Cancer screening

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Abstract

Cancer screening is a source of much debate. At the interface between public health, specialist care, economics and public health policy, it creates tensions between professional groups, politicians, the media and the public. A screening test may be cheap but applying it to a population (with rigorous quality control and effective downstream processing of patients with abnormal results) creates a huge workload and cost. Screening can also have profound psychological effects. People with false-positive results require investigation yet are usually eventually found not to have cancer. Unless screening can be shown to reduce mortality from specific cancers, the resources used are better spent on improving care, and this has led to disparities in screening recommendations between countries. Advances in understanding the genetic basis of cancer are likely to provide new approaches to cancer risk assessment and new challenges for developing screening strategies, by risk-banding populations based on polymorphisms in low-penetrance cancer risk genes. The American Cancer Society guidelines for cancer screening, reviewed annually, represent a global gold standard that is difficult to emulate in most healthcare economies because of cost and under-capacity for downstream processing of abnormal findings. Tailoring cancer screening recommendations to a country's health economy is an essential public health intervention.

Keywords Breast; cancer detection; cervical cancer; colon; lung; prostate

Key points

- Patient choice is increasingly used when the overall benefits of screening are uncertain (e.g. mammography in 40—50-year-olds, prostate-specific antigen (PSA) for prostate cancer, ultrasonography and CA125 concentrations for ovarian cancer and low-dose computed tomography (CT) scanning for lung cancer)
- Partial automation of image analysis will reduce the cost of image analysis in both cytology and radiographic interpretation
- Low-penetrance cancer risk genes are being discovered for several common cancers and will soon allow the effective risk-banding of populations
- New imaging technology with lower radiation risk is becoming available to assess patients with equivocal screen-detected abnormalities
- New private-sector providers of health and genetic screening are emerging and will reduce costs and increase consumerism in this area. Suppliers of boutique clinics for the 'worried well' are being created, offering a wide range of screening tests including whole-body CT scanning in asymptomatic individuals

Introduction

Cancer screening seems so logical to all healthcare workers and patients alike. We all know that early cancer is curable in the majority of cases and later stage disease is not. So, picking up cancer before a patient has symptoms would seem ideal. The problem is that none of the tests available are perfect. And the resources spent on screening programmes may well be better spent on speeding up appropriate referral of symptomatic patients. Here, we will consider the advantages of screening along with the downside for the common cancers.

The long-awaited publication of the independent review on national cancer screening programmes in England makes grim reading.[1] Two disastrous information technology failures — one in breast cancer and the other in cervical cancer — were revealed in 2018. Thousands of patients were simply deleted from the computer database by accident. New technologies such as the faecal immunochemical test (FIT) and once-only colonoscopy programmes are still not fully rolled out even though plans were unveiled 8 years ago. And although much talked about, artificial intelligence currently plays little part in data interpretation except in research settings. Crucially, the consumer uptake of each of the three major programmes — breast, colon and cervix — is in decline, especially in deprived areas. The impact of coronavirus disease (COVID-19) has been severe and services are only just beginning to clear the huge backlog generated.[2]

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Definitions

Cancer screening is defined as the systematic application of a test to individuals who have not sought medical attention because of symptoms. It can be opportunistic (offered to patients consulting their doctor for another reason) or population-based (covering a predefined age range, with elaborate call and recall systems). Britain's NHS has rightly concentrated on the latter, allowing it to be at the global forefront of population screening procedures. The risk of dying from a cancer always increases with its degree of spread or stage. The aim of screening is to detect cancer in its early, asymptomatic phase. The problem is that many screening tests are relatively crude, and cancers can have metastasized before they are detected by screening.

Sensitivity varies between tests. A 100% sensitive test detects all cancers in the screened population. The most rigorous means of calculating sensitivity is to determine the proportion of expected cancers not presenting as interval cases between screens. Good cancer registration is essential when making this calculation.

Specificity is the proportion of negative results produced by a test in individuals without neoplasia. A 100% specific test gives

no false-positive results. Investigation of patients without cancer is a major factor in the cost of screening.

