from lack of sensitivity or specificity to cost issues, TVS remains the major detection tool. The use of the Risk of Malignancy Index (RMI), which incorporates menopausal status, CA 125 and TVS, has also been proposed. The RMI version developed by IJ Jacob and co-workers has a pooled sensitivity of 78% (95% CI 72–84%) and pooled specificity of 90% (95% CI 81–95%), with an inverse correlation between sensitivity and specificity [8,9]. Other computerised expert systems and a variety of scoring systems based on the combination of ultrasound image characteristics, serum CA 125 level and various other clinical and patient-related parameters have also been tried, but have proven to be less effective than RMI (7) or TVS performed by expert ultrasonographers [10].

Various serum biomarkers have been proposed, like the CA 125, or some blood protein profiles that would represent biological signatures of ovarian cancer, but none of these biomarkers has shown superiority to echography, and furthermore their large-scale application leads to many false positive results and unnecessary laparatomy procedures [11].

On-going trials in the USA [12] and in the UK [8] aim at assessing the value of ultrasound and biomarker-based tests. Their results will not be available for several years. In the meantime, currently available methods prove quite unable to detect ovarian cancer early [13], and new technologies are eagerly awaited.

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4.12 Screening for Lung Cancer

Summary

- Lung cancer is a good candidate for screening, but early attempts based on X-rays and cytology did not prove to be effective
- The search for serological biomarkers for early detection of lung cancer is an active area of research
- Pulmonary spiral CT-scan results in the identification of early lesions with good prognosis, but the possibility of lead-time bias and over-diagnosis cannot yet be ruled out
- Currently, no methods can be recommended for population-based screening of lung cancer

Lung cancer has one of the poorest survival rates of all cancers, mainly due to the lack, in the majority of patients, of symptoms and signs during the early phases of neoplastic growth. This fact, together with the high risk in specific groups of the population, namely smokers (the cumulative risk at age 75 reaches 15% or more in continuous smokers [1]), workers exposed to occupational carcinogens, and women exposed to high level of indoor air pollution, make lung cancer a good candidate for targeted pre-clinical detection.

Early efforts to identify an effective approach to screen pre-clinical cases of lung cancer concentrated on X-ray examinations, search of abnormal cells in expectorate, and the combination of the two (see [2] for a review). Unfortunately, although screen-detected cases had a longer survival than clinically detected cases, the difference was accounted for by lead-time bias, that is, the fact that an earlier detection of a cancer would generate a longer survival even if the natural history of the disease is not altered (i.e. mortality is not affected), and by over-diagnosis, that is, the fact that the screening detected slow-growing lesions that by their nature have a long survival [2].

In the past decade, two new approaches have been proposed for screening lung cancer in high-risk populations. First, efforts are being made to identify disease biomarkers, typically in serum, using novel molecular techniques, notably proteomics (i.e. the systematic analysis of proteins and protein fragments). Although promising, this approach has not yet led to the identification of a valid biomarker [3].

The second approach relies on CT-assisted, low-energy X-rays, notably the so-called spiral CT-scan, which generates a high-resolution, tridimensional image of the lungs. Non-randomised studies of spiral CT scan in high-risk populations have resulted in the identification of a relatively large number of nodules in the lungs, which can be removed surgically, and in the majority of cases are shown to be early forms of lung cancer [4]. The survival of the patients whose early cancers are removed is excellent, but two issues remain to be elucidated before one can conclude that spiral CT scan should be implemented in population-based screening [5]. First, the occurrence of spiral CT scan-detected nodules is higher than that of clinically diagnosed cancers in a comparable population, suggesting that a proportion of the nodules are 'false positives', i.e. represent slow-growing neoplastic lesions that would not have become clinically relevant (so-called over-diagnosis). Second, a reduction in mortality in a screening population has not yet been demonstrated (i.e. the possibility of lead-time bias has not been excluded). These two possible biases are illustrated in Figure 4.12.1.

Randomised trials ongoing in the United States and Europe should provide the final evidence on the effectiveness of spiral CT scan as screening method for lung cancer. In the meantime, national and international authorities generally recommend against the implementation of population-based screening programs for lung cancer [6].

