Cancer Screening: Global Debates and Cuban Experience
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ABSTRACT
A review was conducted of screening strategies for detecting the main cancer sites for which screening has been recommended, assessing WHO and other international organizations’ positions, as well as the requirements of Cuba’s cancer control strategy. Universally, screening is recommended for cervical, breast and colorectal cancer, all included in the Cuban strategy. Additionally, in Cuba, PSA testing is indicated for men considered at risk (aged >45 years with family history) and those aged >50 years who request it; annual oral exams and teaching of oral self-examination are recommended for the entire population; and for adults aged >35 years, active annual oral cancer case finding. Screening for skin cancer is performed by physical examination of individuals at risk. To maximize benefits of early cancer detection, greater coverage is needed as well as studies of how well screening is performing under current Cuban conditions.

KEYWORDS Cancer, early detection, screening, secondary prevention, breast cancer, cervical cancer, colorectal cancer, skin cancer, oral cancer, Cuba

INTRODUCTION
A national cancer control program is a public health program designed to reduce cancer incidence and mortality and improve cancer patients’ quality of life, through systematic and equitable implementation of evidence-based strategies for prevention, early detection, treatment and palliative care, making the best possible use of available resources.[1]

Early detection is based on diagnosis early in a cancer’s development, in pre-symptomatic stages, when treatment is more likely to be effective. Early detection depends on two main components: education and screening.[1] An estimated 30% of cancers could be cured with early detection and appropriate treatment.[2]

Screening is the presumptive identification of unrecognized disease by means of tests that can be applied rapidly to separate the healthy from the possibly sick.[3] While appropriateness of some specific tests is still debated, cancer screening as such is accepted by the international medical community based on the evidence.

Screening program success depends on various factors related to the disease, the proposed test and the health system. The cancers chosen for screening should be common and associated with high morbidity and mortality, and there should be treatment available that can reduce these indicators. The screening test should be acceptable to the population for which it is designed, sufficiently sensitive to detect early lesions, feasible for use in medical practice, and relatively inexpensive.[1] It should be sensitive enough to detect cancer in those who have the disease and specific enough to correctly rule out individuals without the disease. Two other important test characteristics depend on sensitivity and specificity, but also on disease prevalence in the population screened: positive predictive value, or extent to which those who test positive actually have the disease; and negative predictive value, or extent to which those who test negative are actually disease free.[1]

Characteristics of national health systems also influence which screening approaches are appropriate. The system must have the resources to deliver screening to a sufficiently large proportion of the population to obtain the expected benefits, and it must also have the capacity to provide subsequent diagnosis, treatment and followup. In developing such screening strategies, WHO recommends that national cancer control programs should not impose the advanced technologies of high-income countries on countries with more limited resources. Hence, policies will undoubtedly differ among countries.[1]

Early detection is a strategic component of Cuba’s Comprehensive Cancer Control Program. This in turn comprises three different approaches: population screening (of apparently healthy people), targeted screening (of individuals at risk) and case finding in symptomatic patients. The Program is considering organizing pilot areas to validate study findings in asymptomatic populations, to assess generalizability of screening trial results.[4]

In each of Cuba’s 168 municipalities, a Center for Comprehensive Active Screening has been set up, reporting to the municipal health department. These are laboratories outfitted with ultramicroanalytic system (SUMA, the Spanish acronym) technology, staffed by personnel trained in its use. Havana’s Immunoassay Center supports laboratory operations through reagent distribution, technical assistance with equipment repair and maintenance, and analytical assistance as requested by clients or in response to results of external audits. The laboratories were conceived to expand diagnostic capabilities beyond traditional techniques and to conduct other activities for program development and quality assurance, as well as to enable early detection of cancers included in screening programs, to conduct screening studies on population groups according to risk stratification and population health status, and to ensure comprehensive services for improved diagnostic quality and health outcomes.

This paper reviews screening strategies for the main cancer sites for which screening is recommended and assesses the criteria and results of studies by WHO and other international organizations, as well as the recommendations of Cuba’s cancer control strategy.

