Screening for Cancer in Low- and Middle-Income Countries

R. Sankaranarayanan, MD

ABSTRACT

Background: Screening programs involve testing asymptomatic individuals with an accurate screening test to identify those likely to have the disease of interest and to further investigate them to confirm or exclude the disease. The aim of cancer screening is to prevent cancer deaths and improve quality of life by finding cancers early and by effectively treating them. A decision to introduce a screening program in public health services depends on the evidence that the benefits outweigh the harms of screening, disease burden, availability of suitable screening test, effective treatment, adequate resources, and efficient health services. Screening programs should achieve high participation for testing, diagnosis, and treatment to be effective and efficient.

Objective: To describe the current status of cancer screening programs in low- and middle-income countries (LMICs).

Method: A review of literature and on-going cancer screening initiatives in LMICs was made to discuss cancer screening in these countries.

Findings: Although population-based programs offering Papanicolaou testing every 3 to 5 years have reduced cervical cancer incidence and mortality in high-income countries, such programs have been less successful in reducing cervical cancer burden in LMICs due to poor organization, lack of coverage, and lack of quality assurance. The challenges in introducing high-quality cytology screening in LMICs have led to evaluation of alternative screening approaches such as visual inspection with acetic acid (VIA), human papillomavirus (HPV) testing-based screening, and novel paradigms such as a "single-visit screen and treat" in which treatment with cryotherapy or cold coagulation is provided to screen-positive women without clinical evidence of cancer. Both HPV testing and VIA have been found to prevent cervical neoplasia and cervical cancer deaths in clinical trials. Although mammography screening reduces breast cancer mortality, associated overdiagnosis and overtreatment and the balance between benefits and harms have received much attention in recent years. Although introduction of clinical breast examination screening in LMICs should wait for evidence from ongoing trials, improving breast awareness and access to early diagnosis and treatment in health services is a valuable breast cancer control option in LMICs. Organized colorectal cancer screening programs are still evolving and are in early stages of development in many high-income countries. To date, there is insufficient evidence to support the introduction of population-based stomach, lung, ovarian, and prostate cancer screening in public health services.

Conclusions: Implementation of VIA screening in several LMICs is conducive to future HPV screening programs when affordable HPV tests become widely available. Both HPV vaccination and HPV screening have a huge potential to eliminate cervical cancer in LMICs. A mammography screening program is a complex undertaking involving substantial resources and infrastructure that may not be feasible in many LMICs.

Key Words: breast cancer, cervical cancer, colorectal cancer, cytology, early detection, fecal occult blood test, HPV testing, oral cancer, screening, visual screen

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INTRODUCTION

Screening programs involve large populations of apparently healthy people tested with a simple, easy-to-use, acceptable, and affordable screening test to identify those likely to have the disease of interest. Screenings then use diagnostic investigations either to confirm or exclude the disease. Most people participate in screening to be reassured that they are healthy rather than to find out they are not. The aim of cancer screening is to prevent death from invasive cancer and to improve quality of life by finding tumors or precancerous lesions as early as possible and by effectively treating them. A screening program is more than just offering a screening test to a large number of people; it involves diagnostic investigations for those with a positive test, confirming or excluding the disease, treatment and follow-up care of those diagnosed with disease, quality assurance of

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From the Head, Early Detection & Prevention Section, International Agency for Research on Cancer (WHO-IARC), Lyon, France. Address correspondence to R.S.; e-mail: sankarr@iarc.fr

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Table 1. Criteria for Introduction Screening Programs in Public Health Services

- Disease is suitable for screening
- A suitable screening test exists
- An effective, affordable, and accessible treatment exists in local health services for the condition detected
- High-quality evidence, preferably from randomized trials, exist that the screening program reduces morbidity and mortality from disease
- Evidence exists that the potential benefit from the screening program outweighs potential physical and psychological harms from testing, diagnosis, and treatment
- Well-developed public health services adequately supported by adequate infrastructure, human and financial resources capable of supporting the demands of creating awareness, information dissemination, providing the screening tests, diagnosis, treatment, and follow-up care arising from the screening program and program evaluation
- Appropriate cost-effectiveness and cost-benefit analyses have been carried out
- Social and ethical issues have been taken into account; provision of appropriate information to enable participants to provide valid informed consent
- There is significant public demand for the introduction of the program

program inputs and documentation of data pertaining to the program information systems, and ongoing monitoring and evaluation. A decision to introduce a screening program in public health services depends on a number of criteria (Table 1). Policies on introducing screening programs may differ significantly between high-, middle-, and low-income countries. The underdeveloped health services and lack of resources precludes the introduction of screening programs in many low-income countries.[1] Introducing pilot programs covering a region of a country before national scale-up is a prudent way of introducing screening programs.[2-4] In this review, I will specifically discuss screening for suitable cancers.