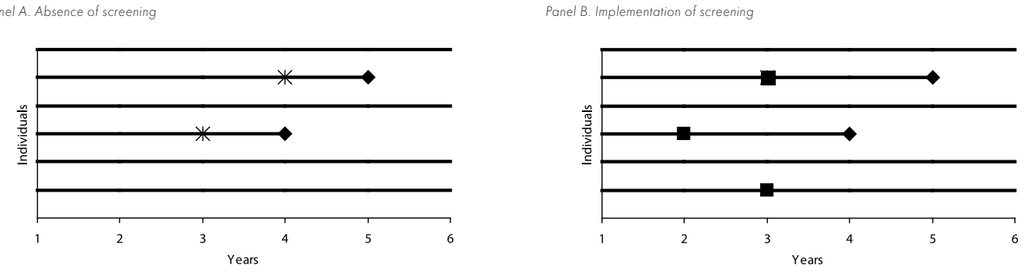

Fig. 4.12.1 *Illustration of lead-time bias and over-diagnosis in a hypothetical screening program of six individuals*
Asterisk: clinical diagnosis; squares: screening-based diagnosis; diamonds: death
In panel A, two cancers with 1-year survival are diagnosed
In panel B, the diagnosis of the two cases is anticipated by one year and one additional case is diagnosed. Mortality, however, is not affected. The screening program apparently increases survival of cases (lead-time bias) and leads to the identification of clinically irrelevant cases (over-diagnosis)

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4.13 Screening for Cutaneous Melanoma

Summary

> There is at present no established method for detection of cutaneous melanoma

> Methods proposed to date are poorly cost-effective and result in identification and expensive treatment of melanoma that would likely never have become life-threatening

The goal of screening is to prevent deaths from cutaneous melanoma through detection of the cancer at an early, curable stage. The commonest methods for early detection of melanoma are whole-body skin examinations (WBSE) and skin self-examination (SSE)[1].

Cutaneous melanoma has two characteristics of a good candidate for screening: the absence of treatment for advanced disease while detection at an early stage may guarantee cure with surgery; the screening method is an (apparently) simple skin examination.

In spite of the apparent simplicity of screening for cutaneous melanoma, no randomised trial has ever shown that such screening could save lives or indicated how many. Other factors fuel controversies regarding population screening of this cancer.

1. Cutaneous melanoma remains a rare disease in many light-skinned populations, and screening for rare cancer is known to be poorly cost-effective;

2. The nodular type (about 10–15% of all cutaneous melanoma) is a fast-growing, aggressive type of cancer, and screening will most probably not be able to detect it at a curable stage;

3. In practice, WBSE is a luxury for most health care systems, as WBSE takes time and health professional have little extra time available for such screening;

4. Many individuals will have nevi or in situ melanoma removed instead of invasive melanoma, and this will contribute to further increasing costs of screening, lead to disfiguring scars and finally negatively impact quality of life;

5. Many screen-detected cutaneous melanoma will consist of indolent cancer that would most probably never have become life-threatening;

6. Mortality from cutaneous melanoma concentrates in the elderly, mainly in men over 60 years of age, because of delay to consult a doctor when a pigmented lesion develops, or because the melanoma develops on a hidden skin area such as the back and the shoulders. Also, it is known that elderly men would have low compliance to skin screening [2].

7. Evaluation of pilot programmes have shown that individuals attending screening often constitute a selected fraction of the population that are more concerned about their health, and also are healthier than non-attendees [3,4].

8. Following logically from the previous point, costs of screening may be considerable in comparison to eventual health benefits. It may appear more appropriate to test the efficacy of screening for melanoma in a subset of high-risk subjects, for instance individuals with a strong family history of cutaneous melanoma or siblings of melanoma patients [5], or of patients with numerous nevi or atypical nevi, or sun-sensitive individuals living in sunny climates. It remains to be shown (ideally via randomised trials) whether a targeted screening strategy may be efficient. In Queensland, Australia, where the incidence of cutaneous melanoma is the highest in the world, a randomised trial of WBSE is ongoing [6,7]. This trial devotes much effort toward having men 50 years old and older participating in the screening programme [8].

