

Chapter 12

Screening for Cancer: Considerations for Low- and Middle-Income Countries

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INTRODUCTION

The goal of cancer screening is to detect cancer or precancerous lesions in asymptomatic individuals at a point when cancer is more likely to be prevented or cured than if the patient waited for symptoms to develop (Morrison 1992). A screening intervention can be successful only if the disease is more likely to be cured when detected early, and for which effective treatment for early-stage disease is available, affordable, and acceptable to the individual, the community, and the jurisdiction of interest. This chapter briefly describes the principles and pitfalls of cancer screening, based largely on the experience in high-income countries (HICs); summarizes the evidence for screening “best buys” relevant to low- and middle-income countries (LMICs); and highlights opportunities to avoid some of the costly and vexatious problems associated with screening in HICs and LMICs. The chapter focuses principally on existing projects and recent literature on cancer screening in LMICs.

Policy considerations regarding whether and in what manner to implement a cancer screening program should be based on systematic evaluation of several factors, including at a minimum: the burden of the cancer in the population of interest (those at risk), the cost effectiveness of the proposed screening intervention, and how well a given screening test performs in the target population. How well the test works can be judged by how many individuals must be screened to

prevent one death from that cancer, balanced with how many people who undergo screening have a positive or abnormal test result when they do not have cancer (false-positive test), and how many have a normal result when they in fact do have cancer (false-negative test). The number of individuals with positive results who will actually proceed to follow up and receive treatment is a critical issue to consider for a given population. Other critical considerations include the cost effectiveness of a screening intervention when moving from initial trials to scale and the health system requirements needed to ensure the success of a given program. (See chapters 11, 16, and 17 for more on health systems.)

In this chapter, we selected three cancer sites for which there is the most evidence for screening effectiveness in LMICs—breast, cervical, and colorectal—and three promising candidate conditions.

DEFINITIONS OF AND CRITERIA FOR CANCER SCREENING

Opportunistic versus Organized Screening

Opportunistic screening or *case finding* occurs when an asymptomatic individual actively seeks a screening procedure or a health professional offers a screening test to an asymptomatic individual.

Organized screening occurs when there is an organized, population-based program with a structured

public health approach. Organized screening has six elements (IARC 2005):

- An explicit policy that specifies eligible age categories, methods, and screening intervals
- A defined target population
- A dedicated and responsible management team responsible for implementation
- Associated teams for decision and care
- Specified methods for quality assurance
- Screening methods to identify cancer occurrence in the target population.

In *population-based screening*, the elements of the screening pathway are planned for an entire population and are delivered, monitored, and evaluated for effectiveness and quality to ensure that the benefits are maximized in a cost-effective way. Although the approach to implementation may be phased or staged geographically or by age intervals, the intention for population screening is to capture all at-risk individuals in the appropriate age interval. Organized screening is expensive and can succeed only if adequate resources exist to achieve the full trajectory of screening, with program quality assurance, including effective reach to all in the target population group (appropriate age, gender, and risk category) and follow-up for disease assessment, diagnosis, and treatment if disease is discovered.

High-risk screening targets known subpopulations of men or women who may be at considerably higher risk for specific cancer because of their genetic or risk exposure backgrounds. In HICs, such high-risk screening has included known single-gene mutations associated with breast or ovarian cancer—such as BRCA1 and BRCA2 mutations, or family history of breast or ovarian cancer—as well as similarly rare forms of hereditary colon cancers. In LMICs, a pragmatic example of screening of high-risk groups in South and Southeast Asia for oral cancer could apply to heavy smokers and drinkers who chew betel, areca nut, paan, and gutka.

The target age range of a screening program depends on several factors, including the following:

- Burden of the cancer in a given population
- Age-specific trends of the cancer, which may vary widely between countries
- Screening modality, the type of test used, for example, visual inspection with acetic acid (VIA) versus human papilloma virus (HPV) testing or combinations of these for cervical cancer
- Considerations regarding the capacity of local health systems.

Cervical cancer screening should begin only after a woman has become sexually active. When considering the choice of screening method, HPV screening is not advised until a woman is 30 years of age, as younger women are more likely to naturally “clear” the virus through the immune system. Overtreatment, particularly of young women, may lead to fertility problems in the future (chapter 4 in this volume [Denny and others 2015]).