Cervical cancer The purpose of cervical cancer screening is to detect precancerous lesions as well as in situ or very early invasive cancer, when treatment is most effective. Three different types of tests are available: conventional (Pap) and liquid-media cytology, visual inspection with acetic acid, and HPV testing for oncogenic HPV types. Screening with appropriate followup can attain significant reductions in incidence and mortality from advanced cervical cancer.[2] One risk of such screening is that detection of low-grade squamous intraepithelial lesions in young women may lead to followup tests and possibly unnecessary treatment. There is also the chance of false positive results, causing anxiety, and of false negative results that can delay medical treatment.[5]

The US National Cancer Institute (NCI) and the US Preventive Services Task Force (USPSTF) recommend that women aged...
Breast cancer The purpose of breast cancer screening is early detection. With appropriate facilities, screening by mammography, with or without physical breast examination, plus followup of individuals with positive or suspicious findings, can reduce breast cancer mortality by up to one third.[1] Such screening also has risks. It can lead to diagnosis of cancers that never would have caused symptoms or death and in so doing, expose patients to treatment risks and side effects. In addition, false positive results sometimes occur, engendering further diagnostic testing and creating anxiety. On the other hand, false negative results can delay diagnosis and treatment. Radiation itself also increases breast cancer risk.[11]

Colorectal cancer Screening for colorectal cancer is based on detecting adenoma, a specific preneoplastic lesion that can be treated effectively. More than 90% of colorectal cancer cases are preceded by these premalignant changes. Lifetime risk of colorectal adenoma is 20%, with peak incidence at ages 55–65 years. Lifetime probability of colorectal cancer is 4%–6%, with maximum incidence at ages 65–75 years; it affects men and women equally. Some 75% of individuals who develop colorectal cancer have no personal or family history of the disease, so risk-group screening is not done, since it would detect only about 20% of cases. Early detection can lead to cure in 80%–90% of cases.[13] The tests most recommended for early detection of colorectal cancer are the fecal occult blood test, sigmoidoscopy and colonoscopy. Double-contrast barium enema is another imaging procedure that has been recommended for screening. Other techniques, such as computerized tomographic colonoscopy or virtual colonoscopy, have also been applied but have not yet been shown effective.
to reduce mortality rates. Trials are under way to assess tests for human DNA in fecal matter or blood samples.[14–16]

Colonial cancer screening does have potential negative effects. Sigmoidoscopy and colonoscopy can be uncomfortable, even painful. They can also, albeit infrequently, cause complications such as perforation, hemorrhaging or cardiovascular events. Fecal occult blood testing can produce false positives that can lead to further testing—with attendant iatrogenic risks—or false negatives (if the lesion bleeds only intermittently, or not at all), which can delay diagnosis.[17]

In 2007, the World Gastroenterology Organization published the International Digestive Cancer Alliance Practice Guidelines, based on review of the various screening options. The Guidelines involve a screening cascade, with recommendations for settings at six different resource levels, from minimum to high.[13] NCI and USPSTF recommend three options for screening individuals aged ≥50 years for colorectal cancer: annual fecal occult blood test, sigmoidoscopy every 5 years with fecal occult blood test every 3 years, or colonoscopy every 10 years.[18] WHO recognizes that screening with sigmoidoscopy and annual fecal occult blood testing reduces mortality from colorectal cancer and emphasizes the need for higher population coverage to obtain greater benefits in proportion to costs generated.[1,2]

In Cuba, it is recommended that asymptomatic patients aged ≥50 years have an annual fecal occult blood test and flexible rectosigmoidoscopy or double-contrast barium enema every 5 years. Patients with a family history of colorectal cancer should have a colonoscopy every five years. Since 2013, in addition to the traditional guaiac test for fecal occult blood, a rapid qualitative immunological test to detect occult human blood in fecal matter has been available. Called SUMASOHF, it was designed by the Immunoassay Center and is distributed throughout Cuba by TecnoSuma International. It is a highly sensitive sandwich-type chromatographic immunoassay for early diagnosis and followup of gastrointestinal disorders that provoke bleeding. In 5 minutes, human hemoglobin levels as low as 0.2 µg/mL can be detected in fecal matter.[19] In 2013, SUMASOHF was introduced in the 116 Cuban municipalities with the highest colorectal cancer mortality rates. A total of 50,756 individuals aged >50 were screened, coverage of only 2.7%; positivity was 10.4% (data from Form 241-509-01, SUMA Technology 2013, Statistical Information System, MINSAP). Screening coverage must be increased as quickly as possible to reduce mortality from colorectal cancer, the third leading cause of cancer deaths in Cuba, with 2089 deaths in 2012 (18.6 deaths per 100,000 population).[10]