A form of screening requiring fewer resources than WBSE is the promotion of regular skin self-examination (SSE) for self-detection of changes in nevi appearance [9]. Promotion of SSE requires ensuring rapid accessibility to medical services for checking (and eventually removing) self-detected suspected lesions. Simply disseminating a message about SSE and the importance of early detection without providing opportunities to have lesions examined and excised will seriously hamper preventive efforts and lead to reduced reliability in health messages given to the population. One case–control study found that SSE could reduce de development of advanced cutaneous melanoma [10], but results on screening efficacy from this kind of study design require verification by more robust designs such as a randomised trial.

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4.14 Genetic Testing

Summary

> Genetic testing of high-risk cancer susceptibility genes is becoming an important part of clinical cancer genetics in some high-income countries, but is not often available in middle- or low-income countries

> The main beneficiaries of the genetic information gleaned from this type of genetic testing are the unaffected relatives of the individuals who are tested

> The most commonly tested high-risk susceptibility genes are BRCA1 and BRCA2 (primarily for breast and ovarian cancer) and MLH1 and MSH2 (primarily for colon and endometrial cancer). However, there are many other genes for which testing is available under specific circumstances

> Medical and surgical interventions have been developed for the carriers of high-risk mutations in the more-often tested genes. Although the interventions involve quality of life tradeoffs, they do, on average, add years to the lives of these at-risk patients

In North America, Europe, Japan and Australia, genetic testing of high-risk cancer susceptibility genes is becoming an increasingly important component of the clinical management of at-risk patients and their close relatives. In 1996, the American Society of Clinical Oncology [1] developed recommendations covering when genetic testing should be offered to patients; these recommendations were updated in 2003. The fundamental ASCO recommendations are "that genetic testing be offered when 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer." In addition, ASCO recommends that testing only be performed in a setting where patients can receive counselling both before the decision to request testing is taken and after test results become available [1].

The vast majority of genetic testing of cancer susceptibility genes is directed towards the established high-risk breast cancer and colon cancer susceptibility genes. De novo testing of an at-risk patient usually involves a mutation screen of the whole open reading frame of the underlying susceptibility gene(s), often augmented with a screen for duplications or deletions of individual exons [2]; consequently, the tests are technologically demanding and relatively expensive. In order to maximise testing efficiency, the first individual from an at-risk family to be tested will usually be a cancer case considered to have a high prior probability of carrying a mutation based on age at diagnosis, family history, and perhaps tumour immunohistochemical profile. If the index case is found to be a mutation carrier, the genotype information may well influence their subsequent medical and surgical management. Two further consequences flow from the identification of a specific mutation in an index case. First, it must be understood and emphasised that the main beneficiaries of the genetic information will be the unaffected relatives of the index case. This is because for unaffected mutation carriers there are medical and surgical interventions that can either reduce the risk of disease or aid in early detection thus improving survival. Second, with very few exceptions, the at-risk relatives of the index case need only be tested with a specific test targeting the exact mutation that was identified in the index case. Mutation-specific tests are much less expensive, and have higher sensitivity and specificity, than do de novo whole gene tests.

Breast cancer

The principal high-risk breast cancer susceptibility genes are BRCA1 and BRCA2; predisposition due to inherited mutations in either of these genes is often referred to as Hereditary Breast-Ovarian Cancer Syndrome (HBOC). The genes were first characterised in 1994 and 1995, respectively [3-5]. Although the absolute risks conferred by inheritance of high-risk mutations in these genes have been somewhat controversial, a combined analysis of 22 studies estimated that BRCA1 mutation carriers have a cumulative risk of 65% and a cumulative ovarian cancer risk of 39% by age 70. For BRCA2 carriers, the cumulative breast cancer and ovarian cancer risks by age 70 were 45% and 11%, respectively [6]. Because these risks are very high, women who carry mutations in these genes will often opt for surgical intervention as a form of primary prevention. At this time, the preferred approach is probably prophylactic bilateral salpingo-oophorectomy. Removing the ovaries and fallopian tubes directly and dramatically reduces the risk of ovarian cancer, and can also reduce the risk of breast cancer by approximately 50% [7,8]. At the same time, tantalising new evidence suggests that tumours arising in BRCA1 and BRCA2 carriers have an Achilles heel that can be exploited to improve their treatment. Specifically, these tumours appear to be differentially sensitive to chemotherapeutic agents that induce DNA-crosslinks, and even more sensitive to poly-ADP ribose polymerase (PARP) inhibitors [9-11]. If these laboratory pharmaco-genetic observations can be converted to effective treatments, then data from the BRCA1 and BRCA2 genetic tests will provide important benefits to both unaffected and affected mutation carriers.

