

CHAPTER 1

Global perspectives surrounding cancer prevention and screening

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SUMMARY BOX

- The primary approach to cancer control will always be the provision of basic treatment and care. It is inconceivable that this would not be the case because of the immediacy of caring for a sick patient. Without treatment, increased awareness, early diagnosis, and screening are pointless.
- Globally, the biggest challenges and greatest successes come from tobacco control and vaccination (against hepatitis B virus and human papilloma virus).
- Although not currently associated with any concerted global action, obesity and alcohol control are the next most important challenges for cancer prevention.
- Cervical screening is the exemplar of a simple test with the potential to prevent the majority of a particular cancer. Even so, cervical cancer remains a major health problem in most low-income countries.
- Most other forms of cancer screening rely on early detection of invasive cancer and their widespread introduction has been restricted to countries with facilities for diagnosis and treatment.
- Screening for early cancers relies on expensive technologies; attempts to use cheap and simple tests have not been successful at a national population level.
- Undoubtedly, early diagnosis of cancer has a large impact on morbidity and survival (and subsequent mortality). There is evidence from developed countries that stage distribution has improved over time (more early-stage disease with a subsequent decline in late stage at presentation). Today, stage distribution in low- and middle-income countries lags behind that of high-income countries.
- Stage at diagnosis can be improved by awareness campaigns, but only when care is available, accessible, and affordable.

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Principles of cancer control strategy

Noncommunicable diseases, including cancer, are a current challenge to health services, and one which will increase with the ageing of the world population and changes in lifestyles [1]. The World Health Organization (WHO) strategy is to promote National Cancer Control Programmes (NCCPs) as the most effective approach for reducing the morbidity and mortality from cancer [2]. The development of an NCCP requires adequate information in order to evaluate the nature and magnitude of the cancer burden (and the availability of health-care infrastructure), as well as the potential impact of the various possible strategies in prevention, early diagnosis/screening, treatment, and palliative care.

Prevention of cancer has to be set within the context of prevention of other noncommunicable diseases, because they have many (but not all) risk factors in common, notably those that are lifestyle related, such as smoking, alcohol, diet, overweight/obesity, and lack of physical exercise. We do not, in this chapter, discuss biomedical approaches to prevention (medication, surgery), because globally they have no role at present.

Early diagnosis is a public and health professional awareness activity, to encourage people to recognize early signs of the cancer and to seek prompt medical attention. Screening involves encouraging asymptomatic individuals to undergo tests to detect early cancer, or precancerous states. Both early diagnosis and screening have to be set within an existing health infrastructure that provides adequate resources for the management of detected cancers (without which such programmes would be ineffective). Because of the considerable resources involved, population screening programmes should be undertaken only when the prevalence of the disease to be detected is high enough to justify the effort and costs of screening, and where resources (personnel, equipment, etc.) are sufficient to cover diagnosis, treatment, and follow-up of those with abnormal results.

Magnitude of the problem: Proportion of cancer globally attributable to preventable causes

Noncommunicable diseases accounted for about two-thirds of deaths occurring in the world in 2008 [1]. Considering cancer as a single group, the estimated 7.9 million deaths in that year constituted the leading cause of death (Figure 1.1). In 2012, the most commonly diagnosed cancers were lung cancer (13% of all cancers), breast cancer (11.9%), and colorectal cancer (9.7%); the most common causes of cancer death were lung cancer (19.4% of cancer deaths), liver cancer (9.1%), and stomach cancer (8.8%) [3]. Figure 1.2 shows the numbers of cases and deaths for the most common cancers for males and females.

According to Danaei et al. [4], the major environmental causes of cancer death (in 2001) were tobacco, alcohol, and low consumption of fruit and vegetables.

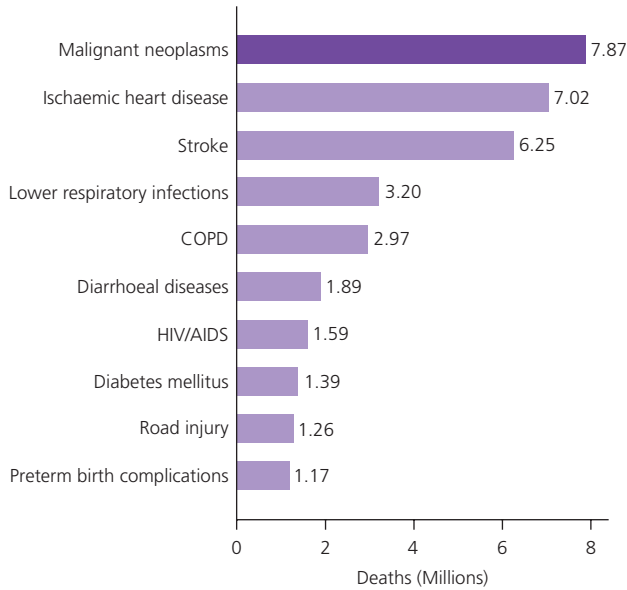


Figure 1.1 The estimated 7.9 million deaths attributed to cancer in comparison to other causes of death. COPD, chronic obstructive pulmonary disease. Source: Global Health Observatory Data Repository.