The optimal frequency or interval for cancer screening depends on the capacity of the health system, as well as the cancer’s natural history, which includes the rate of growth. Fast-growing cancers are less amenable to screening, while slower-growing, indolent cancers with a more predictable natural history (for example, colonic polyps or cervical precancerous lesions) are more obvious candidates for a screening intervention (Esserman, Thompson, and Reid 2013). Breast cancer has many different subtypes (for example, estrogen and/or progesterone receptor positive and negative, her2neu positive and negative) with a broad range of growth rates, patterns of spread (metastases), and prognoses (Carey and others 2006; Van de Vijver and others 2002). This complex natural history of breast cancer and the expense of subtyping breast cancer are among the reasons for the ongoing debate regarding the utility of screening mammography in HICs.

It is important to consider potential sources of bias when evaluating the effectiveness of organized cancer screening programs. Three such forms of bias are lead-time bias, length bias, and overdiagnosis.

- **Lead-time bias**

Survival time for cancer patients is usually measured from the day the cancer is diagnosed until the day they die. Patients are often diagnosed after they have symptoms. If a screening test leads to a diagnosis before symptoms develop, the survival time is increased because the date of diagnosis is earlier. This increase in survival time makes it seem as though screened patients are living longer when that may not be the case. This is called *lead-time bias*. Screened patients may die at the same time they would have without the screening test.

Lead-time bias has been a particular challenge for screening with prostate specific antigen in HICs. As part of the American Board of Internal Medicine’s Choosing Wisely campaign, the American Society of Clinical Oncology added prostate screening to its updated “Top Five List” of oncology practices that should be stopped because they are not supported by the evidence or are considered wasteful (Schnipper and others 2013).

- **Length bias**

Another source of potential bias is apparent when screening detects mostly indolent, slowly progressive tumors while missing the more aggressive ones. As an example, some types of breast cancer are indolent and can be asymptomatic for years; others are much more aggressive and have a far shorter asymptomatic period. The latter are more likely to cause symptoms between screening intervals and may cause a patient to seek medical attention prior to ever participating in cancer screening. Consequently, a screening test will detect more slow-growing than fast-growing cancers, giving a false impression that screening lengthens survival, when in fact it is merely detecting a subset of a more treatable disease (Family Practice Notebook 2011).

- **Overdiagnosis**

Interest in cancer screening in LMICs is growing at a time when concerns about overdiagnosis and overtreatment, with resulting costs to the health care system, as well as the psychosocial, physical, and economic risks incurred by individuals are increasingly a matter of concern in HICs. *Overdiagnosis* is the diagnosis of disease that will never cause symptoms or death during a patient's lifetime. It can be viewed as a side effect of testing for early forms of disease that may turn people into patients unnecessarily and may lead to treatments that do no good and perhaps do harm. This is especially relevant for breast and prostate cancer (Esserman, Thompson, and Reid 2013; Welch, Schwartz, and Woloshin 2011; Yaffe and Pritchard 2014). Overdiagnosis in breast screening is discussed further in the section on breast screening in this chapter.

Another important debate in HICs is about how much screening causes harm from a false-positive screening test, which often leads to significant wait-times for additional imaging tests and/or a tissue biopsy for what ultimately proves to be a benign finding. False-positive screens must be balanced against the benefits conferred by finding screen-detected cancers that genuinely extend survival and reduce mortality.

Criteria for Cancer Screening

Screening for cancer can be effective if the criteria are met. The Wilson-Junger (1968) criteria (box 12.1) set out a series of considerations that, notwithstanding updates in an era of molecular and genetic diagnostics, remain worthy criteria to help make an assessment. Modern variants of the criteria extend to the consideration of genetic susceptibility, in addition to preclinical disease or precursors (Goel 2001).

Box 12.1

Principles of Early Disease Detection

Condition

- The condition should be an important health problem.
- There should be a recognizable latent or early symptomatic stage.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.

Test

- There should be a suitable test or examination.
- The test should be acceptable to the population.

Treatment

- There should be an accepted treatment for patients with recognized disease.

