CANCER PEDIA

CANCER CONTROL

EARLY DETECTION AND SCREENING

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CHAPTER
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A. INTRODUCTION

The goal of cancer screening is to reduce the morbidity and mortality associated with cancer.

Screening tests may detect precancerous lesions that can be treated before they become malignant. An example is the Pap test for cervical cancer. It has been successful in reducing the incidence, burden and mortality of cervical cancer.

Screening tests can also identify cancer that is less advanced and easier to treat. An example is mammographic screening, which aims to detect masses in the breast before they can be clinically detected. A successful screening program using this mechanism decreases mortality from cancer. It does not decrease the incidence of the disease.

B. CLASSIFICATION OF SCREENING MODALITIES

Screening modalities can be classified according their target population and how they are delivered.

1. MASS SCREENING AND HIGH-RISK SCREENING

Mass and high-risk screening programs differ in the populations they target. In mass screening, all members of a target population are encouraged to undergo screening. For example, Ontario's ColonCancerCheck program encourages all adults aged 50 to 74 years of age to undergo colorectal cancer screening by fecal occult blood test or colonoscopy.[1]

In contrast, high-risk screening programs focus on individuals who are known to be at increased risk of cancer. These programs tend to have an increased frequency or intensity of screening. For example, the Ontario Breast Screening Program's High Risk Screening program and Cancer Australia offer magnetic resonance imaging (MRI) in addition to mammography for women who have an especially high risk of breast cancer, based on various risk factors.[2,3]

2. OPPORTUNISTIC SCREENING AND ORGANIZED SCREENING

Opportunistic or ad hoc screening (also known as case-finding) typically occurs at the primary care level. Opportunistic screening requires a person to seek care from a medical professional, who either performs screening tests in-office or refers the patient for screening. Opportunistic screening may not be checked or monitored.

In contrast, an organized or comprehensive screening program promotes, delivers and follows-up on screening services independently, without requiring a medical referral. Organized screening programs require adequate resources to achieve program quality assurance and the full trajectory of screening, including effective reach to the target population group (i.e., appropriate age, gender, and risk category) and follow-up for disease assessment, diagnosis, and treatment, if disease is discovered.[4]

C. CRITERIA FOR IMPLEMENTING SCREENING TESTS

Since all screening programs – regardless of their mechanism, target population or mode of delivery – are resource-intensive, it is important to have evidence for the effectiveness and cost-effectiveness of a program before it is offered to a population. In North America and Europe, a cost of $50,000 per Quality Adjusted Life Year gained is often considered a threshold of cost-effectiveness.[5] Health service planners and policy-makers must ensure that a screening test meets key evaluation criteria before integrating it into a mass screening program and introducing it at the population level.[6]

Examples of key criteria include the following:

- Reduces mortality.
- Accurate and acceptable.

- Screens for a disease that accounts for a significant burden of disease and has a recognizable pre-clinical stage of disease.
- Supported by evidence that outcomes are improved by treatment at earlier stages of disease.
- Compatible with the resources available to provide the test and follow-up on a continuous basis, with adequate diagnostic and treatment facilities.

It is critical that all screening tests undergo the same level of scrutiny and meet the same criteria. This rigorous evaluation is especially important given the multitude of molecular tests now being proposed as potential screening modalities. This growth is due to increasing knowledge about the molecular profile of common cancers and emerging technologies that enable the decoding of the genomes, transcriptomes, proteomes and metabolomes of tumours and biological fluids.

D. CANCER SCREENING PROGRAMS

Although there are challenges with assessing the effectiveness of screening tests, screening programs for breast, colorectal and cervical cancer are accepted and provided in high-resource settings.

3. BREAST CANCER SCREENING

Breast cancer is a major cause of morbidity and mortality worldwide. In the last three decades, the incidence and mortality of breast cancer have increased, with the most rapid increases in low-resource settings.[7]

Mammography is the primary modality for breast cancer mass screening in high-resource settings. As Harford notes, "there is increasing demand for health care systems in [low- and middle- resource countries] to emulate high income countries by adding mammographic screening and policy makers are feeling pressure from national and international advocacy groups to pay for a mammography program".[8]

One issue related to implementing a mammography screening program is variable best practice guidelines. Screening guidelines for mammography may vary depending on the issue and jurisdiction. For example, the age to initiate regular screening and the frequency of screening are often debated. In Mexico, biennial mammographic screening is recommended for women 40 to 69 years of age, with annual clinical breast examinations for women 25 years of age and older.[9] The Canadian Task Force on Preventive Health Care updated its guidelines in 2011. Although the current recommendation is for women 50 to 74 years of age to undergo mammographic screening every two to three years, the task force noted that uncertainty exists about the quality of evidence supporting this recommendation.[10]

The patterns of breast cancer incidence and mortality in low- and middle-income countries are distinct from those in high-income countries. Available breast cancer screening guidelines are generally based on disease and population characteristics in Western countries. These do not consider resource limitations or the distinct age distribution and age-specific incidence of breast cancer in emerging economies, two factors that affect the design of a successful screening program.[11] These differences must be considered when developing screening guidelines.