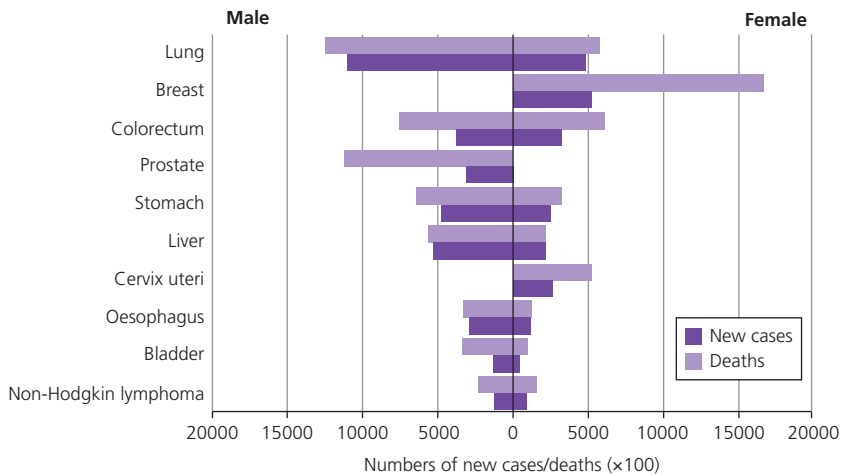


Figure 1.2 The most commonly diagnosed cancers in 2012 for males and for females.

Tobacco smoking is undoubtedly the most important preventable cause of cancer. As estimated by the WHO [5], tobacco was responsible for 22% of the deaths from cancer in 2004 (32% in men, 22% in women), with the major contribution (58% of cancer deaths) coming from lung cancer.

Second in importance in terms of preventable causes of cancer is infection. In 2008, it was estimated that about 16% of the global cancer burden (around 2 million cancers per year) was attributable to infectious agents [6]. The fraction is much larger in low-income than in high-income countries. Each of the three principal infectious agents – *Helicobacter pylori* (stomach cancer), human papilloma virus (HPV; ano-genital, especially cervical, and oropharyngeal cancer), and the hepatitis viruses HBV and HCV (liver cancer) – is responsible for approximately 5% of the global cancer burden. Much smaller fractions are due to Epstein-Barr virus (nasopharynx cancers and some lymphomas) and human herpes virus 8 (Kaposi sarcoma), as well as to parasites such as *Schistosoma haematobium* (liver cancer) and liver flukes (cholangiocarcinoma).

The International Agency for Research on Cancer (IARC) [7] considers that there is *sufficient evidence* that alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma), and female breast, and also that an association has been observed between alcohol consumption and cancer of the pancreas. The IARC estimated that alcohol was responsible for some 337 400 cancer deaths in 2010, 4.2% of all cancer deaths, with the largest contributions from cancers of the liver and oesophagus (about 23% of such deaths), breast, oral cavity, and colorectum (about 12% each) [7].

Approximately 2.8% of deaths worldwide are attributable to low fruit and vegetable consumption [8]; adequate consumption of fruit and vegetables reduces the risk for cancers of the oral cavity, oesophagus, stomach, and colorectum [9].

Dietary contaminants are a significant problem in some regions; for example aflatoxins, produced by moulds that contaminate cereals and nuts, cause liver cancer, especially in individuals infected with HBV. Aflatoxin has been estimated to have a causative role in 5–28% of all hepatocellular cancers [10].

In 2002, the IARC concluded that overweight and obesity are related to cancers of the colon, endometrium, kidney, and oesophagus (adenocarcinoma), as well as postmenopausal breast cancer. In addition, the report by the World Cancer Research Fund [11] considered that there was convincing evidence for an association with cancers of the pancreas and rectum, and a probable association with cancers of the gall bladder. Overweight and obesity are generally evaluated in terms of body mass index (BMI), with, in ‘western’ countries, a BMI of 25–29.9 kg/m² being considered overweight, and over 30 kg/m² obese. Using this definition, Renehan et al. [12] estimated that 5.7% of cancers in Europe in 2008 (3.2% of those in men, 8.6% in women) were caused by overweight/obesity, a figure which is considerably in excess of the 3% estimate (for 2004) for high-income countries by Danaei et al. [4].