Screening Program

- There should be an established policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available. The cost of case-finding, including diagnosis and treatment, should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a "once and for all" project.

Source: Adapted from Wilson and Junger 1968.

SYSTEM REQUIREMENTS FOR ORGANIZED CANCER SCREENING

Infrastructure, Education, and Advocacy

The reality in many LMICs is quite different from that in HICs with longstanding cancer health promotion efforts and organized screening programs. Organized approaches to screening risk straining the burden on already thin health care and public health resources. Delayed presentation for cancer is the norm in many LMICs and within low-resource or geographically remote regions in upper-middle-income countries. This delay exists for a variety of structural, equity, and sociocultural reasons (Knaul, Frenk,

and Shulman 2011; Story and others 2012). Structural obstacles include the following:

- Strained health infrastructure, for example, the lack of available human and technical resources for proper diagnosis and disease management
- Long distances and poor road conditions that render proper care inaccessible
- Sociocultural barriers, including extreme poverty, myths, and stigma about cancer
- Gender inequity, which is especially relevant to breast and cervical cancer (Errico and Rowden 2006; Ginsburg 2013; Price and others 2012; Vorobiof, Sitas, and Vorobiof 2001)

Such obstacles underscore the need to incorporate a range of decisions in LMICs to inform the optimal approach to screening. Options vary from an opportunistic case-finding approach, to a population-based screening model, to a high-risk screening approach. Regardless of the approach taken, a new cancer screening program will contribute to increasing 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, diagnostic, and treatment facilities. In regions with severely constrained health infrastructure, the effects of the screening program 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, sociocultural contexts, health systems, infrastructure, human resource capacity, community acceptability, and local political will.

Irrespective of the approach to screening, to scale up organized screening projects, initial plans require rigorous evaluation as well as knowledge translation and exchange to all relevant stakeholders, including community agencies and patient advocacy groups. 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. Follow-up for those with a positive (for example, abnormal) screening test should include a well-developed care pathway to ensure timely referrals for further evaluation, which may include another imaging modality (for example, breast ultrasound), a biopsy, or surgery, as well as a timely

and accurate pathology result. For those with a cancer diagnosis, appropriate referral for evidence-based and resource-appropriate treatment planning is essential, begging again the capacity to make it so in LMICs. Those with a negative screening test should be offered “invitations” for their next round of screening, according to local guidelines (for example, a woman age 60 years who is of average population risk can be invited by mail or telephone to schedule her next screening mammogram two years from the last negative screen).

Cost-Effectiveness Considerations

Cost considerations should include excess direct and indirect health care expenditures for cancers detected at an advanced stage, including out-of-pocket expenses and caregivers’ time away from work. Any analysis should also consider the case for such investment, describing macroeconomic cost models and potential savings from treatment and prevention of cancer sites for which prevention or early detection can have the largest impact on morbidity and mortality (Knaul, Frenk, and Shulman 2011). Estimated losses are presented with more- or less-conservative estimates of avoidable deaths.

According to these models for 2010, global investments in cancer care and control might have saved from US\$10 million to US\$230 million in disability-adjusted life years (DALYs), or US\$531 million to almost US\$1 trillion in value of statistical life. Further, Knaul, Frenk, and Schulman (2011) highlight greater cost savings from adopting a prevention/early detection-and-treatment approach versus a treatment-only approach for breast and cervical cancer. Cancer screening policy may be framed in terms of *investments*, although the timeline to downstream benefits (such as DALYs saved or citizens remaining in the workforce longer) will certainly outspan the political cycle and will depend on how robust and effective the screening program becomes. Cost-effectiveness analysis should also consider the opportunity costs of not screening, specifically for cancers where early detection and appropriate treatment may significantly improve survival rates, such as breast, cervical, and colorectal cancer.

Ethical Considerations

In addition to economic considerations, ethical obligations require jurisdictions to ensure that benefits outweigh harms and that the diagnostic and treatment resources are sufficient to justify from the outset the initiation of a screening program. Recently, some investigators have suggested that the informed population’s

preference should also be a factor in such deliberations (Harris and others 2011). The informed population may have a fair say in the design and buy-in for new screening programs, but countries with established cancer screening policies may find it problematic to separate informed preferences from the popular view that earlier detection is invariably better.