The three main alternatives to mass mammography include breast self-examination, clinical breast exams and high-risk screening. Each of these modalities may be used in conjunction with mammography.

Breast self-exams tend to be part of breast awareness campaigns and ask women to look for irregularities in their breasts on a regular basis. Although self-exams are likely to increase awareness, one very large randomized trial concluded that breast self-exams cause more harm than benefits in breast cancer mortality.[12]

Clinical breast exams show promising evidence of benefit. Annual clinical breast exams for women between 40 and 60 years of age is predicted to be nearly as efficacious as biennial mammography in reducing breast cancer mortality, and at half the cost.[13] Based on findings of mortality reduction and the importance of follow-up visits if the clinical breast exam has suspicious findings, the Breast Health Global Initiative recommended that in middle-resource settings, "breast cancer early detection programs…should include clinical breast examination with or without mammography and should be coupled with active awareness programs".[14]

Many jurisdictions with an organized breast cancer screening program include protocols for women who are at higher than average risk for breast cancer. These women are more likely to be diagnosed with breast cancer at a younger age, and with a more aggressive type of cancer. ***High-risk breast cancer screening programs*** typically extend the age of eligibility for screening to include younger women, and may include different and more sensitive modes of imaging (e.g., MRI).

The traits typically associated with high risk for breast cancer include the following:[15]

- A mutation in the BRCA1 or BRCA2 gene (or a first degree relative with a mutation).
- A first-degree relative, such as mother or sister, diagnosed with breast cancer at 40 years of age or younger.
- A personal history of breast cancer, including ductal carcinoma in situ, lobular carcinoma in situ or atypical hyperplasia.
- Radiation to the chest area during childhood or young adulthood.
- A mutation to the TP53 or PTEN genes, or a first-degree relative with relative with one of these mutations, which can lead to Li Fraumeni syndrome, Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome.

The American Cancer Society and the National Comprehensive Cancer Screening Network offer very specific guidelines for women with these traits, and specific screening protocols depending on the traits that are present.[16]

The definition of and recommended screening protocols for high-risk women will vary based on the jurisdiction, resource availability and the priority given to breast cancer screening. Offering MRI, for example, is unlikely to be feasible in lower-resource settings; however, an understanding of who is at the greatest risk of breast cancer and who might benefit most from screening is worthwhile in any setting.

4. COLORECTAL CANCER SCREENING

Worldwide, colorectal cancer is the third most common cancer in men and the second most common cancer in women. Annually, there are an estimated one million new cases and over 600,000 deaths due to the disease globally.[17]

There are two major types of colorectal cancer screening: stool tests and structural examinations. Tests using each of these methods are widely accepted, based on substantial evidence of their ability to reduce colorectal cancer incidence and mortality. These screening modalities have also repeatedly been shown to be cost-effective.[18,19]

Stool tests or fecal occult blood tests (FOBT) aim to detect cancer or precancerous lesions by looking for evidence of blood in a fecal sample, which could be caused by cancer, adenomas or polyps. If the test is positive, the patient is referred for an endoscopic examination to biopsy or remove any polyps that are present. FOBT is the primary colorectal cancer screening modality in most of Europe and Australia.

The two most common types of FOBT are the guaiac-based fecal occult blood test (gFOBT) and the fecal immunochemical test (FIT).

gFOBT uses a reaction with hydrogen peroxide to identify whether hemoglobin is present in the stool. Randomized controlled trials have shown that gFOBT is associated with a 14 to 16 per cent reduction in mortality from colorectal cancer.[20] The test also appears to have good acceptability: a United Kingdom study found 52 percent participation in the first round of screening.[21] Based on extensive evidence, gFOBT is currently recommended in Europe for men and women 50 to 74 years of age. It has been suggested that the screening interval should not exceed two years and that some benefit of gFOBT is incurred in adults 40 to 80 years of age, but that 60 to 64 years of age is the most critical time frame. The authors of these guidelines suggest that this age range be expanded based on local resources.[19]