Colon cancer

The two best-understood colon cancer susceptibility syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC or Lynch syndrome). The majority of cases of FAP are due to germline mutations in the colon cancer susceptibility gene APC, identified as such by Groden et al. and Nishisho et al. in 1991 [12,13]. Patients who carry fully penetrant mutations in FAP will typically present with hundreds or even thousands of colon polyps by their mid-20s, and the incidence of colon cancer in these individuals is essentially 100%. Accordingly, the preferred treatment for these patients is prophylactic colectomy, which can add decades to the lives of patients who are detected and treated early as compared to patients who are not diagnosed with FAP until they present with colon cancer [14-16]. For this syndrome, the genetic concept that the first-degree relatives of FAP patients and APC mutation carriers need to be assessed very early is the key to adding years to their lives.

HNPCC is due to germline mutations in the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2, with about 90% of explained cases attributed to mutations in one of the first two of these four genes. The proteins encoded by these genes help repair small single-strand DNA lesions that occur constantly due to endogenous and exogenous mutagenesis. Tumours arising due to loss of function in these genes exhibit increased frequencies of point mutations and instability in the length of microsatellite repeats, termed microsatellite instability. Cumulative risk of colon cancer due to germline mutations in these genes has not been studied as thoroughly as has been the case for BRCA1 and BRCA2. However, a recent population based case-family study concluded that the cumulative risk of colon cancer for carriers of mutations in one of these four genes is slightly greater than 40%, with greater risk to males than females (45% vs. 38%, respectively) [17]. In contrast to FAP patients, the preferred medical management of HNPCC patients focuses on colonoscopy beginning in their early to mid 20s, at intervals of 1 to 2 years [15,18]. This approach should reduce the incidence of invasive colorectal cancer in HNPCC carriers by more than 50% compared to carriers who do not receive routine screening [19-21]. Identification of unaffected HNPCC carriers by age ~25 requires that an older index case from the patient's family underwent testing and was found to be a mutation carrier, hence the role of genetic testing. But to whom should testing be offered? For some time, the decision of who to test for mutations in these genes has been guided by a combination of the family history-based Amsterdam criteria and assessment of tumour microsatellite instability under the Bethesda Guidelines [22,23]. However, new models that make a more detailed analysis of family history, perhaps supplemented with detailed assessment of tumour pathology features, may supplant these criteria [24-26]. In addition, antibodies against MLH1, MSH2, MSH6, and PMS2 that work well in immunohistochemical staining procedures are now available and may be used to prioritise patients for gene mutation screening [27].

While genetic testing for cancer susceptibility is dominated by testing for germline mutations in the HBOC and HNPCC susceptibility genes, there are many less common cancer susceptibility syndromes for which at least some of the underlying susceptibility genes are known. Many of these are summarised in Table 4.14.1. Genetic testing can be conducted for mutations in any of these genes, though in many cases the testing is done on a research basis rather than an established clinical or commercial basis.

Returning to the ASCO recommendations for when genetic testing should be offered, there are important caveats to each of the three criteria. First, with respect to personal and family history, identification of at-risk patients has, to date, depended heavily on family history criteria. However, at least for BRCA1 and BRCA2, the majority of breast cancer cases who carry mutations do not have sufficient family history to suggest that they are likely to be mutation carriers [28]. Thus, strict adherence to family history criteria for testing will deny the benefits of this genotype information to a large fraction of mutation carriers. However, it is now becoming evident that tumours in many BRCA and mismatch repair mutation carriers can be recognised by immunohistochemical, expression profiling, or array CGH criteria [27,29,30]. Thus, in the sense that a patient's personal history includes the molecular characteristics of their tumour, personal history is set to become an increasingly important component of the decision of whom to recommend for genetic testing.

Second, with respect to interpretation of test results, roughly 90% of the high-risk mutations present in the BRCA and mismatch repair genes can be recognised directly from the mutation screening data. However, a significant fraction of sequence variants observed during clinical mutation screening, mostly missense substitutions, are initially unclassified. Further analysis of the individual unclassified variants to determine which are clinically important is a multi-disciplinary problem that is attracting considerable research interest [31-33].