This viewpoint is attributable in part to what Gilbert Welch refers to as the *popularity paradox*, whereby the very modest benefits of some forms of screening are interpreted by the individuals who have detected early-stage disease as having had their disease cured or survival improved as a function of screening (Welch, in Raffle and Gray 2007). Few cancer care professionals and few screening policy makers will counter this view publicly because there is no simple way other than the fullness of time to fully determine whether the disease is “cured.” Nor is there much compassion to be earned for calling into question patients who optimistically, but in many cases mistakenly, believe they have had their disease cured. Counterintuitively, the greater the extent of overdiagnosis and overtreatment, the greater the number of screened individuals who believe they owe their lives to the screening program. While the popularity paradox has been identified in HICs, this experience may provide cautionary advice to LMICs that are contemplating establishing screening programs. By contrast, high-risk areas in LMICs consist of specific countries, regions, and subpopulations that bear the disproportionate burden of premature mortality in a range of lethal cancers, including liver, stomach, esophagus, and oral cancer.

CANCER SCREENING CANDIDATES IN LMICs

Overall and site-specific cancer mortality rates can be gender-specific. For women in LMICs, breast and cervical cancer are the leading causes of cancer death, followed by lung, stomach, and liver cancer. For men in these geographical areas, lung, liver, stomach, esophagus, and colon cancer represent the highest mortality burden. The following sections explore the value of screening among several of these candidate conditions.

Breast Cancer

Breast cancer, the most common cancer in women worldwide, is the leading cause of cancer deaths in women in most jurisdictions with reliable data. More than 50 percent of breast cancer deaths occur in LMICs.¹ These rates will continue to grow with development (Bray and others 2012), which has gone hand in hand with the Westernization of diets and reproductive

patterns—fewer children, later first childbirth, and shorter breastfeeding periods. These are factors that raise the risk of breast cancer (Corbex, Burton, and Sancho-Garnier 2012; Porter 2008).

The debate regarding overdiagnosis is of particular relevance to breast cancer screening; it is estimated that from 10 to 30 percent of breast cancer detected through population-based screening mammography may never have resulted in clinically significant disease but triggers full-scale treatment.

A moderate view is that despite some limitations in all screening studies, breast screening mammography has benefits that outweigh harms, and a frank discussion should take place between health care providers and their patients, so that each woman can make an informed decision. In 2012, the National Cancer Institute (U.S.) convened a task force to address overdiagnosis in cancer screening. The task force concluded that while screening is intended to detect early-stage cancer to improve the likelihood of cure, finding more indolent cancers with “better biology” also contributes to better outcomes. The task force suggested that policies be developed to help mitigate the problems of overdetection and overtreatment, “while maintaining those gains by which early detection is a major contributor to decreasing mortality and locally advanced disease,” (Esserman, Thompson, and Reid 2013, p. 798) and recommend that health care providers and patients openly discuss the issues, which the media should better understand and communicate to the public.

Despite these controversies, breast cancer mortality has been declining in many HICs where mammogram screening programs have been in place for over 20 years (OECD 2011). Many agree that this reflects a combination of newer effective therapies, improved breast awareness, and advocacy campaigns, but the relative contribution of each of these factors is difficult to isolate (Kalager, Adami, and Bretthauer 2014). Of relevance to LMICs, Kalager, Adami, and Bretthauer’s commentary on the Canadian National Breast Screening Study 25-year follow-up noted that the study lacked a “mammogram only” arm, which limited the ability to determine the effects of clinical breast examination (CBE) alone versus mammography alone. The authors allude to the potential risk of generalizing to other countries and suggest that early detection may be of greater benefit in communities where most breast cancers present clinically with more advanced disease. In regions where no such advocacy and awareness campaigns exist, it remains unclear how much early detection for breast cancer (or other cancers for which screening is promoted in HICs) can be achieved by a combination of advocacy and awareness campaigns to reduce stigma

and overcome cancer myths, and by implementing lower-cost but potentially effective screening interventions such as CBE.