SUITABLE CANCERS AND TESTS FOR SCREENING

Not all cancers are suitable for screening. The suitability of a cancer for screening depends on the natural history and the public health burden of the disease, the availability of suitable screening tests, and effective treatment for detecting and curing the disease in early stages. Another important requirement is the availability of efficient health services with adequate infrastructure and trained human resources to ensure access to diagnosis and treatment of screen-positive individuals.

A particular cancer site may be considered suitable for screening if it has a long natural history with a long detectable presymptomatic (preclinical) phase, which facilitates the detection of precancerous lesions, or early invasive cancer before symptoms occur (preclinical cancer). Cervical cancer is a good example of a cancer site with a long natural history and a long preclinical phase, comprising of precancerous lesions such as the high-grade cervical intraepithelial neoplasia (CIN 2-3) a proportion of which become invasive cancer if left untreated over a period of 1 to 4 decades. It takes several years from becoming infected with one of the high-risk HPV infections, such as HPV16, to the development cervical cancer. A high burden of cancer, as judged by high incidence and mortality, is another important criterion of suitability of a cancer site for screening.

A screening test is used to determine the probability of an early disease in an apparently healthy and asymptomatic individual, whereas a diagnostic test is performed after a positive screening test to confirm or exclude a definitive diagnosis of cancer. Some common screening tests to detect certain cancers are shown in Table 2.

A suitable screening test is one that is easy to apply, noninvasive, safe, acceptable, affordable, and accurate in identifying people with a high probability of having the disease. A combination of high sensitivity and high specificity with a high positive predictive value (PPV) define high accuracy and utility of a screening test. Sensitivity refers to the ability of a test to identify people with disease accurately and the specificity refers to the

Table 2. Screening Tests for Selected Cancers

Screening Test	Targeted Disease
Papanicolaou testing (conventional cervical cytology), liquid-based cytology, HPV testing, visual inspection with acetic acid, visual inspection with Lugol's iodine	Cervical cancer
Breast self-examination, clinical breast examination, mammography	Breast cancer
Chemical fecal occult blood testing), immunochemical fecal occult blood test, barium enema, sigmoidoscopy, colonoscopy	Colorectal cancer
Physical examination of the mouth	Oral cancer
Low-dose computed tomography	Lung cancer
Barium swallow, barium meal series, endoscopy	Esophageal and stomach cancer
Prostate-specific antigen test	Prostate cancer
CA 125 estimation, ultrasonography	Cancer of the ovary

ability to identify those without disease. PPV refers to the proportion of those with a positive screening test who actually have the disease and the negative predictive value (NPV) refers to the proportion of those with negative screening test who actually do not have the disease. PPV primarily depends on the prevalence of the disease in the population and the sensitivity of the test. In summary, if a person tests positive on a screening test, the probability that the person has the disease depends on the prevalence of the disease in the population and the sensitivity and specificity. Reproducibility (or reliability) refers to the probability that the test consistently yields the same result when repeated and indicates the extent of variation in laboratory procedures, within and between test providers and within individuals tested. Most screening tests have sensitivity between 50% and 60%, specificity between 85% and 95%, PPV between 1% and 8%, and the NPV usually exceeds 99%.

If the screening test detects a precancerous lesion or condition, as in the case of cervical cancer screening tests, a reduction in incidence of cancer can be expected. If the test predominantly detects early invasive cancer, as in the case of mammography, a reduction in mortality rather than incidence occurs. The application of screening as a cancer control option in a country will depend on the disease burden (incidence and mortality); an informed decision to initiate screening for priority cancers in the context of public health services; the political determination to support a screening policy and provide funding from the government; and the ability and efficiency of the health care services to meet the demands of diagnostic, treatment, and follow-up care services arising out of a screening program.