Third, at the time that a susceptibility gene is first identified, the requirement of aiding in diagnosis or influencing treatment presents a circular problem: one cannot know for sure that the test results will meet this requirement until a cohort of mutation carriers have been identified; however, one cannot identify a cohort of mutation carriers without doing some testing! To date, the natural process has been that most genetic testing carried out on a newly identified susceptibility gene takes place in a research setting, and growth of the scale of testing (or not) has depended on the perceived utility of the initial results. With high-risk susceptibility genes, genotype-phenotype relationships have almost by definition been fairly clear. However, as cancer genetics research moves towards either intermediate-risk susceptibility genes or complex genotypes based on panels of modest-risk SNPs, genotype-phenotype relationships will become less clear and questions of clinical utility more challenging to answer.

A decade ago, the scale of genetic testing for mutations in cancer susceptibility genes was very modest, and most testing was either carried out in academic labs or in hospital based testing services that had grown out of academic labs. Driven by positive feedback loops between evidence that the clinical decisions based on results from genetic cancer susceptibility tests can add years to patient's lives, public health service interest, and commercial testing interest, the scale of genetic testing has grown dramatically. Still, this growth is limited almost entirely to the practice of medical genetics in high-income

SYNDROMES	GENES	GENE SYMBOLS	CHROMOSOMAL LOCATION
Dominant inheritance			
Familial retinoblastoma	Retinoblastoma, osteosarcoma	RB1	13q14
Familial adenomatous polyposis (FAP)	Colorectal cancer	APC	5q21
Hereditary nonpolyposis colorectal cancer (HNPCC)	Colorectal, endometrial, ovarian, and gastric cancer	MLH1	3p
		MSH2	2p
		MSH6	2p
		PMS1	2q
Hereditary breast and ovarian cancer (HBOC)	Breast, ovarian, prostate, and colon cancer	BRCA1	17q
		BRCA2	13q
Li-Fraumeni syndrome (LFS)	Sarcomas, breast cancer, brain tumors, leukemia	TP53	17p13
Li-Fraumeni syndrome 2 (LFS2) (the syndrome assignment controversial, however, increased cancer risk is clear)	Breast cancer+ weak LFS-like spectrum	CHEK2	22q12
Cowden syndrome and Bannayan-Ruvalcaba-Riley syndrome	Breast, thyroid	PTEN	10q22
Neurofibromatosis, type 1	Neural tumors, leukemia, soft tissue sarcoma, bone tumors	NF1	17q11
Neurofibromatosis, type 2	Acoustic neuromas, meningiomas	NF2	22q2
Multiple endocrine neoplasia (MEN) type 1	Pancreatic islet cell cancer, parathyroid, hyperplasia, pituitary adenomas	MEN1	11q13
Multiple endocrine neoplasia (MEN) type 2a and 2b	Medullary thyroid cancer; pheochromocytoma	RET	10q11
Von Hippel-Lindau syndrome (VHL)	Renal cancer, vascular tumors	VHL	3p25
Familial melanoma	Melanoma, other tumors	INK4A	9p
		CDK4	6q
Gorlin syndrome	Basal cell carcinoma	PTCH	9q31
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	Leiomyomatosis, renal cell tumors	FH	1q42.3-q43
Peutz-Jeghers syndrome	gastrointestinal hamartomatous polyps, gastric, colon, breast, ovarian cancer	STK11	19p

Table 4.14.1 *Cancer susceptibility syndromes and underlying high-risk susceptibility genes*

SYNDROMES	GENES	GENE SYMBOLS	CHROMOSOMAL LOCATION
Recessive Inheritance			
Ataxia telangiectasia	Lymphoma, leukemia, breast cancer	ATM	11q22
MYH associated polyposis	Colon	MYH	1p32-34
Nijmegen breakage syndrome	Lymphoma, leukemia, breast cancer, prostate cancer	NBS1	8q21
Bloom's syndrome	Solid tumours	BLM	15q26
Familial Wilms tumour	Kidney	WT1	11q
Xeroderma pigmentosum	Basal cell carcinoma, squamous-cell carcinoma, melanoma (skin)	XPA	9p34
		XPB	2q21
		XPC	3p25
		XPD	19q13
		DDB2 (XPE)	11p11-12
		ERCC1 (XPF)	16p13
		XPG	13q32-33
		XPV (Pol n)	6p21
Fanconi Anemia		FANCA	16q24
		FANCB	Xp22
		FANCC	9q22
		FANCD2	3p25
		FANCE	6p21
		FANCF	11p15
		FANCG	9p13
		BRIP1 (FANCJ)	17q22-24
		FANCL	2p16
		FANCF	14q21
X-linked lymphoproliferative disorder	Lymphoma	XLP	Xq25