FIT – also known as the immunochemical fecal occult blood test (iFOBT) – uses antibodies to detect the presence of globin of the stool. Despite a lack of evidence to support its effect on colorectal cancer incidence and mortality, studies have shown that FIT is more sensitive and specific than the gFOBT for detecting colorectal cancer and advanced adenomas.[22] Although FIT was initially more expensive than gFOBT, there is some evidence that FIT could be a cost-effective alternative to gFOBT as the price drops.[19] Current guidelines recommend that FIT be offered to men and women 60 to 64 years of age and expanded

based on local resources, and that the screening interval should not exceed three years.[19]

Structural examination or endoscopy uses visual inspection to identify cancer and pre-malignant lesions in the patient. There are three types of endoscopy: colonoscopy; flexible sigmoidoscopy; and computed tomographic colonograpy (CTC), which is an emerging and less-invasive procedure.

Endoscopy by colonoscopy or flexible sigmoidoscopy is necessary for the biopsy or removal of precancerous growths. With the use of FOBT, however, the value of endoscopy as a primary screening modality has been contested.[23-25] Both colonoscopy and flexible sigmoidoscopy are more sensitive than FOBT for the detection of adenomatous polyps, but each has its drawbacks, including lower acceptability due to invasiveness.

Colonoscopy is an endoscopic examination of the colon using a camera on a flexible tube passed through the anus of the patient, and is performed by a Gastroenterologist. Colonoscopy is considered the most accurate test for the early detection and prevention of colorectal cancer. It can visualize the whole colon, and polyps can be removed at the time of screening. Most often, patients are referred for colonoscopy if they have positive results on other screening tests. Observational evidence has found that screening by colonoscopy can reduce the incidence of colorectal cancer by 76 to 90 per cent and decrease mortality from colorectal cancer by 65 per cent.[26] Colonoscopy can also be used as a primary screening modality, though there are some associated disadvantages. The invasive nature of the test makes it resource-intensive and less acceptable to patients, who need to cleanse their colons and may require sedation. Colonoscopy is less effective at detecting neoplastic lesions on the right side of the colon. There is also some risk of complications – such as major bleeding and perforation of the bowel – in up to 0.3 per cent of procedures.[27] Germany, Poland, the United States and other countries have adopted colonoscopy as a primary screening modality. The European Union has suggested that a single screening colonoscopy be performed at age 55.[19]

Flexible sigmoidoscopy is similar to colonoscopy, but visualizes only the distal part of the colon and requires less intense patient preparation prior to examination. Flexible sigmoidoscopy is more sensitive than fecal testing for the detection of adenomatous polyps.[28] It may be less resource-intensive and more cost-effective than colonoscopy, because adequately trained nurse practitioners can perform the procedure as competently as gastroenterologists, and sedation is not required.[29] For patients, flexible sigmoidoscopy is accepted, safe and quick.[30]

The major disadvantage of flexible sigmoidoscopy is that it visualizes only the distal half of the colon; however, this is where two thirds of colorectal cancers and adenomas are located. Consequently, the procedure does have a significant impact on the incidence of and mortality of colorectal cancer. In the United Kingdom, one-time flexible sigmoidoscopy in men and women 50 to 64 years of age reduced the incidence of cancer in the distal colon by 36 per cent and colorectal cancer mortality by 40 per cent after 11 years of follow-up.[31] In the United States, there was a 21 per cent reduction in colorectal cancer incidence and a 26 per cent reduction in colorectal cancer death in adults 55 to 74 years of age who underwent flexible sigmoidoscopy with a follow-up screening three to five years later.[32]

Economic analyses suggest that a once-only flexible sigmoidoscopy screen at 55 or 60 years of age can avoid the costs associated with treating the incident cases of colorectal cancer that would occur if screening was neglected.[33] Evidence-based guidelines from the European Union suggest the screening interval for flexible sigmoidoscopy should be 10 to 20 years.[19]

CTC – also known as virtual colonography or virtual colonoscopy – uses a computed tomography (CT) scanner to visualize the entire colon and the structures around it. CTC may be more comfortable for, and acceptable to, patients, compared to more invasive procedures. Although CTC does still require colon cleansing prior to the procedure and presents low-dose exposure to ionizing radiation, patients tend to prefer the procedure because it is brief, minimally invasive and does not require sedation. CTC is being used routinely in the United Kingdom when optic colonoscopy is contraindicated or incomplete.[34] The cost-effectiveness of CTC is relative; it is cost-effective compared to no screening and to FOBT and flexible sigmoidoscopy, appears less cost-effective than colonoscopy, but fares better when combined with other screening procedures.[35] Since CTC visualizes the colon and the structures around it, the test may uncover suspicious findings outside of the colon. These findings may generate anxiety, and it is unclear whether they save or generate costs.[34] Sebastian observed that, "the best CRC screening test is the one you are willing to have". [36] Although patients do tend to prefer CTC for screening, they must nonetheless undergo a colonoscopy if positive results occur.