EVALUATION OF BENEFITS AND HARMS OF SCREENING PROGRAMS

A potential benefit from screening can be expected if the outcome in terms of reduced incidence and/or mortality and improved quality of life outweighs the potential harms of the intervention, and if most clinical cases of a disease go through a detectable preclinical phase, most of which, in the absence of intervention, would progress to clinically manifest advanced symptomatic disease and death. Overdiagnosis and overtreatment of indolent disease may occur following screening, if a significant proportion of the preclinical cases do not progress to frank clinically symptomatic disease and would not have been diagnosed in the absence of screening. These are important considerations and should be taken into account when assessing any potential benefit from screening.

Although it would seem that screening is beneficial, such an undertaking should be supported by evidence based on operational or input measures, outcomes from well-designed studies, and population-based screening programs. The useful input measures to evaluate screening programs include, among others, the proportion of targeted individuals screened and of screen-positive individuals undergoing diagnostic investigations and treatment, the detection rate of disease, the PPV of the screening test, the total costs of the program, and cost per case found. To be effective and efficient, screening programs should achieve high participation and compliance to screening, diagnosis, and treatment.

The useful outcome measures to evaluate the success of screening programs include stage distribution of cancer, case fatality, survival rates, incidence rate of disease (if the screening leads to the diagnosis of precancerous lesions as in the case of cervical cancer), cancer-specific death rate in the population invited for screening, safety and acceptability of the interventions, quality of life, and cost-effectiveness of the entire program.

The potential harms of a screening program include those associated with false-positive tests such as anxiety, side effects, complications and long-term sequelae of diagnostic investigations, and unnecessary overtreatment; false reassurance of not having a disease and increased risk for advanced disease, toxic treatments and death from false-negative tests; and wasted resources associated with both false-positive and false-negative tests.

ORGANIZED AND OPPORTUNISTIC (UNORGANIZED, SPONTANEOUS) SCREENING PROGRAMS

Screening programs may be organized or unorganized. Organized programs are characterized by centralized screening invitations to a specific target population defined by a lower and upper age limit, systematic recall, investigations, treatment and follow-up care of persons found with abnormalities on screening, centralized quality assurance, and a constantly updated study database with linkages to other information systems such as cancer registries and death registration systems for monitoring and evaluation of the program. Within organized programs, every participant is offered the same quality of services, information, and support. High participation is a primary goal of organized screening programs. Examples of organized programs for cervical, breast, and colorectal cancer (CRC) screenings exist in high-income countries (HICs) such as Finland, the Netherlands, United Kingdom, Australia, Canada, Singapore, and Republic of Korea and upper middle-income countries such as Argentina and Uruguay. Many studies describe organized programs or their individual components and effectiveness as compared with unorganized screening programs.[5,6]

In unorganized or opportunistic programs, screening tests are provided to clients on request or coincidentally during routine health care interactions by clients. Opportunistic screening happens when people request a doctor

or health worker for a screening test or when a test is offered by a doctor or health worker during a routine visit. Screening programs are unorganized in many developed countries such as the United States, France, Germany, Japan, and so on. Organized screening programs have shown a greater effect, while using fewer resources than unorganized programs. The critical components of successful screening programs are high coverage of target populations with accurate, quality-assured screening tests and of screen-positive persons with diagnostic investigations, treatment, and follow-up care. These are most cost-effectively met within organized screening programs.

SCREENING FOR CERVICAL CANCER

Cervical cancer is the most widely screened cancer in the world both in high- and middle-income countries. Population-based cervical cytology screening programs offering Papanicolaou testing every 3 to 4 years have reduced cervical cancer incidence and mortality by up to 80% in developed countries of Europe, North America, Japan, Australia, and New Zealand in the past 5 decades.[7] Cervical cancer has a long preclinical detection phase consisting of slowly progressing precancerous lesions such as CIN 2 and 3 and adenocarcinoma in situ, caused by persistent infection with 1 of the oncogenic types of HPV, particularly HPV 16 and 18. The precursor lesions may progress to invasive cervical cancer over a period of 1 to 4 decades. Screening tests, such as conventional cytology, liquid-based cytology, visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), and HPV testing, can identify women with CIN as well as early invasive cancer, if provided with quality assurance and by well-trained providers (Table 2). Large scale Papanicolaou testing programs are operational nationally in the Republic of Korea, Singapore, Thailand, Hong Kong, and Taiwan in the Asian region and in Argentina, Brazil, Cuba, Costa Rica, Chile, Mexico, Panama, Venezuela, and Uruguay and regionally in Peru, Colombia, Ecuador, and Bolivia. Screen-positive women are investigated with colposcopy and directed biopsies to diagnose high-grade CIN and treated with loop electrosurgical excision procedure (LEEP) or laser excision for CIN in a 3-visit strategy to prevent cervical cancer in cytology programs in high-and middle- income countries.