Air pollution is known to increase the risk of respiratory (including lung cancer) and heart diseases. In recent years exposure levels have increased significantly in some parts of the world, particularly in rapidly industrializing countries with large populations. The most recent data indicate that in 2010, 223 000 deaths from lung cancer worldwide resulted from air pollution [13];

exposure to outdoor air pollution is also associated with an increased risk of bladder cancer [14].

The IARC has evaluated indoor emissions from household combustion of coal as carcinogenic to humans [7]. In their earlier assessment, Danaei et al. [4] estimated that 1% of lung cancers worldwide could be ascribed to this cause, but it would be a much larger fraction in China, where most such cases occur [15].

The IARC has classified 32 chemical or physical agents and 11 occupations and industries (for which the responsible agent is not specified) as associated with an increased risk of cancer. The most important are asbestos, diesel engine fumes, silica, solar radiation, and second-hand tobacco smoke. It is difficult to arrive at global estimates of cancers attributable to occupation, not least because the numbers of exposed persons in a given country may be totally unknown. Driscoll et al. [16] estimated that there were 102 000 deaths from lung cancer, 43 000 from mesothelioma, and 7000 from leukemia due to occupational carcinogens in 2000 (2.4% of cancer deaths). The total of all occupationally induced cancers would clearly be much greater – estimates for developed countries are in the range of 4–8% [7].

Primary prevention strategies globally

Population attributable fractions give an idea of the numbers (and percentages) of cancers that are, at least in theory, preventable. Almost all of those we have discussed have been the object of preventive efforts, ranging from public education and exhortation, to environmental modification and legislative action at a national or more local level. Globally, there are several well-defined strategies for reducing the burden of cancer.

Tobacco smoking

When the dangers of tobacco smoking became clear, and widely publicized, it was supposed that there would be a reduction in smoking among the public. However, it was soon realized that this was optimistic, and more complex approaches were needed to reduce smoking initiation and promote cessation. Tobacco control programmes are part of national health policy in many countries. Internationally, the WHO initiated a 'framework convention on tobacco control' (FCTC), which became a treaty, signed by member states, in 2003 [17]. By June 2013 there were 176 signatories to its legally binding provisions. These include the following:

Demand reduction

- Article 6. Price and tax measures to reduce the demand for tobacco.
- 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. Reduction measures concerning tobacco dependence and cessation.

Supply reduction

- Article 15. Illicit trade in tobacco products.
- Article 16. Sales to and by minors.
- Article 17. Provision of support for economically viable alternative activities.

The WHO FCTC also contains provisions for protecting public health policies from commercial and other vested interests in the tobacco industry.

Implementation of the FCTC is monitored by a regular review by the signatories, allowing them to share best practice and present a united, cohesive front against the tobacco industry.

Vaccination

Vaccines are available for two of the important cancer-causing infections: hepatitis B and Human Papilloma Virus (HPV).

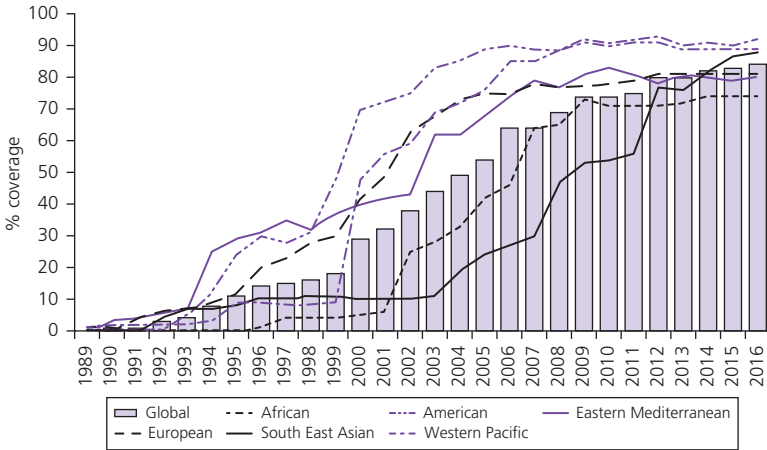
Hepatitis B virus (HBV)

HBV is transmitted by percutaneous and permucosal exposure to infected body fluids. The surface antigen of HBV (HBsAg) may be detected in serum 30–60 days following infection and may persist for widely variable periods of time, with some individuals becoming chronic carriers. The prevalence of HBsAg in the general population globally varies considerably: HBsAg prevalences of more than 8% are typical of highly endemic areas, prevalences of 2–7% are found in areas of intermediate endemicity, whereas in areas with low endemicity under 2% of the population is HBsAg positive. Effective vaccines against HBV have been available since the mid-1980s and immunization beginning at birth has been introduced into vaccination schedules in many countries (Figure 1.3). Vaccination results in a dramatic reduction of HBV transmission. This will result in a reduction of HBV-related chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). In Taiwan, where infant vaccination was introduced in 1984, there has been a marked reduction in the incidence of HCC in individuals born since that date, compared with preceding birth cohorts [19].