Advantages and disadvantages of screening

The advantages and disadvantages of screening (Table 1) must be considered carefully and vary between cancers and tests. The three main problems in assessing the benefit of any screening test for cancer — lead-time bias, length bias and selection bias — all impair the effectiveness of screening as a method of reducing cancer mortality:

- **Lead-time bias** advances the diagnosis but does not prolong survival, for example when the disease has already metastasized but the primary tumour is still small. Individuals die at the same time as if the disease had not been detected early.
- **Length bias** results in the diagnosis of less aggressive tumours. Rapidly growing cancers with a poorer prognosis present in the screening interval, reducing the value of the screening process.
- **Selection bias** occurs even in the best-organized healthcare systems. Worried but healthy individuals (who would present early with cancer symptoms) comply with screening programmes obsessionally, whereas less well-educated and socially disadvantaged individuals do not. In the UK, compliance with the NHS breast cancer screening programme varies between communities depending on relative deprivation, ethnic mix and degree of social exclusion.

Developing a screening programme

Rational decision-making about cancer screening requires a detailed analysis of factors that can vary between populations:

- The cancer should be common, and its natural history properly understood. This enables a realistic prediction of the proposed test's likely value.
- The test should be effective (high sensitivity and specificity) and acceptable to the population. Cervical smears are difficult to perform in many Islamic countries, where women prefer not to undergo vaginal examination, and the take-up rate for colonoscopy is low in asymptomatic individuals because it is uncomfortable and sometimes unpleasant.
- The healthcare system must be able to cope with patients who produce positive results and require investigation. This can be a particular problem at the start of a population-based study.
- Ultimately, screening must improve the survival rate in a randomized controlled setting.

The natural history of many cancers (including incidence and mortality) can change over time for reasons that are poorly understood and lead to increasing overdiagnosis in cancer screening. In Europe, the incidence of stomach cancer has decreased dramatically over recent few decades; however, breast cancer deaths reached a peak in the UK in 1989 and have decreased slightly each year since, associated with earlier stage at presentation, better care pathways with increased personalization and a significant increase in ductal carcinoma-*in-situ*.

Outside pressures

Well-meaning lobby groups often exercise political pressure to implement screening programmes (even when their effectiveness is undemonstrated), and manufacturers of equipment or suppliers of reagents can exercise commercial pressure. In fee-for-service-based provider systems such as the USA, there is a huge financial inducement for doctors to screen and investigate, because doing nothing simply earns no money.

The launch of the NHS breast screening service by the UK government in 1989 was viewed by many as a pre-election vote-winning exercise rather than a rational public health intervention. There are now similar pressures to introduce prostate cancer screening, although uncertainty remains about the management of men with slightly elevated concentrations of prostate-specific antigen (PSA; see below). Primary care is a great advocate for screening as a means of disease prevention. Breast screening has led to early diagnoses, as has the cervical screening programme.

Guidelines

Many groups (government, medical charities, health-maintenance organizations, professional bodies) have produced their own cancer screening guidelines. These vary widely between countries, reflecting bias in interpretation of evidence and cultural values in the practice of medicine; for example, annual PSA testing and digital rectal examination in men >50 years of age are recommended by the American Cancer Society (ACS) but not advocated in most other countries.[3] The USA carries out more cancer screening on populations that can afford it, through either insurance or direct payment, than any other country. Table 2 compares

Advantages and disadvantages of screening

Advantages	Disadvantages
• Better outcome	• Longer morbidity if prognosis is unaltered
• Less radical therapy needed	• Over-treatment of borderline abnormalities
• Reassurance for individuals with negative results	• False reassurance for those with false-negative results
• Psychological benefit to population	• Unnecessary investigation of false-positive results
• Attractive to politicians	• Risks of screening test and investigations
• Savings because therapy is less complex	• Resource costs of screening system

Table 1

Comparison of ACS and UK Department of Health and Social Care guidelines in 2010 for common cancers

	USA	UK
Breast	40+ years Yearly mammogram	47–73 years 3-yearly mammogram
Colon	50+ years Yearly FOBT 5-yearly sigmoidoscopy	60+ years One-off FOBT
Prostate	50+ years Yearly PSA	50+ years Patient choice
Lung	None	None
Cervix	18–70 years 2-yearly smear	25–50 years 3-yearly smear 50+ years 5-yearly smear

FOBT, faecal occult blood testing.

Table 2

the current ACS guidelines with those of the UK Department of Health and Social Care.

Developing countries

The incidence of a particular cancer in a particular country and the economics of screening must be considered carefully – the cost of the technology required must correspond with the gain. Low-cost, direct-inspection techniques for oral and cervical cancer by non-professional health workers seem attractive for achieving tumour downstaging and hence better survival results; however, the overall effectiveness of cervicoscopy programmes in India and China has been surprisingly poor. It remains to be seen whether intravital staining with acetic acid can enhance specificity at little extra cost.