Contrary to the success in HICs, cytology-screening programs in many middle-income countries have performed suboptimally in reducing cervical cancer burden due to poor organization, coverage, and lack of quality assurance. This under performance is due to the considerable challenges in improving and introducing high-quality Papanicolaou testing programs there.[1,8,9] This led to the evaluation of alternative screening approaches such as VIA, VILI, HPV testing-based screening and novel paradigms such as a "single-visit screen and treat" in which treatment with cryotherapy or cold coagulation is provided immediately, or soon after the screening test, to screen-positive women without clinical evidence of cancer instead of the conventional triage with colposcopy, biopsy, and histological confirmation of CIN before treatment[10,11]; in situations with sufficient capacity for colposcopy and histology, colposcopy-directed biopsies may be provided before cryotherapy or cold coagulation treatment in a single-visit screen-and-treat approach so that histological nature of the lesion treated may be obtained a posteriori.[12,13] VIA permits a single-visit approach in low- and middle-income countries (LMICs) in view of immediate test results. On the other hand, HPV testing-based screening will require a 2-visit approach because of the need for high-volume testing and the time required for processing, unless rapid, affordable, low-volume point-of-care HPV testing platforms are developed and made available. Both HPV testing and VIA have been found to be effective in preventing cervical neoplasia and deaths caused by cervical cancer in clinical trials.[12,14-16]

Recently, the World Health Organization (WHO) provided recommendations for screen-and-treat programs for comprehensive cervical cancer prevention and control intended for policymakers, program managers, and other health professionals responsible for choosing strategies for cervical cancer prevention, at country, regional, and district levels. Where resources permit, a strategy of screen with HPV tests and treat with cryotherapy (or LEEP when not eligible for cryotherapy) or a strategy of screen with HPV testing followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) is advocated.[17] The WHO also advocated in a recent guidance note that the lower age limit of cervical screening should not be under 30 years in LMICs and if HPV testing is used for screening it should not be repeated in less than 10-year intervals.[18]

In view of its feasibility and affordability, VIA has been widely implemented in several LMICs in Asia and Africa. This can lay the foundation for future HPV testing-based screening programs when affordable HPV tests become widely available. Introduction of both HPV vaccination and HPV screening has a huge potential to eliminate cervical cancer in due course. The effectiveness of HPV vaccination in reducing the frequency of vaccine-targeted HPV infections and high-grade CIN is already in evidence in countries such as Australia and Denmark, which introduced HPV vaccination around 2007.[19,20] The reductions in HPV prevalence following widespread HPV vaccination in the next few decades will necessitate fewer lifetime HPV testing (e.g., beginning at age 35 years and repeated once or twice at 10-year intervals) as primary screening globally.

SCREENING FOR BREAST CANCER

Breast cancer is the No. 1 cancer among women in the world accounting for 1.7 million new cases in 2012.

Although mammography is a valuable screening test for detecting early breast cancers, its inability to differentiate between progressive and some nonprogressive early nonpalpable breast cancers leading to overdiagnosis (estimates vary from 10% to 30%) and overtreatment and the estimation of benefits and harms (mental stress, biopsies, surgery, and side effects of chemotherapy and hormone therapy associated with overtreatment) have received much attention in recent years.[21-23] There is evidence from randomized trials that screening women aged 50 to 69 years with mammography is associated with a 25% reduction in breast cancer mortality, while the benefits in women aged 40 to 49 years are less certain.[24] Critics of mammography screening argue that the 19% reduction in breast cancer mortality observed in a pooled analysis of 7 randomized trials was an unreliable outcome due to differential misclassification of cause of death, with excess surgeries and radiotherapy.[22] A recent study based on long-term follow-up of the Canadian trial concluded that annual mammography in 40- to 59-year-old women did not reduce breast cancer mortality beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available.[23]