**Prostate cancer** Expert opinion on the PSA test has varied over the years. Until recently, many physicians and organizations recommended that men be tested annually beginning at age 50; and men at higher risk even earlier, at 40 or 45 years. Several randomized trials of PSA screening have been conducted, with contradictory results. A study by US NCI concluded that incidence was rising but mortality was not falling, while the European Randomized Study of Screening for Prostate Cancer (ERSPC) did find a drop in mortality (a trend that seems to be supported by sustained lower rates over a longer period of followup).[20–22]

The majority of urological associations have concluded that generalized population screening with PSA is not appropriate and early detection should be offered only to individuals well informed of the risk of detecting some prostate cancers that would never have inflicted health problems and that could lead to overtreatment. Despite this, many insurance systems cover PSA testing, including Medicare in the United States.[23] The issue remains controversial. In March 2014, the US National Comprehensive Cancer Network (NCCN) published updated guidelines for use of PSA testing in prostate cancer screening, recommending routine screening of men aged >45 years, with frequency of subsequent screening dependent on results of baseline screening with PSA and digital rectal examination.[24]

WHO's position is that digital rectal examination is not sufficiently sensitive to detect early stages of the disease, and it is not yet clear whether PSA reduces mortality. WHO insists on the need to establish PSA's effectiveness with well-designed randomized trials, currently under way.[1,3]

In Cuba, PSA is recommended for symptomatic patients; men aged ≥45 years with a family history of prostate cancer; and those aged >50 years who request it.[4] The test used is UMELISA PSA, an assay designed by the Immunoassay Center to quantify total and free PSA in human serum samples.[25]

Prostate cancer is the second leading cause of cancer deaths in Cuban men, and crude mortality rates have risen in recent years, from 1844 deaths (33.1 per 100,000 men) in 2000 to 2703 deaths (48 per 100,000) in 2012.[10] In 2013, 238,799 PSA tests were performed in the national health system, in 14.5% of the male population aged >50 years, with 14.8% positivity (data from Form 241-509-01, SUMA Technology 2013, Statistical Information System, MINSAP). Research is needed to assess the results of PSA testing in Cuba's health system. An as-yet unpublished study in the province of Santiago de Cuba is under way, but focusing on PSA screening's impact on incidence, not on mortality.

**Oral cancer** According to NCI and USPSTF, it has still not been demonstrated that oral cancer screening by direct visual examination reduces mortality from the disease.[26] The Cochrane Oral Health Group concludes that there is insufficient evidence to determine whether screening by visual inspection reduces mortality rates, and there have been no trials of other screening methods. However, there is some evidence that screening may help reduce mortality in patients who use tobacco and alcohol, although the only study included that showed benefits may have been affected by bias due to faulty randomization.[27] WHO agrees that detection of precancerous lesions or early-stage tumors has not yet been shown to reduce oral cancer mortality.[1,2]

Cuba's strategy recommends an annual mouth-and-throat exam and teaching oral self-examination for the entire population, and active annual case finding in the community to seek individuals aged ≥35 years at risk, who are then referred for examination.[4] Control actions for this cancer have been carried out in Cuba since 1982, as part of a national oral cancer detection strategy.[28] Data have not been published that could help assess extent and results of the strategy’s implementation.

In 2012, cancer of the lip, oral cavity and pharynx was the ninth leading cause of cancer mortality in Cuba in both sexes, with 641 deaths (5.7/100,000 population), up from 492 in 2009.
In Cuba, screening by physical examination is recommended for individuals at risk for skin cancer.[4] Data needed to assess the success of this strategy have not been published. In 2000, there were 271 deaths from skin cancer (2.4/100,000 population), while in 2012 there were 386 (3.4 per 100,000). In both years, it was the 13th most frequent cause of cancer deaths.[10]

Other cancer sites Today, screening tests for cancer at various sites are being evaluated through a range of trials that include so-called advanced technologies. Policymakers in each country must decide whether to include screening innovations in national programs, based on emerging scientific evidence as well as their own epidemiological and economic conditions.

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