A major cost in instituting any screening procedure is in informing the public and then developing the logistics, often under difficult geographical conditions. Cultural barriers can be insurmountable without better education, particularly of girls, who as mothers will become responsible for family health. Low-technology tests have low specificities; as a result, hard-pressed secondary care facilities are inundated with patients with non-life-threatening abnormalities.

Detailed field assessment, preferably in a randomized setting, is essential before firm recommendations can be made, but political factors often interfere with this. The well-meaning charitable donation of second-hand mammography units to some African countries has led to a haphazard introduction of breast screening in populations where the incidence of breast cancer is low and there are few resources to deal with abnormal results.

Assessing the benefits of screening programmes

The ultimate measure of success in a screening programme is a demonstrable reduction in mortality in the screened population. However, this needs large numbers of individuals, and at least 10 years' assessment for most of the common cancers.

Although randomized studies can show conclusive benefit, it must be remembered that the expertise and professional enthusiasm available to a study population can be considerably greater than that achievable under subsequent field conditions. Quality of mammography interpretation and investigation of breast abnormalities are good examples and may explain the relatively disappointing results of breast screening in practice. Case-control studies using age-matched individuals from the same population and non-randomized comparisons between areas providing and not providing screening can give useful indications but are not as conclusive as randomized trials.

Surrogate measures of effectiveness can be used to assess a programme with relatively small numbers of patients soon after its implementation (Table 3), but are insufficient to prove that screening saves lives:

- When a population is first screened, a higher than expected incidence of cancer should be seen because screening is detecting cancer that would not present with symptoms for several years. Subsequent rounds of screening are less productive.
- Tumour down-staging is a second measure of impact. An increase in early-stage cancer detection and, consequently, a reduction in advanced disease are expected over 3–5 years.
- The third, short-term evaluation is a comparison of the survival of screen-detected patients with those presenting symptomatically.

Success in terms of these three indices is not necessarily translated into a useful screening programme. In the 1970s, a study of routine chest radiography and sputum cytology to detect lung cancer showed a 5-year survival of 40% in screen-detected patients, compared with an overall figure of 5%, but reduced mortality from lung cancer has not been seen in large populations.

Specific screening programmes

Screening programmes have been investigated in a wide range of cancers. It is vital that good evidence of mortality reduction is obtained before such tests are adopted on a population basis.

Cervical cancer

Cervical cytology reduces the incidence of and mortality from cervical cancer. Dyskaryosis and cervical intraepithelial neoplasia are early markers of malignancy, identifying a group of women in whom more intense local treatment and subsequent surveillance are required. In many countries, the incidence of cervical cancer was decreasing before the introduction of screening, but the rate of decrease has been significantly greater in countries with population-based screening programmes. The test is cheap, safe and usually effective, but depends on the skills

Methods used to assess screening programmes

- Increase in cancer yield
- Shift in stage distribution
- Better survival in screen-detected patients
- Better survival after introduction of screening
- Case-control studies
- Non-randomized area comparison
- Randomized controlled trial of screening

Table 3

of large numbers of screening cytologists who are relatively poorly paid and often demotivated, which has led to errors. Computer scanning has proved difficult to implement.

New technologies, including liquid-based cytology, thin-layer methods and human papillomavirus (HPV) DNA hybrid capture analysis, are beginning to increase specificity. Many populations with a high incidence of cervical cancer exhibit a high prevalence of certain HPV subtypes, and screening for HPV DNA by polymerase chain reaction analysis can be valuable in identifying high-risk women. Clinical trials of HPV vaccines are underway and may further reduce the incidence of cervical cancer.

In 2003, the UK National Institute for Health and Care Excellence issued guidelines to the health service on the wide implementation of liquid-based cytology. This has led to a greater centralization of cytology services with more rigid quality control. It has also stimulated interest in automated pre-screening of samples by computer image analysis. All women aged 25–64 years are eligible for free cervical screening every 3–5 years. Considering evidence published in 2003, the NHS cervical screening programme offers screening at different intervals depending on age. This means women are provided with a more targeted and effective screening programme. The recommended frequency of screening by age is:

- 25 years – first invitation
- 25–49 years – 3-yearly
- 50–64 years – 5-yearly
- ≥65 years – only those who have not been screened since age 50 or have had recent abnormal tests.