Table 4.14.1 *(cont.)*

countries. For the most part, middle- and low-income countries lack some combination of the laboratory infrastructure required to carry out clinical-quality genetic testing, the medical infrastructure of physicians and/or genetic counsellors who are trained in medical genetics and able to communicate concepts of genetic risk to patients, and the medical insurance infrastructure required to pay for these activities. Consequently, it may be many years before our current knowledge of the genetics of cancer susceptibility begins to provide noticeable benefit to genetically high-risk patients and their close relatives in middle- or low-resource countries.

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CANCER IN THE SOUTH-EAST ASIA REGION (SEA)

Rapidly progressing epidemiological transition taking place in the South-East Asia (SEA) Region of WHO has reached an advanced stage, characterised by predominance of chronic noncommunicable diseases (NCDs). With an age-standardised mortality rate of 111 per 100 000 and 9% share in total deaths, cancer has become an important public health priority. In 2000, there were an estimated 1.3 million cases and 0.9 million deaths from cancer in the Region, with cervix uteri, breast, oral cavity and lung cancer the most prevalent. Unlike in more developed regions of the world, where most of cancers are related to lifestyle and environmental risk factors, in the SEA Region chronic infections caused by Human papillomavirus (HPV), hepatitis B and C viruses; *Helicobacter pylori* and liver fluke are also of high importance.

Effective cancer control requires a comprehensive national cancer control policy and programme with adequate resource allocation, development of diagnostic and therapeutic capacity and good resource utilisation in palliative care. High levels of female illiteracy, gender discrimination and other socioeconomic inequalities, as well as lack of awareness of the risk factors and poor enforcement of tobacco, alcohol and food legislation, all hinder the efforts of cancer control programmes. Widespread inaccessibility of preventive, early detection and treatment services for large segments of the population in the Region due to the geographical and financial constraints contribute to poor health outcomes. As out-of-pocket payment for the treatment of cancer could economically devastate families and individuals, the creation of appropriate financing mechanisms to cover the cost of treatment needs to be addressed.

Member countries of the SEA Region are taking action to reduce the burden and risk factors of cancer and improve the quality of life of the patients and their families—thus contributing to implementation of the WHO Strategy for Prevention and Control of Cancer. To further strengthen commitment and capacity of Member countries to tackle cancer and other major NCDs (i.e. cardiovascular diseases, chronic respiratory diseases and diabetes), the Regional Framework for Prevention and Control of NCDs has been developed. The WHO Regional Committee for the South-East Region, at its Sixtieth session in September 2007 in Thimphu, Bhutan, endorsed the Regional Framework; it also adopted, for the first time in its history, a Resolution on the Prevention and Control of NCDs. The resolution urges Member countries to formulate, update and strengthen national policies, strategies and programmes for integrated prevention and control of NCDs; to establish suitable infrastructure and appropriate funding mechanisms for this purpose; and to promote multisectoral collaboration for integrated prevention and control of NCDs.

There is an increasing capacity in the Region to address the health and socioeconomic burdens of cancer. Selected information collected through the regional survey conducted by WHO in 2006–2007 is shown in Table 1. Cancer registries, either hospital or community-based such as those set up with WHO support in India, Indonesia, Sri Lanka and Thailand, serve an important role in providing information about the area-specific prevalence of different types and locations of cancer. Since 2001 when WHO began to promote the STEP-wise approach to NCD Risk Factor Surveillance (STEPS) in the Region, most countries have gathered standardised information on NCD risk factors (Table 2). Locally available data on tobacco use, unhealthy diet, physical inactivity and alcohol consumption facilitate planning, implementation and evaluation of preventive action on cancer and other NCDs.