The use of mammography for mass screening for breast cancer requires expensive machinery, with its own measurable risk, adequate distribution of radiologists and radiographers, and complex quality controls. Moreover, as overall incidence rates remain lower in LMICs relative to HICs and the average age of women with breast cancer is lower than in HICs, the overall benefit-to-harm ratio will be correspondingly lower whether mammography or simpler techniques, such as CBE with a skilled trainee, are used.

A recent systematic review of economic analyses of breast cancer control in LMICs concludes that the evidence base for guidance on screening modality (for example, CBE versus mammography), the frequency of screening, and the target population is limited and of poor quality (Zelle and Baltussen 2013). Anderson and others in chapter 3 explore in detail the most promising of the early detection studies reviewed by Zelle and Baltussen and recommend that early detection programs in LMICs be carefully designed to facilitate early phase evaluation.

Self-screening or breast self-examination in LMICs appears to present greater harms than benefits based on one large Asian trial (Thomas and others 2002). A lower risk of mortality or advanced breast cancer was found in a meta-analysis of breast self-examination only in studies of women with breast cancer who reported practicing breast self-examination before diagnosis (Hackshaw and Paul 2003); no difference was found in the death rate in studies on women who detected their cancer during an examination. Despite conflicting evidence for CBE in some low-income and lower-middle-income country settings (Nguyen and others 2013; Pisani and others 2006), Anderson and others in chapter 3 of this volume note that a case remains to be made for CBE as a means of stage shifting, especially in populations where the average tumor size at presentation is considerably larger than that in most of the breast screening studies to date. Reasonable evidence suggests that formal training in CBE for primary care professionals can improve the sensitivity of the procedure and reduce the number of false positives (Vetto and others 2002).

The Breast Health Global Initiative has developed an evidence-based, resource-stratified approach to early detection and screening, as well as diagnosis, treatment, and most recently, supportive care and quality of life (Anderson 2013). Recommendations for resource allocation include not only the screening modalities such as CBE, mammography, and diagnostic ultrasound, but culturally-sensitive and linguistically-appropriate

local programs to teach the value of early detection as well as risk factors and breast health (Anderson 2013). Evaluation goals are included for each resource level for public education and awareness, as well as detection methods. Recognizing that great differences in health systems and infrastructure often exist within countries, most notably from urban centers to rural areas, stratification is based on on-the-ground capacities, rather than a single country-level determination, such as gross domestic product per capita.

There is an important role for improved breast cancer awareness among the general population in LMICs as well as primary care practitioners; this can be an entry point to any early detection program. In the absence of evidence of the benefits from a systematic assessment of CBE-based organized screening, we will await the final results from the Mumbai trial (Mittra and others 2010) and the Trivandrum trial of CBE in India (Sankaranarayanan and Bofetta 2010) for any definitive story on CBE as an organized screening tool. Notwithstanding the absence of definitive experimental evidence for implementing organized CBE-based screening as a preferred approach to screen for breast cancer, there is value in trying to strengthen primary care skill in CBE to improve early case-finding and diagnostic activity among symptomatic women, since the large majority of breast cancers are diagnosed in women with breast lumps.

Cervical Cancer

Cervical screening may have the greatest potential for screening-detected reductions in cancer mortality in less developed regions, where about 85 percent of all new cases and 87 percent of deaths from cervical cancer occur (Ferlay and others 2013). The incidence of cervical cancer is highly correlated with country income group, the prevalence of high-risk subtypes of the causal agent HPV (particularly HPV 16 and 18, which account for approximately 70 percent of the case burden), and whether the country or region of interest has had a longstanding population-based screening program (see chapter 4 in this volume). In terms of DALYs, which depend also on the average age at which individuals are affected, cervical cancer ranks highest by, and is correlated with, a lower human development index, a composite measure that includes life expectancy, education, and income (Soerjomataram and others 2012).

Despite the efficacy of cytology-based mass screening programs, Papanicolaou, or Pap, testing is costly, complex, and requires robust health systems. Chapter 4 in this volume notes the poor penetration of widespread Pap testing owing to such costs. The unequal burden of mortality as a consequence reflects unequal access in less

developed countries. Newer and less expensive strategies to prevent cervical cancer have been evaluated and the introduction of new HPV vaccines offers real prevention prospects for the first time.