Breast cancer

More work has been undertaken on screening for breast cancer than any other cancer.[3] Many randomized controlled studies, case-control studies and geographical area comparisons demonstrate its benefit. In the UK NHS Breast Screening Programme, 75% of women aged 50–64 years invited for screening in 2002 were tested (1.2 million individuals) and almost 7000 cancers were detected – a yield of 0.006%. A well-organized quality control process is established, and breast surgeons have been meticulous in collecting data and making them public. Quality standards have been set for various components of the programme and an annual review is produced.

The NHS breast screening programme provides free breast screening every 3 years for all women aged ≥50 years. Because the programme is a rolling one that invites women from general practices in turn, not every woman is given an invitation as soon as she is 50, but she will receive her first invitation before her 53rd birthday. The programme is now phasing in an extension of the age range of eligibility for breast screening to 47–70 years; this started in 2010 and is now nearly complete.

In September 2000, research was published demonstrating that the NHS Breast Screening Programme had lowered mortality rates from breast cancer in the 55–69-year age group. In 2010, research demonstrated that the benefit of mammographic screening in terms of lives saved is greater than the harm in terms of overdiagnosis. Between 2 and 2.5 lives are saved for every overdiagnosed case.

There is no doubt that the UK Breast Screening Programme saves lives, but it is difficult to assess the true cost per life saved; estimates range from £250,000 to £1.3 million. Critics of the programme want to see the money spent on ensuring the application of best practice once a diagnosis has been made. A balanced view would be to continue with screening but to ensure that systems are established to deal with all patients effectively, however they present.

In developing countries, 80% of patients with breast cancer present with advanced and often fungating disease. Public and professional education and effective referral networks for simple basic surgery are more effective than mammography. There is no evidence that formal teaching of regular breast self-examination has any impact on mortality. The future of mammography is to develop suitable interpretation programmes based on artificial intelligence.[4]

Lung cancer

The overall 5-year survival in lung cancer is about 10%, even with optimal care. Randomized studies have failed to demonstrate any reduction in mortality with screening by chest radiography and sputum cytology. Trials of low-dose spiral computed tomography (CT) screening in heavy smokers have shown that patients with screen-detected cancers have better outcomes. However, many of the extra cancers picked up by screening would probably have never caused clinical disease, while the most aggressive tumours have already metastasized at the time of screening.

Colorectal cancer

Symptomatic cancer presents with symptoms of intestinal obstruction or rectal bleeding and consequent anaemia. Small tumours that have not invaded the muscle coat of the colon are easier to cure than those that have done so (the basis of the Dukes staging system). In many individuals, carcinoma evolves from adenomatous polyps, even when there is no family history; thus, identification and endoscopic removal of polyps seems reasonable.

Increased yield and fewer patients presenting with advanced-stage disease have been demonstrated with both faecal occult blood tests (FOBTs) and colonoscopy, but the survival benefit is less certain.[5] About 10% of patients with colorectal cancer have a family history of the disease and, because their relatives are at increased risk, genetic testing can form part of a more intensive screening programme. Better technology might improve specificity. Detection of abnormal DNA fragments in stool combined with virtual colonoscopy using electron beam CT may revolutionize the early detection of colorectal cancer without the need for endoscopy.

The NHS Bowel Cancer Screening Programme offers screening every 2 years to all men and women aged 60–69 years. People >70 years old can request a screening kit by calling a freephone helpline. NHS Digital runs a single Bowel Cancer Screening System for England that maintains organization-related information, manages the lists of people eligible for screening, sends invitations and manages appointments, sends out test kits, records test results and provides operational and strategic reports.

A UK programme for colorectal cancer screening has been implemented for people aged 60–69 years based on faecal occult blood sent through the post. The FIT uses specific antibodies to detect human blood in the stool; it is more definitive for indicating colorectal cancer than other types of stool tests such as the

qualitative guaiac FOBT. Guaiac tests can result in false-positive results from other types of blood that can be in the digestive system, such as from red meat. The FIT is both more sensitive and more specific than the FOBT. The FIT uses a simple faecal collection device that is more hygienic and acceptable to patients for collecting their stool specimen. It only requires one sample rather than the three required for FOBT. These features combine to promote greater uptake in screening programmes.

Prostate cancer

In the USA and much of Europe, the prevalence of prostate cancer has increased by >100% in the last 10 years. Greater longevity is partly responsible, but the principal reason is earlier detection using serum PSA testing. Post-mortem examinations of men aged >70 years have consistently shown a prevalence of prostate cancer of >50%. When PSA screening is introduced in asymptomatic populations, the reported incidence of the disease increases dramatically for several years.