Human papilloma virus (HPV)

Randomized trials have shown the efficacy of two HPV vaccines in preventing infection with virus types 16 and 18 (responsible for about 70% of cervical cancer cases globally) and, more importantly, in preventing cervical intraepithelial neoplasia (CIN) 2 and 3 in females aged 15–25 years [8]. Current vaccines are purely prophylactic; they do not clear existing HPV infection or treat HPV-related disease. They have been approved and are in use in many countries. The primary target group is young adolescent girls (before the onset of sexual activity); current WHO recommendations [20] are for a two-dose schedule if vaccination is initiated

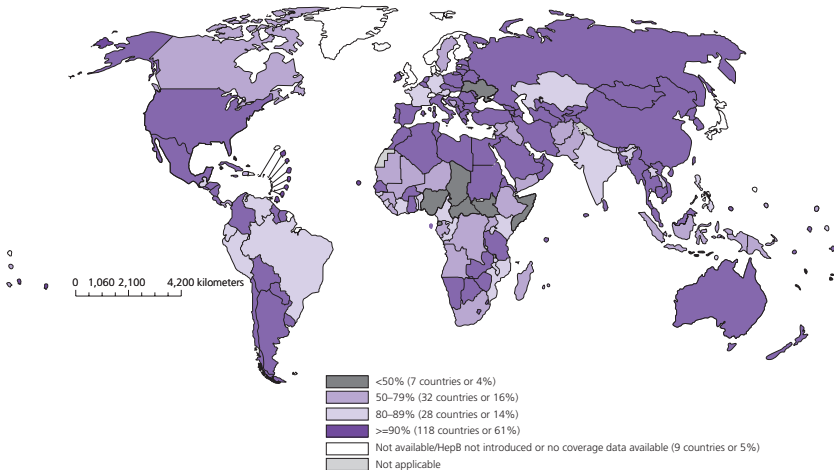
Global Immunization 1989–2016, 3rd dose of Hepatitis B (HepB3) coverage in infants global coverage at 84% in 2016



Source: WHO/UNICEF coverage estimates 2016 revision, July 2017. Immunization Vaccines and Biologicals, (IVB), World Health Organization. 194 WHO Member States. Date of slide: 26 July 2017.



Immunization coverage with HepB3 in infants, 2016



Source: WHO/UNICEF coverage estimates 2016 revision, July 2017. Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization. 194 WHO Member States. Date of slide: 24 July 2017.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2015. All rights reserved.



Figure 1.3 Prevalence of chronic hepatitis B virus infection among adults. Source: Ott 2012 [18]. Reproduced with permission of Elsevier. Note: This map shows the prevalence of chronic HBV infection among adults (aged 19–49 years) globally in 2005; because this analysis grouped countries together regionally, individual country prevalence may be higher or lower than reflected on the map.

prior to age 15 years and a three-dose schedule if immunization is initiated later, but many countries still recommend three doses for all ages.

Routine HPV vaccination has been introduced in many high-income countries (e.g. most of the European Union (EU) [21] and North America [22]), although coverage rates are lower than expected where vaccination is not school based. However, in low- and middle-income countries (where 86% of cervical cancer cases occur), vaccination has often been implemented, if at all, on a limited scale, frequently as demonstration and pilot projects, funded and operated by nongovernmental organizations (NGOs). Certainly, the challenges are greater and include, in addition to financial constraints, problems in reaching girls for two or three doses in settings where school attendance is low and/or irregular [23].

Other prevention programmes

Preventive strategies to reduce cancer incidence are present in many NCCPs, with the emphasis on the exposures most relevant locally. They may include programmes that aim to reduce overweight and obesity (e.g. through reducing consumption of refined sugars), promote exercise and a healthy diet, reduce alcohol consumption (especially by fiscal measures, or reducing access), and salt intake (voluntary or legislative action on the salt content of foods; the World Cancer Research Fund concluded that ‘salt is a probable cause of stomach cancer’ [24]). None has been the subject of international action like that taken for tobacco and infection.