VIA in combination with cryotherapy (screen-and-treat) was trialed in a demonstration project in Ghana and was well accepted by the communities involved (Blumenthal and others 2007). This effort underlines the value of simple and effective technologies for low-resource settings despite inadequate coverage and significant numbers lost to follow-up. A one-time screening at 35 years of age with VIA or HPV testing reduced the lifetime risk of cervical cancer by approximately 25 to 36 percent and cost less than US\$500 per year of life saved (Goldie and others 2005).

Two exciting trials reporting on test-and-treat models in India (Sankaranarayanan and others 2009) and South Africa (Denny and others 2010) have highlighted the superiority of a screen-and-treat approach that uses relatively more expensive HPV testing over VIA, whether followed by colposcopy in the Indian trial or cryotherapy in the South African trial. The Indian trial showed that a single round of HPV testing can reduce the incidence of advanced cancers and deaths from cervical cancer. The South African study showed benefits in the VIA group, but HPV DNA testing most effectively reduced the incidence of advanced invasive cancer that developed more than 12 months after cryotherapy. HPV DNA testing, with or without VIA, shows the greatest promise; however, given the current state of pathology infrastructure and cost considerations for less developed regions and, in particular, for rural populations in LICs and lower-middle-income countries, the introduction of mass screening with VIA may be the most prudent real-world approach.

In addition, several combination modes of preventive HPV vaccination in preadolescent girls, combined with various screening measures in adult women, appear promising as a comprehensive method to reduce the burden of cervical cancer and reduce HPV infection. In Sub-Saharan Africa in particular, a strong case exists for screening with VIA and rapid HPV tests to ramp up prevention and detection services to screen, treat, or refer. This approach would allow for the opportunity to deal with any other gynecological issues. Populations with coterminous HPV and HIV infections are at highest risk and have the highest need for cervical cancer prevention focus (Sahasrabudde and others 2012).

With respect to the cost effectiveness of cervical screening programs, recent analyses demonstrate that there are promising opportunities to prevent cervical cancer in different world settings. As stated in chapter 4, HPV vaccination for preadolescent girls and/or screening

of adult women, even only three times per lifetime, can avert a significant proportion of cervical cancer cases in a cost-effective manner. In addition to many other critical inputs to health decisions, such as political will and cultural acceptability, evidence on the cost effectiveness and affordability of HPV vaccination and screening from rigorous model-based analyses can help to inform decision makers and stakeholders in their deliberations of how best to prevent cervical cancer worldwide.

Colorectal Cancer

Lambert, Sauvaget, and Sankaranarayanan (2009) advance a strong argument that the burden of colorectal cancer, while high and growing in HIC regions (about 12 percent of deaths from cancer), remains low on the list of common cancers and primary causes of cancer-related mortality in less developed regions (about 6 percent of deaths from cancer). Lambert, Sauvaget, and Sankaranarayanan argue that the expense of mounting a mass screening effort in most LMICs is not currently justified, given the significant costs of colonoscopy and follow-up services. The authors do allow that the growth of more Western lifestyles in large urban centers in upper-middle-income countries may represent areas where colon screening may be more justifiable.

By contrast, as noted in chapter 16 of this volume, at least one report suggests that screening colonoscopy may be cost effective in Sub-Saharan Africa (Ginsberg and others 2012), at least in the urban areas of upper-middle-income countries, where the incidence of colorectal cancer is increasing because of population aging and the adoption of Western lifestyles.

The International Colorectal Cancer Screening Network (2013), which works to document and standardize the best jurisdictional approaches to colorectal screening, identifies the need for screening program experience on every continent, although membership is currently limited to more developed regions. Research in progress may offer a range of promising and less invasive methods to detect early-stage colon cancer, which may offer better options to reduce colon cancer mortality in LMICs.

A phased introduction of colorectal cancer screening by immune sensitive fecal occult blood testing in Thailand, beginning with a pilot evaluation in Lampang province, shows promise for reducing colon cancer mortality. The program is based on a five-year interval for immune fecal testing, which is supportable by the health system infrastructure and appropriate, given the relatively lower colon cancer rates compared with other countries with screening programs (Khuhaprema and others 2014).