Tobacco use remains the major preventable behavioural risk factor for lung and some other types of cancer. Member countries of the Region are taking strong anti-tobacco measures within the provisions of the WHO Framework Convention on Tobacco Control (WHO FCTC). Out of 11 SEA countries, 10 have signed and ratified the WHO FCTC, and 5 already have tobacco control legislation in place. In addition to smoking, tobacco is often chewed, leading to cancer of the oral cavity—the third most common type of cancer in the SEA Region.

Physical activity, avoidance of obesity and frequent daily intake of fresh fruit and vegetables reduce the risk of several cancers. Implementation of the WHO Global Strategy on Diet, Physical Activity and Health (DPAS) will lead to significant reduction in the mortality and morbidity of cancer and other major NCDs. In the SEA Region, the DPAS is being implemented in three countries, with five more countries in the process of initiating its implementation.

Cancer of the uterine cervix is the most common cancer among women in the Region. Though its rates are dropping in some countries as a result of improved socioeconomic conditions, further improvement requires the introduction of an active screening programme. Broad implementation of cytology-based screening and treatment for cervical cancer is hindered by financial constraints and inadequate health infrastructure and outreach. Alternate strategies such as visual inspection with acetic acid are being introduced in some countries, including India

and Thailand. Currently WHO is supporting Maldives and Thailand in engaging in the research project on delivery of HPV vaccine to adolescents.

Childhood immunisation against hepatitis B is the most cost-effective strategy to prevent adult mortality from liver cancer. Following 1992 World Health Assembly Resolution WHA45.17, most countries of the SEA Region have introduced hepatitis B vaccine in their routine national immunisation programmes. This process was further accelerated by the Global Alliance for Vaccines and Immunization (GAVI).

A majority of countries of the SEA Region already have national cancer control programmes in place. Most often these programmes are at the early stage of development. WHO is supporting the national governments in strengthening their capacity to prevent and control cancer. This is being done through advocacy for and technical support in development and strengthening of cancer control programmes and plans encompassing cancer prevention, early detection, management, palliative care and surveillance and research. Member countries are being supported in setting up surveillance systems (cancer registries) and in addressing major behavioural risk factors of cancer in line with FCTC and DPAS. Technical assistance is provided in implementing the hepatitis B immunisation and cervical cancer prevention programmes. WHO is involved in cancer control partnerships such as the Programme of Action on Cancer Therapy (PACT), aimed at strengthening diagnostic and treatment capacity of cancer in developing countries.

Technical support of WHO at the national level is being executed in close collaboration with the ministries of health, in line with long-term WHO country cooperation strategies, and focuses on strategic planning, capacity building, advocacy, networking and research. In support of the National Cancer Control Programme (NCCP), the WHO India Country Office provides technical support in the area of cancer surveillance (see the Atlas of Cancer in India, Figure 1); development of training manuals, guidelines and awareness materials; demonstration programmes for community-based cancer control; and capacity building of health personnel. It supports initiatives for pain relief and palliative care and facilitated oral morphine availability in India. The Country Office is supporting the revision of NCCP strategy to achieve an optimal mix of preventive, curative and palliative care and will continue to support the implementation and evaluation of comprehensive cancer control in India.

In Indonesia, WHO is helping to develop national policy and strategy on cancer prevention and control by bringing together policymakers, professionals and NGOs. It supports the development of hospital-based cancer registries in Jakarta and also has facilitated the development and use of guidelines for comprehensive cervical cancer prevention. In Myanmar, WHO support focuses on providing fellowships to various categories of health professionals in the areas of surveillance, prevention, early detection, effective treatment and palliative care. WHO collaborative work includes also development of information, education and communication (IEC) materials (Figure 2) and creating community awareness on early detection of cancer. Technical support to epidemiological research on cancer is also provided.

In Thailand, the WHO collaborative work includes assessment of exposure to occupational carcinogens, development of an occupational and environmental cancer surveillance system, networking of community health personnel and volunteers and strengthening of communities and local authorities to assess and tackle environmental threats. Also, in other Member States of the SEA Region, including Bangladesh, Bhutan, DPR Korea, Maldives and Sri Lanka, WHO country offices are providing technical support in development of NCCPs and in implementing specific cancer control activities.