One area where there is a strong international framework for action is in occupational health. The constituents of the International Labour Organization [25] draw up conventions which are legally binding treaties that may be ratified by member states. Ratifying countries commit to applying the convention in national law and reporting on its application at regular intervals. The conventions most relevant to cancer prevention are as follows:

- The Radiation Protection Convention, 1960 (No. 115), setting out basic requirements with a view to protecting workers against the risks associated with exposure to ionizing radiations.
- The Occupational Cancer Convention, 1974 (No. 139), which provides for the creation of policy to prevent the risks of occupational cancer caused by exposure to chemical and physical agents of various types present in the workplace.
- The Working Environment (Air Pollution, Noise and Vibration) Convention, 1977 (No. 148).
- The Asbestos Convention, 1986 (No. 162), indicating reasonable methods of reducing occupational exposure to asbestos to a minimum.
- The Chemicals Convention, 1990 (No. 170), providing for the adoption and implementation of a coherent policy on safety in the use of chemicals at work (their production, handling, storage, transport, and disposal).

Medication (tamoxifen or aromatase inhibitors for breast; aspirin for bowel) and prophylactic surgery (oophorectomy and/or mastectomy for *BRCA* carriers) as approaches to cancer prevention are not discussed here because of their limited scope globally.

Screening

On a global scale, of all the approaches to cancer control, screening is the least effective. The reasons for this are primarily organizational and monetary. Although screening by NGOs is widespread, there is minimal evidence regarding the effectiveness of these well-meaning interventions, and globally their impact has been minimal.

General principles

Medical screening is an approach to systematically identifying unrecognized disease. In cancer, screening can either be with the intention of identifying cancer early when it has a better chance of being cured, or with the intention of identifying precursor disease that can be treated, thereby preventing it from progressing to cancer.

There is no universally accepted definition of medical screening, but all definitions are based around offering a test to individuals who have not sought medical attention, to identify those who might benefit from further intervention [26]. By definition, testing individuals who consult because of symptoms (no matter how vague) is not screening and will be discussed in the section on early diagnosis.

In 1968, the WHO published the ‘Wilson and Jungner criteria’ for introducing medical screening [27]:

- 1 The condition should be an important health problem.
- 2 There should be a treatment for the condition.
- 3 Facilities for diagnosis and treatment should be available.
- 4 There should be a latent stage of the disease.
- 5 There should be a test or examination for the condition.
- 6 The test should be acceptable to the population.
- 7 The natural history of the disease should be adequately understood.
- 8 There should be an agreed policy on whom to treat.
- 9 The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
- 10 Case-finding should be a continuous process, not just a ‘once and for all’ project.

Although the criteria have been debated and modified, they are still widely accepted as sensible. For screening aiming at early diagnosis, it is essential that early-stage disease should have much lower case fatality than late-stage. When screening for cancer precursors, one requires that an affordable, acceptable, and effective treatment of the precursor exists.

When most people think about screening they focus on the screening test, but the existence of an accurate test is just one requirement of a successful screening programme. One needs to consider the whole process, from identifying and contacting the target population, through the screening contact (e.g. obtaining a sample or an image), processing that material (e.g. laboratory testing), communicating the result, arranging triage of those who screen positive, and treatment for those with disease. For many screening modalities, a single screen provides only limited protection and it is necessary to arrange for individuals to be rescreened after a

suitable interval (e.g. every three years). All these activities need to be quality assured. The history of screening is plagued by stories such as cervical smears being collected using a finger rather than a spatula; slides being looked at by an inexperienced nonspecialist in a poorly lit room; results not being communicated to the individual screened (or worse, the wrong result being communicated); lack of fail-safe measures to ensure that those in need of treatment receive it; and inadequate treatment that causes more harm than good. It should be clear from this discussion that screening is a multidisciplinary activity that should involve a variety of health-care professionals. All these activities need to be coordinated and that requires considerable infrastructure. Without such an infrastructure, even the best screening test will have little or no impact in reducing morbidity or mortality.

As with all medical interventions, the most robust evidence for the efficacy of screening comes from randomized controlled trials in which it is demonstrated that those offered screening have a lower incidence of or mortality from a particular type of cancer. Nevertheless, it will usually be necessary first to show an impact on surrogate end-points. Occasionally the evidence in favour of screening from nonrandomized trials will be so great that there will no longer be equipoise between screening and no screening.

One surrogate that is often discussed in the context of cancer screening is 'stage shift'. Although a shift in stage is not proof that screening is effective, it is highly unlikely that screening will lead to a reduction in mortality if it does not cause a shift in stage. When claiming a stage shift, many studies simply show that the proportion of cancers diagnosed at early stage has increased. While this is a necessary first step, it is much less powerful than showing that the absolute number of advanced-stage cancers has been decreased. Almost inevitably, early diagnosis through screening will lead to an (initial) increase in early cancers. However, in order for screening to reduce mortality, it must lead to a reduction in advanced cancers.