Promising New Candidates

Simple visual screening methods in high-risk areas for oral cancer in South Asia and Southeast Asia represent an excellent example of pragmatic screening (Sankaranarayanan and others 2005). These cancers are highly linked to tobacco and alcohol consumption, as well as to chewing betel and areca nut and paan and gutka (see chapter 5). Increasing evidence suggests that HPV is a risk factor in oral, head, and neck cancers. Most cost-effectiveness studies come from HICs, but one very promising study from India suggests that oral cancer screening by visual inspection has an incremental cost-effectiveness ratio of US\$835 per life year saved (Subramanian and others 2009). Further, the authors note that the most prudent approach for limited resource settings should include only higher risk populations, such as heavy users of tobacco and alcohol. There is now some trial evidence that visual screening can reduce oral cancer mortality in users of tobacco and alcohol (Sankaranarayanan and others 2013).

By contrast, in HICs, a recent assessment from the U.S. Preventive Services Task Force has concluded that the case for mass screening for oral cancers in the relatively lower risk United States is insufficient to justify the harms of mass screening of asymptomatic adults (Moyer and U.S. Preventive Services Task Force 2014).

Gastric cancer is a close tie with liver cancer as the second leading cancer-related cause of death and is a particular challenge in the East Asia and Pacific region. Promising programs are being mounted in Japan and the Republic of Korea and in trials in China to screen for the bacterium *Helicobacter pylori*, the cause of a large fraction of gastric cancer, and to eradicate infections detected. However, *H. pylori* eradication, which reduces gastric cancer risk, is hampered by emerging regional antimicrobial resistance to antibiotics used to treat it and the lack of a means to target a high-risk population. Gastric cancer remains a screening and prevention candidate in need of more refined trials (Park and others 2013).

SPECIAL CONSIDERATIONS FOR CANCER SCREENING IN LMICs

Screening Priorities in LMICs

Promising cancer screening candidates in each of the less developed regions warrant attention. The joint report of the World Economic Forum/Harvard School of Public Health and the World Health Organization highlights a set of affordable, feasible, and cost-effective intervention strategies to reduce the economic impact of noncommunicable diseases in LMICs (WEF 2011).

The most promising evidence in LMICs suggests that the highest priorities are breast and cervical cancer screening, possibly followed by colorectal cancer or stomach cancer screening, if programmatic infrastructure can be established in a stepwise fashion. Carefully planned programs for breast screening, according to local context and resource capacity as highlighted in the Breast Health Global Initiative documents, and VIA with cryosurgery or colposcopy (with or without HPV testing, where available) can appropriately be recommended as first cancer screening priorities in LMICs.

Role of Innovation

Many opportunities already exist to exploit the potential impact of programs for early detection and screening. Considering a given screening strategy for which locally-sourced evidence demonstrates at least proof of concept in terms of efficacy and cost effectiveness, transition-to-scale projects can take advantage of a variety of innovative approaches to optimize participation, follow-up for an abnormal screening, as well as monitoring for treatment-related toxicities and survivorship care. These approaches include telemedicine; telepathology; institutional twinning; task-shifting; and “m-Health” (WHO 2011a, 2011b), models of care enhanced by the use of mobile phones, which are widely available and affordable in most LMICs (Ginsburg 2013). Large technical platforms can give way to cloud applications, which allow for easy and secure storage and compilation of information for screening programs. However, this still requires a basic information and communications technology infrastructure, computer availability, and up-to-date software, which are missing in many countries.

Similarly, not all screening activity needs to involve only primary care physicians or specialty care providers, if reliable evidence is used to build from project-to-scale programs. In this fashion, trained community care workers, nurses, and other care providers can assist in building capacity, promoting screening activities, and being effective screening agents in LMICs.