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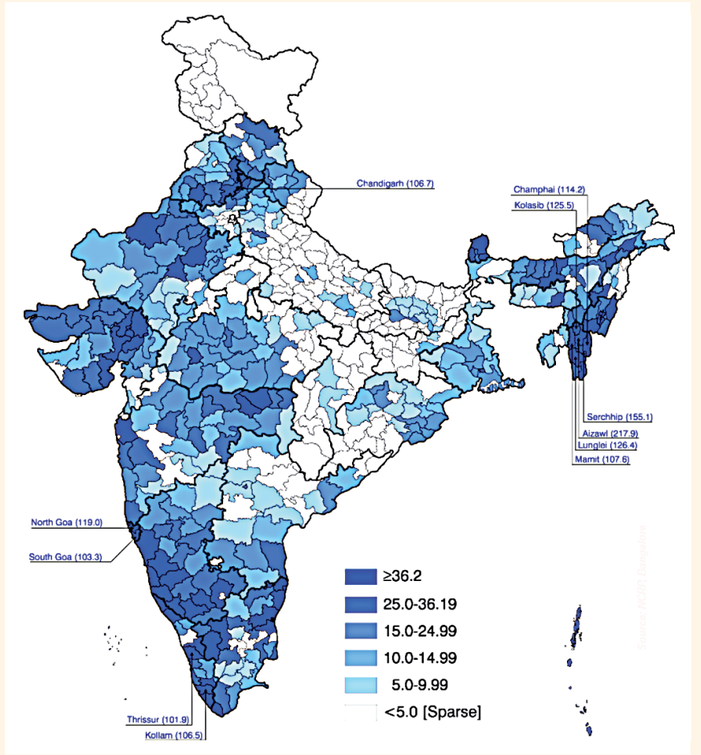

Figure 1. *Minimum incidence of all cancers in India (men)*
Source: Cancer Atlas (ICMR)

Figure 2. *IEC poster produced jointly by the Ministry of Health and WHO in Myanmar*

Area	Indicator	No. of countries (total 11)
Policy/programme	National health policy addresses cancer and other major NCDs	5
	National plan/ programme for cancer control	8
Infrastructure	Presence of a NCD unit or department in ministry of health	8
	Presence of national cancer reference centre	9
Legislation/regulation	Anti-tobacco	10
	Food and nutrition (related to NCDs)	5
Surveillance	Surveillance systems for major cancers	4
	Population- based cancer registries	3
	Hospital-based cancer registries	8
	NCD risk factor (STEPS) surveys conducted	9
Management	Availability of guidelines for cancer management	6
	Anti-neoplastic medicines accessible and affordable for low-income groups	2

Table 1. *Capacity of SEA Member countries to prevent and control cancer: select indicators*
Modified from "Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Capacity for noncommunicable disease prevention and control in countries of the South-East Asia Region: results of a 2006-2007 survey". SEA/RC60/9 -INF DOC1

Country/site	Current smokers (%)	Current consumers of alcohol (%)	Proportion (%) eating < 5 servings of F & V	Proportion (%) physically inactive	Proportion (%) overweight and obese
Bangladesh – R	25.3	NS	NR	NR	8.6
Bangladesh – U	21.9	NS	NR	NR	36.5
DPR Korea	31.1	NS	NS	NS	NR
India – R	17.8	26.4	84.6	10.0	13.3
India – U	15.7	20.7	81.4	23.8	39.4
Indonesia*	32.0	3.3	94.5	7.8	22.3
Maldives	22.7	NS	84.6	NR	44.2
Myanmar – R	24.4	18.0	98.2	3.5	23.3
Myanmar – U	22.9	18.4	99.1	7.3	36.5
Nepal	20.6	40.5	99.1	NR	16.5
Sri Lanka	19.6	40.5	96.8	14.9	28.8
Thailand*	18.6	40.1	85.0	NR	37.5
TOTAL (range)	**16-32**	**3-41**	**81-99**	**4-24**	**9-44**

Table 2. *Prevalence of select behavioural risk-factors in the SEA Region (age 25–64; both sexes)*
Source: "Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Risk factors: results from surveys using the STEPS approach." SEA/RC60/9 -INF DOC 2.
**Only national surveys, other are sub-national surveys; F & V – fruits and vegetables; NR – not reported; NS – not studied; R – rural; U – urban.*