A recent review of published literature during 1960 to 2014 indicated that mammography screening was associated with 19% overall reduction in breast cancer mortality for women aged 40 to 70 years and the overdiagnosis was estimated at 19%; the review concluded that the benefits of mammography screening may be maximized by individualized decisions based on risk profiles and informed preferences.[21]

A mammography screening program is a complex multidisciplinary undertaking and its success depends on the quality of the individual components and involves substantial resources and infrastructure, which are not within the reach of most LMICs where fragmented health systems with uneven capacity and, thus, mammography screening is not feasible. The fact that mammographic screening is not feasible in LMICs has prompted the assessment of breast self-examination (BSE) and clinical breast examination (CBE) as alternative screening approaches. Intensive instruction in BSE did not reduce mortality from breast cancer in a randomized trial in China.[25] To our knowledge, no population-based program exists that solely relies on CBE or BSE as screening methods. Evidence for the efficacy and cost-effectiveness of CBE in reducing breast cancer mortality in randomized trials is essential before population-based CBE screening programs can be recommended. Final results from 2 randomized trials of CBE screening in India may be valuable for public health policy decisions on introducing CBE-based screening programs.[26,27] There is also a need to address the value of increasing breast awareness and in improving accessibility for early clinical diagnosis and prompt treatment in health services as compared with a systematic CBE-based screening program to support appropriate breast cancer control policies in LMICs. There is reason to believe that most of the gains in breast cancer mortality before widespread mammography screening and the introduction of adjuvant chemotherapy and hormone therapy in HICs might have been due to improved awareness about breast symptoms and signs and the value of locoregional treatment in improving survival outcomes of early-stage breast cancers.

SCREENING FOR COLORECTAL AND ORAL CANCERS

Screening for colorectal cancer (CRC), with the fecal occult blood tests (FOBT), has shown a 16% decrease in CRC mortality.[28] The immunochemical (iFOBT) test, in contrast to the guaiac (gFOBT) test, requires no restrictions on diet or medication. Sigmoidoscopy, colonoscopy, and imaging investigations, such as double-contrast barium enema, are used to triage FOBT-positive individuals. Effective screening can reduce incidence by detecting and removing precancerous lesions in adenomatous polyps and reduce mortality by detecting cancers confined to the mucosa. Organized CRC screening programs are still in the early stages of development in many HICs. The feasibility of introducing and scaling-up CRC screening using iFOBT was successfully demonstrated in Thailand recently as a prelude to national scale-up.[4]

Oral cancer has a long preclinical detection phase consisting of potentially malignant disorders such as leukoplakia, submucous fibrosis, erythroplakia, and early preclinical invasive cancers presenting as painless, small ulcers or growths that can be clinically detected through careful visual inspection and palpation of the oral mucosa. Oral visual screening was followed by a 34% reduction in oral cancer mortality among users of tobacco or alcohol or both and a much higher reduction in those complying with all rounds of screening in a randomized trial in India.[29-31]

SCREENING FOR OTHER CANCERS

There is no sufficient evidence supporting the introduction of population-based screening for stomach, lung, ovarian, and prostate cancers in public health services.[32-35] It has not yet been proven that benefits of prostate-specific antigen-based prostate cancer screening outweigh harms associated with overdiagnosis and overtreatment.

CONCLUSIONS

Organized cancer screening programs do not exist in most LMICs including China, India, Indonesia, Nigeria, and South Africa. Their existing health-service infrastructure, human resources, and meagre health-service investments often preclude the possibility of introducing and sustaining

effective screening programs. Substantial investments in improving health care infrastructure, human resources, and improvisation systems will be required to improve early detection and treatment of cancers in many countries. In HICs, existing cervical cancer screening programs will require reorganization as HPV vaccination becomes widely used and its impact emerges. Careful monitoring and evaluation of organized breast cancer screening in HICs has the potential to resolve controversies surrounding mammography screening and clarify the value of new emerging imaging modalities such as digital mammography and the role of magnetic resonance imaging.

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