5. CERVICAL CANCER SCREENING

The increased availability and uptake of cervical cancer screening have resulted in decreasing rates of cervical cancer mortality over the last several decades.[17]

There are three major types of cervical cancer screening: cytological tests; human papillomavirus (HPV) tests; and visual inspection with acetic acid.

Cytological tests aim to identify abnormal cells in the cervix based on their appearance. There are two cytological screening tests. The first – the Pap smear – is conducted by swabbing cells from the inside of the cervix using a spatula and spreading them onto a glass slide, to be examined under a microscope for signs of abnormality or neoplasia. The second – liquid-based cytology – also collects cells from inside the cervix and examines them under a microscope, but a small brush is used to swab the cells, which are then kept in a preserving liquid medium. Many of the current guidelines across North America and Europe recommend routine use of cytological screening to reduce the mortality and morbidity associated with cervical cancer.[37]

HPV tests look for infection by the human papillomavirus, which is a cause of cervical cancer. A positive HPV test typically leads to a referral for cytological screening and/or biopsy. The HPV test has two major advantages over cervical cytological tests. First, the test is more sensitive than cytology for identifying cervical intraepithelial neoplasia.[38,39] This means the test rarely misses a true positive result. In addition, HPV testing has a very high negative predictive value, such that if the test suggests a patient is not infected with HPV, it is unlikely to be a false negative. This provides greater confidence in a negative result and a potentially longer interval until the next screen is necessary, thereby reducing the burden of screening on the patient and on the system.[40,41] A meta-analysis indicated that a negative HPV test was much more protective than negative cytology, which led the authors to suggest that a six-year screening interval for HPV testing was feasible.[42] The second major advantage of HPV testing is that women can self-test. Women have a high acceptance of and positive attitudes towards self-collected HPV testing, since it removes some of the common barriers to screening, including transportation to and from a clinic, physical discomfort, and cultural or religious beliefs.[43]

Currently, cytology and HPV testing are best used in conjunction with one another. Recent evidence-based guidelines from the United States suggest that women should begin screening at age 21 with cytology alone every three years, until 30 years of age. After 30 years of age, women should be co-tested with HPV and cytology together every five years. Women should cease screening at 65 years of age if they have a history of negative tests. If women have a history of cervical intraepithelial neoplasia or a more severe diagnosis, they should continue routine screening for at least 20 years following the suspect result. Women can also cease screening if they have undergone a hysterectomy. At the present time, women who have been vaccinated against HPV are recommended to follow the general age-specific guidelines.[44]

If resources are unavailable for liquid-based cytology screening or HPV testing, low technology ***visual inspection with acetic acid*** may be a viable primary mode of cervical cancer screening. In this test, the vaginal canal is swabbed with acetic acid (i.e., vinegar) and inspected with or without magnification for abnormal cells, which appear in contrast to the rest of the tissue once acetic acid has been applied. When linked to proper follow-up and treatment for positive results, the use of visual inspection with acetic acid screening for precancerous and cancerous cervical lesions is a safe, simple, well-accepted, low-cost and efficient alternative to cytologic testing.[45] Due to the nature of the test, results are immediately available, which enables prompt referral for confirmatory testing. Performing the test requires a low-level of infrastructure and equipment and minimal technical skill. When linked with effective treatment, visual inspection with acetic acid can lead to reduced cervical cancer morbidity and mortality in high-risk, low-resource countries.[45]

E. INFRASTRUCTURE AND KEY CONSIDERATIONS

The World Health Organization determined that an effective screening program requires that at least 70 percent of the target population be covered (i.e., follow guidelines and participate in screening).[46]

Organized cancer screening programs – where members of the target population are systematically invited to screening, reminders are sent when they are due for another screen, and infrastructure exists to facilitate

and track the follow-up for positive screens – are highly encouraged.[47] Organized screening may reduce inequalities by potentially serving a whole population, rather than only those who access health services through their medical professional.[48] The costs of a comprehensive cancer screening program infrastructure can be prohibitively high and may not be feasible in all settings; however, it is recommended that planning focus on scaling up to this model.