Several techniques are being developed to improve the performance of the PSA assay in distinguishing aggressive from indolent cancer. These include the use of free and complexed PSA ratios, PSA density (relating serum PSA concentration to gland volume), age-adjusted PSA, rate of increase of PSA and variation in the cut-off level. As holistic genomic and proteomic methods become more widely used, it is likely that improved understanding of the natural history of the disease in an individual will lead to more personalized therapy after needle biopsy to access tissue.

The best treatment for screen-detected patients has not been determined. Many die of another condition with no morbidity caused by their prostate disease. Localized prostate cancer can be managed by radical surgery or radiotherapy, or by doing nothing. Younger patients favour more active treatment but must cope with the potential adverse effects, which include incontinence, impotence, strictures and disordered bowel habit that often persists for many years. A large, population-based study from the USA has shown no survival advantage after 11 years in men offered intensive screening.

An authoritative review by the UK Department of Health concluded that there is currently no place for screening programmes, but that there is a need for a properly conducted randomized trial. Current UK practice is not to deny PSA testing to men >50 years of age who request it and have been given reliable information about its benefits and hazards. Although evidence does not yet support population screening for prostate cancer, there is considerable demand for the PSA test among men worried about the disease. In response to this, the Prostate Cancer Risk Management Programme was introduced over a decade ago. This provides high-quality information to enable men to decide whether or not to have the PSA test based on available evidence about risks and benefits. After considering this information, and in discussion with their general practitioners, men aged >50 who choose to have the test can do so free of charge, on the NHS. However, PSA still remains a useful investigation in all men with symptoms of urinary outflow obstruction.

Other cancers

Various lobby groups or commercial providers often call for a screening of other cancers such as skin, ovary, endometrium and thyroid. Although an investigation of abnormal symptoms is fully warranted, only rigorous population-based research can validate the cost-effectiveness of introducing new screening programmes.

The future

New technology such as the microanalysis of circulating DNA — so-called liquid biopsy — could radically change the situation. Future changes in cancer screening will lead to profound ethical, educational, commercial and medical challenges. Completion of the Human Genome Project, the ability to handle large volumes of sequence data, and rapid and inexpensive assays for mutations using gene-chip technology will transform the assessment of cancer risk. Commercial pressures have caused the major pharmaceutical companies to invest heavily in genomics, and their interest will lead to the discovery of new drugs and more specific tailoring of therapies to individual patients. It is likely that groups of individuals with no family history of cancer will be identified as being at significantly increased risk of developing cancer. Devising optimal screening schedules for such groups will be a major challenge.

The biggest problem of all is motivating the customers. The compliance rate varies enormously across the world, driven by education, socioeconomic factors and deprivation.[5] The educated worried well are likely to go for every free test offered by the health system. The socially excluded residents of the neighbouring poorer districts on the wrong side of the tracks will not visit the doctor until they have advanced stage 4 cancer. And yet private clinics offer top of the range health screening for >£3000 of scans and tests to the gullible wealthy with no evidence of benefit. To save lives most effectively, we must target the poor.

Yet we all know the problem — the system is cumbersome for everyone. Consumer organizations such as budget airlines, supermarkets and online shopping systems make it easy for everyone to navigate their offerings. In this digital age the smartphone is the way forward; yet my wife still gets 'snail-mailed' for her breast screening with a poorly set-out, rather unfriendly letter giving her a specific time and place to turn up. No chance to book online. Making everything convenient is the key for everybody. And as we all know, the politics of breast cancer means that everybody gets an incomprehensible leaflet talking about risk and deliberately undermining the validity of the process. No wonder many women simply ignore the invitation.

NHS population-based cancer screening is for breast, cervical and colorectal cancer only and has an excellent call—recall system. The latter comes from general practitioner lists so if the addresses are wrong in the surgery, no invitation comes. The key problems in all three programmes are the same:

- clunky access systems for clients
- huge variations in uptake
- lack of downstream processing capacity
- workforce shortages at all levels
- confusion in management — local, community, NHS England, Public Health England (the euphemism used is *multi-layered*)
- lack of interest in primary care
- lack of short-term positive feedback.

The key to success, as the Richards Report stresses,[1] is good IT — which is not a feature of the NHS. This needs drastic improvement. ◆

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