Another surrogate end-point is survival. If screening for occult cancer does not lead to an improvement in survival post diagnosis, it cannot possibly have an impact on mortality. However, a survival benefit alone is not enough, because screening will create a *lead-time bias* and screen-detected cancers will also have a *length bias* in their survival.

Most cancer screening is offered periodically. The interval between screens should depend on the natural history of the cancer, but will largely come down to cost and what a society is willing to spend for a given improvement in life expectancy or health (often measured in quality-adjusted life years or QALYs). Typically the costs of all screens are very similar, but the benefit from a second screen will be less than that of the first. The first time individuals are screened there will be a lot of occult disease (whether that be precancer or cancer) in the population. The next day, the only undiagnosed disease will be disease that was missed by screening. With time, and no further screening, there will be more incident occult disease. Eventually the prevalence of occult disease will be the same as in an unscreened population. At that point, the benefit of repeat screening should be equal to that of initial screening. The situation may be more complicated,

however, because the benefit of screening (with a given test and treatment) depends not only on the prevalence of occult disease, but also on its progressive potential and the likelihood of early intervention being of benefit.

Another cost-effectiveness issue is how long one must wait before benefiting from screening. If screening detects (and then treats) precancer that would on average take 15 years to become invasive and a further 5 years to become fatal, then there is little point in screening someone whose residual life expectancy is only 10 years.

Existing screening options

Specific screening tests will be considered in subsequent chapters. Here, we emphasize the difference between low-tech tests that may require frequent use and high-tech tests that are often expensive and require considerable infrastructure, but can be used infrequently. There are two reasons why low-tech tests often need to be used frequently in order to have a substantial impact. The first is that they may lack sensitivity. That is, on a given test, a theoretically screen-detectable neoplasia may be missed. The second is that the low-tech test may often only be able to detect disease fairly late in its occult natural history. By contrast, one would hope that a high-tech test would be sensitive to very early changes.

The standard method for breast cancer screening is mammography. It is also the only method that has been shown to reduce mortality in randomized controlled trials. Although mammographic screening is standard in many developed countries, other screening modalities which do not require X-ray or other imaging continue to be studied in low- and middle-income countries. Where the infrastructure for mammography is lacking, there is much interest in breast examination performed by a trained health worker. Studies of self-examination have all been negative [28, 29], but many organizations campaign for women to be 'breast aware', which aims at early diagnosis rather than formal self-screening (see the next section). Trials of clinical breast examination are under way in India [30], but whereas such screening can certainly lead to the early diagnosis of breast cancer, it has not yet been demonstrated that it can have an impact on mortality. The Canadian Breast Screening Trials found that physical examination could lead to cancers being screen detected, but also showed that many mammographically detected breast cancers were not palpable. Since, however, they found no mortality benefit of mammography compared to clinical examination, the researchers concluded that the nonpalpable cancers detected by mammography were overdiagnosed. That is, those cancers were indolent and would not have been fatal even in the absence of treatment. A large cluster randomized trial of clinical breast examination (CBE) in the Philippines concluded:

Although CBE undertaken by health workers seems to offer a cost-effective approach to reducing mortality, the sensitivity of the screening program in the real context was low. Moreover, in this relatively well-educated population, cultural and logistic barriers to seeking diagnosis and treatment persist and need to be addressed before any screening program is introduced. [31]

Cervical screening has seen an explosion of available tests, after many years in which screening was synonymous with the Pap smear. Molecular testing for HPV DNA has become the norm in several developed countries, and visual inspection after application of acetic acid (VIA) is widespread in several low-income countries. Whereas cervical cytology (Pap smear) is subjective and requires repeat screening at relatively short intervals because of poor sensitivity, HPV testing is objective and highly sensitive. Additionally, because HPV infection is the first step in cervical carcinogenesis, a process that typically takes many years, it is sufficient to screen at extended intervals. The downside of HPV testing is that it is less specific (than cytology) for high-grade CIN (the precursor lesion that is treated if found). The majority of women with a cervical HPV would never develop cervical cancer even with no intervention. A drawback of both cytology and HPV testing is that the results are not instant – the collected samples are analysed later in a laboratory. VIA is offered as a simple alternative where facilities are limited and the ability to provide an instant result is considered important. Although a trained nurse can carry out VIA with a couch, a speculum, a simple light source, some acetic acid, and a pair of examination gloves, the results can be very variable. Several studies have shown good sensitivity and specificity for VIA, but it is difficult to quality assure and there has been concern regarding the lack of an independent gold standard to assess sensitivity in some studies. Nevertheless, it is unclear which would be more cost-effective, twice-in-a-lifetime HPV testing (at ages 30 and 45, say) or three-yearly VIA from ages 25 to 60.