Screening priorities must be determined based on available resources, local circumstances, and best knowledge about the incidence of and mortality from cancer in the population. Low- to middle-income countries should consider a range approaches to screening. In many settings, a reasonable path involves beginning with high-risk screening, working to raise health awareness, and scaling up the program as health service capacity and community awareness improve.[8]

Ultimately, the success of a cancer screening policy and its associated program depends not only on the evidence base, but also on the willingness of the public to take part in the screening process. This, in turn, depends to a great extent on how the benefits and risks of the procedure are communicated, and how the program fits within the healthcare system and with other health messages, including cancer prevention.[49]

Community awareness and acceptance of cancer screening will affect both the initial coverage of the screening test and adherence to follow-up procedures. Whether in low-, middle- or high-income settings, key factors for community acceptance and success include early and high levels of engagement with community and medical leaders, education, advocacy, and the establishment of adequate infrastructure and information systems to promote screening and capture initial diagnosis, treatment and active follow-up information.

Knowledge, attitudes and beliefs about screening have been studied thoroughly in high-resource countries and, to a lesser extent, in low-resource settings. After a patient attends an initial screening appointment, compliance with follow-up visits has a large impact on program effectiveness. The most frequently cited reasons for non-compliance with follow-up are avoidance, denial and fatalism.[50] In settings where treatment for cancer is not fully covered, fears about the costs resulting from a diagnosis are also likely to deter people from seeking screening and diagnostic services.

Literature is weak on how to improve awareness, transfer knowledge and alter beliefs to promote screening.[51] It is known that barriers to screening in Arab populations are anticipated because of social and health beliefs about cancer. However, work is needed to identify the extent of these barriers, their root causes and methods to overcome them.

Regardless of the approach taken, a new cancer screening program may result in an increase in the number of prevalent cases. This additional burden of disease can be substantial and should be viewed as a potential strain on local capacity at all levels—public health, primary care, and diagnostic and treatment facilities. The program must consider growth in the demand for the service, and for staff and other resources, at a rate in keeping with the growth of the population. Middle-resource countries face unique challenges in designing and implementing cancer screening programs. Rapid economic and social development leads to a pattern of disease commonly seen in high-resource countries; however, the health infrastructure and human resource capacity in middle-resource countries – its quantity, quality and accessibility – may not keep pace.[14]

In regions with a severely constrained health infrastructure, the effects of screening must be carefully considered prior to planning and implementing an organized screening program. Decisions regarding the choice of cancer sites, screening strategies, and target populations should be informed not only by cost considerations, but also by an understanding of the local burden of disease, socio-cultural contexts, health systems, infrastructure, human resource capacity, community acceptability and local political will. Adopting a diagonal approach – that is, integrating cancer screening into existing health platforms, infrastructure and resources – can result in reduced costs and increased participation. An example of this is the Pink Ribbon Red Ribbon campaign, a program in African and Latin American countries that added breast and cervical cancer screening to an existing HIV program. Because HIV-infected women are five times likelier to develop cervical cancer, this type of program can address the needs of a particularly high-risk group with a low marginal cost.[52]

Innovative approaches to cancer screening program scale up may also be considered. These include: telemedicine; telepathology; institutional twinning; task shifting; and models of care enhanced by the use of mobile phones, which are widely available and affordable in most low- and middle-income countries.

Large technical platforms may also give way to cloud applications, which allow for easy and secure storage and compilation of information for screening programs; however, a basic information and communications technology infrastructure, computer availability and up-to-date software are still required, and are missing in many countries.

To ensure the maintenance of a high-quality cancer screening program, programs should be monitored and measured against key indicators and targets. For example, the *Ontario Cancer Screening Performance Report* highlights the performance of Ontario's three organized screening programs in domains such as participation and retention, diagnostic intervals, positive prediction values, sensitivity, specificity and detection rates.[53] See the *Cancerpedia: Cancer Control Oversight and Policy* chapter for more information on the benefits of public reporting.

F. CANCER SCREENING GUIDELINES

- The Breast Health Global Initiative evidence-based, economically feasible and culturally appropriate guidelines for international breast health and cancer control in low- and middle-income countries[54]
- The American Cancer Society Recommendations for the Early Detection of Breast Cancer[55]
- The Canadian Task Force on Preventive Health Care *Recommendations on screening for breast cancer in average-risk women aged 40-74 years*[10]
- *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis*[56]
- *American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer*[44]

G. THE FUTURE

Screening for prostate and lung cancer is the subject of debate.

Current evidence suggests that prostate-specific antigen testing in healthy men does more harm than good. Its low specificity (i.e., many subjects without the disease will screen positive) may result in needless psychological distress for those with positive screens.

Lung cancer screening, especially for high-risk individuals, is promising and is being introduced in many jurisdictions. Advanced countries are now beginning CT screening for lung cancer every two years. Large-scale lung cancer screening programs are in their infancy and, as a result, evidence to guide implementation and target populations is lacking.[57]

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