Diagonal Approach to Strengthen Health Systems

From a programmatic perspective, the breast and cervical cancer studies also indicate some merit in an integrated approach to screening under the umbrella of maternal or reproductive health policy, as suggested in the trial in Mumbai (Mittra and others 2010) and the approach taken in Morocco.² The Global Task Force on

Expanded Access to Cancer Care and Control (2011) has championed this diagonal approach, “the proactive, supply-driven provision of a set of highly cost-effective interventions on a large scale that bridges health clinics and homes” (Sepúlveda 2006). While the age intervals best chosen for a first screening intervention may not be an exact match, for women undergoing simultaneous screening efforts, there is at least the prospect of having both screening procedures performed during the same visit, a predictor of better participation than multiple visits, an observation now being mimicked in HICs. “Pink Ribbon Red Ribbon” (UNAIDS 2011) is an example of a program that added breast and cervical cancer screening to an existing program for another health condition, namely, HIV. HIV-positive women have a greater chance of developing invasive cervical cancer and higher mortality rates than their HIV-negative counterparts. This type of program can address the needs of a group at particularly high risk with a low marginal cost.

Such a diagonal approach is not limited to women’s health services. Integrating cancer screening into existing health programs can also help to build primary care capacity. Harnessing the synergies between traditionally vertical programs can build platforms onto which additional preventive and wellness care (such as vaccinations, smoking cessation, and nutritional counseling) may be added to reduce the incidence and mortality from other cancers (such as lung, stomach, or oral), as well as other high-burden chronic noncommunicable diseases. Modeling such programs can also help to convince policy makers that cancer screening and cancer control in general will not necessarily siphon off scarce resources from competing health priorities.

Policy Considerations for Cancer Screening in LMICs

Cancer screening policies and the programs they create become part of established health care systems in governments and societies, each with its own norms and standards. Although the evidence base may be global for any particular cancer, policies and programs vary considerably across the globe, not just between countries according to level of wealth, but among countries of similar economic status. Some differences mirror the huge variation in the incidence of different cancers, but many are caused by differential weighting of evidence and other factors.

Developing a screening policy for cancer involves many decisions, including choice of diagnostic technologies and follow-up interventions, the age groups targeted, referral and enrollment strategies,

and quality assurance processes. The heterogeneity of cancer screening policies across LMICs reflects differences in health care structures as well as the political and cultural factors that shape policy. The governance mechanisms for the development of screening policy may also vary. Some countries use a legislative approach to mandate screening, thus opening policy development to political influence. In other countries, policy development is delegated to technocrats who rely on advice from expert committees or ad hoc groups. Screening policy in LMICs often involves several layers of organization, including transnational actors (for example, the United Nations Population Fund), national health ministries, and experts in various disciplines, as well as prominent domestic and global advocacy groups. The respective roles of authorities is another source of variation, as is the degree of reliance on or participation in the development of policy at the transnational level (for example, guidelines) and how this is shaped by the institutional processes of decision making (Flintcroft 2011).

Cancer screening policies sometimes run counter to what would seem to reflect the best evidence (Nutley, Walter, and Davies 2007). Knowing the diversity of factors (political, social, and economic) that contribute to the development of the health policies reinforces the understanding that the way that research influences policy is not linear and not necessarily determined by the quality of the research alone (Humpreys and Piot 2012; Nightingale and Scott 2007). In fact, many accepted models of public health policy making for cancer screening (research utilization) have likened the process to a complex dance (Edwards 2001), a garbage can of ideas waiting to be needed (Cohen, March, and Olsen 1972), and parallel streams awaiting a social, political, or economic reason to stimulate a convergence and therefore the formation of policy (Kingdon 2003). The policy process can become more transparent and outcomes more predictable (although still respecting national differences) with standardized decision making systems that encompass the principles of health technology assessment for all policy decisions that involve weighing evidence on effectiveness, costs, and societal factors.

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 (McCormack and others 2011) and how the program fits within the health care system and with other health messages, including cancer prevention.

ACKNOWLEDGMENT

The authors express special thanks to Signy Roland for her support in the compilation and extraction of the studies discussed in this chapter and to Sandra Hofstetter for her support in compiling the manuscript.

NOTES

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US\$1,045 or less
- Middle-income countries:
 - Lower-middle-income: US\$1,046–US\$4,125
 - Upper-middle-income: US\$4,126–US\$12,745
- High-income countries: US\$12,746 or more

1. <http://www.who.int/cancer/detection/breastcancer/en/index1.html>.
2. “Importance of the Screening,” Fondation Lalla Salma Prévention et Traitement des Cancers, accessed March 8, 2014, http://www.contreleccancer.ma/en/importance_du_depistage.

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