The US Preventive Services Task Force recommends colorectal cancer screening for men and women aged 50–75 using high-sensitivity annual fecal occult blood testing (FOBT), five-yearly flexible sigmoidoscopy (with three-yearly FOBT), or ten-yearly colonoscopy. By contrast, the UK National Health Service (NHS) Bowel Cancer Screening Programme offers two-yearly FOBT to men and women aged 60–74 and is piloting the offer of flexible sigmoidoscopy at age 55. Colonoscopy is not offered for general population screening in the UK. The reason that the screening interval (once in a lifetime in the UK) with endoscopy is much longer than with FOBT is because FOBT works primarily by detecting cancer early, whereas during endoscopy all visible polyps are removed, thereby reducing the risk of developing cancer over the next decade. Since flexible sigmoidoscopy only examines the distal bowel, it is often combined with FOBT in order to provide protection against mortality from proximal tumors. Colonoscopy is a much more invasive and expensive procedure compared to sigmoidoscopy, which is why it is only justified in an individual at high risk, either because of a strong family history or a positive result on a simpler screening test. Nevertheless, colonoscopy is still used for bowel screening in some high-income countries.

Screening for other cancer sites is practised in various countries, but is not universally accepted as being effective or cost-effective. Oral screening is mostly by visual inspection of the oral cavity. It has been studied in India [32, 33] and Cuba [34]. The Indian study did not find a reduction in mortality from oral cancer overall, but widely reported a reduction in smokers and drinkers. Undoubtedly,

quality assurance is an issue with simple visual inspection. In developed countries there is interest in enhancing visual inspection through use of stains such as acetic acid and devices such as the VELscope Vx, which relies on differential fluorescence of precancerous lesions.

Although incidence rates are declining, gastric cancer remains common in many parts of the world (especially East and Central Asia and South America), and the prognosis when clinically diagnosed is relatively poor. Screening for early disease has been introduced in Japan (barium contrast imaging) and Korea (barium swallow or endoscopy every two years to individuals aged 40 years and older). However, with increasing evidence that treatment of established *H. pylori* infection (by a combination of antibiotics and proton pump inhibitor drugs) can reduce the risk of the disease, there is more interest in programmes of screening for, and treatment of, such infection. At least in relatively affluent countries, these programmes may be cost effective. Currently it is suggested that implementing such programmes should be based on 'local considerations of disease burden, other health priorities, and cost-effectiveness analyses' [35].

Early studies of lung screening using X-rays resulted in downstaging of lung cancer and improved survival, but had no impact on mortality [36]. More recent studies using spiral computed tomography (CT) scanning have shown that this form of screening in individuals at high risk of lung cancer can be effective in reducing lung cancer mortality [37]. Lung screening is still not widely used anywhere and it seems unlikely that it will have a role in cancer control in low- and middle-income countries due to the lack of infrastructure.

Prostate cancer screening remains perhaps the most controversial of screening programmes. While prostate-specific antigen (PSA) testing undoubtedly leads to the diagnosis of occult prostate cancer, many of those cancers are indolent, and many men with screen-detected prostate cancer would have died from other causes before their prostate cancer became symptomatic. Nevertheless, the European Randomized Study of Screening for Prostate Cancer (ERSPC) has shown that screening using PSA testing results in a reduction in mortality from prostate cancer [38]. Of course, it is not the overdiagnosis per se that is so bad, but the side effects of the treatment offered to men with screen-detected cancers.

The harms of screening

Like all medical interventions, screening has the potential to do harm, and it is important to ensure that the benefits exceed the harms before offering screening. The imperative to consider this balance is perhaps even greater for screening than it is for treatment of a medical problem for which the patient has sought help.

The most obvious harm of screening can come from the test itself, but this is very rare, because screening tests with a substantial risk of harm are not used. Harms are more often associated with the work-up of screen-positive individuals. False-positive screening test results are almost always associated with a small amount of harm coming both from anxiety (which will typically resolve after a

negative work-up) and the invasive nature of the work-up. In the low-dose CT arm of the National Lung Screening Trial, only 3.8% of individuals with a positive screening had lung cancer; however, the majority of those with a positive screen did not have a biopsy, and of those with a biopsy 53% had cancer [39]. It is also possible that a false-negative test can have a negative impact by providing false reassurance for an individual who subsequently develops symptoms. Such a negative impact can be minimized by providing appropriate information regarding screening with messages such as 'low risk not no risk'.

Targeted screening

From a public health perspective, the greatest gain comes from offering screening to the population at large, but the cost-effectiveness of screening may be improved by offering it only to high-risk groups. Such targeted screening may be offered to groups identified by occupational exposure or to individuals with a strong family history of a particular cancer. Studying the effectiveness of screening in a group already identified as being at very high risk presents a challenge. Globally such targeted screening is of limited importance.

The biggest hurdles to cancer prevention and early diagnosis in low- and middle-income countries relate to social norms and lack of infrastructure rather than the lack of a screening test. As the Breast Health Global Initiative concluded:

The biggest challenges identified for low-income countries were little community awareness that breast cancer is treatable, inadequate advanced pathology services for diagnosis and staging, and fragmented treatment options, especially for the administration of radiotherapy and the full range of systemic treatments. The biggest challenges identified for middle-resource countries were the establishment and maintenance of data registries, the coordination of multidisciplinary centers of excellence with broad outreach programs to provide community access to cancer diagnosis and treatment, and the resource-appropriate prioritization of breast cancer control programs within the framework of existing, functional health-care systems. [40]

Early diagnosis

Historical importance: Reasons for late presentation

The rationale for early diagnosis is simple: earlier diagnosis improves outcome. Late diagnosis of cancer is thought to relate to inadequate public awareness of cancer signs and symptoms, and barriers (perceived or real) to presentation and diagnosis in the health system.

Many studies have investigated factors related to delayed presentation of cancer patients. Typically, these include demographic factors (age, socio-economic status) as well as disease-related factors (symptoms/signs) [41], and more difficult to define psychological and personality factors [42].

Research in the UK found that (in 2012) the public fear cancer and are largely unwilling to enter a conversation about early diagnosis or vigilance for potential cancer symptoms, and that this is because they feel that there is little to be gained

by doing so. Many people see cancer wholly negatively: cure is believed to be unlikely and treatment perceived to be as bad as the disease itself. Individuals likely to present late were characterized as follows:

- Live for Today's
- Unconfident Fatalists
- Balanced Compensators
- Health Conscious Realists
- Hedonistic Immortals.

Approaches to promote early presentation generally aim to increase awareness of the significance of cancer symptoms. A well-known example is the use of the American Cancer Society's seven warning signs (**C**hange in bowel or bladder habits; **A** sore that does not heal; **U**nusual bleeding or discharge; **T**hickening or lump in the breast, testicles, or elsewhere; **I**ndigestion or difficulty swallowing; **O**bvious change in the size, colour, shape, or thickness of a wart, mole, or mouth sore; and **N**agging cough or hoarseness).

Public awareness of the symptoms of cancer is not enough. Early diagnosis requires prompt progression along a pathway from recognition of symptoms through presentation to primary care and general practitioner (GP) referral, to secondary care and prompt diagnosis. The role of primary care delays in late diagnosis globally is unknown, but undoubtedly GPs face a difficult challenge in differentiating between individuals whose vague symptoms are caused by an undiagnosed cancer and the vast majority of their patients. Simple triage tests that can be offered in primary care are desperately needed.

Targeted screening based on nonspecific symptoms

The use of a 'screening test' in those with minor symptoms with the aim of diagnosing cancer while it is treatable by surgery alone (or surgery plus basic radiotherapy) is not screening, because the approach targets symptomatic individuals. The idea is to take a cheap and simple test and to use it in individuals whose risk of having an undiagnosed cancer is low but not negligible. Such an approach has much to offer globally. Currently the only example of such an approach that we know of is the use of PSA testing in men with urinary symptoms. The potential does however exist for offering mammography to women with breast lumps, change in appearance, or discharge from the breast; cervical cytology for women with irregular bleeding or vaginal discharge; and FOBT for middle-aged and elderly adults with persistent change in bowel habits. Such testing should be used to rule in further investigations, not to rule out cancer.

Conclusion

The proportion of cancers attributable to environmental carcinogens (including those in cigarette smoke) and modifiable behaviour globally is substantial, and without concerted efforts in many countries would be even higher. Tobacco control and vaccination are essential components of cancer prevention globally. Increasingly obesity and alcohol control also require coordinated action.

Screening, whether for the identification of precursor disease or the early diagnosis of occult cancer, will most likely always play a relatively minor role in cancer prevention globally, even though it has had substantial impact on specific cancers in many high-income countries. Screening inherently requires a quality-managed system and needs to be continuously monitored to ensure that it remains effective with minimal harms.

The use of drugs such as aspirin and tamoxifen to reduce cancer incidence in high-risk individuals is not discussed in this chapter. Additionally, the use of prophylactic surgery in those at very high risk of a particular cancer is not considered as it is felt to be of little importance globally.

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