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Screening for Cancer: Valuable or Not?

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Screening for cancer has become extremely common. The evidence supporting screening for breast, colon, and cervix cancer is strong, but it is unclear for skin cancer, problematic for prostate cancer, and ineffective for lung cancer. Despite the problems associated with many screening approaches for cancer, enthusiasm by the medical profession and the public remains high. The objective analysis for the major tumor types is presented in this review, but the ultimate decision on whether to be screened lies in the personal and societal arena of values.

Introduction

The practice of oncology can be conveniently divided into two major spheres of intervention: prevention and treatment. The emphasis on treatment has been dominant in oncology training until the past decade, in which advances in imaging and optics and increased understanding of the biologic basis of cancer formation (carcinogenesis) have led to a widespread interest in the early management of human cancer by practitioners in a wide variety of primary care and subspecialty disciplines, including oncology. In general, however, the training and education of oncologists in prevention have remained largely parallel to the treatment paradigm rather than an integrated effort, although a genuine effort has been made to improve this situation recently [1].

Prevention can be conveniently divided into intervention at three levels: primary, secondary, and tertiary [2]. Primary prevention involves abstinence from or discontinuation of substances that are cancer causing or inhibition or detection of cancer before the process becomes clinically evident. Screening of asymptomatic individuals for cancer is an example of primary prevention. Well-accepted examples of successful screening approaches include mammography in postmenopausal women and fecal occult blood testing (FOBT) in individuals aged over 50 years.

Secondary prevention includes detection of cancer in symptomatic individuals or inhibition or reversal of clini-

cally identifiable preneoplastic processes (precancer) by visual, endoscopic, radiologic, or other means. Recently, the focus on precancer has been on intraepithelial neoplasia (IEN) as a target for early detection and active chemoprevention [3•]. Some examples that are particularly amenable to minor surgical interventions include cervical IEN and adenomatous colorectal polyps. Tertiary prevention includes inhibition or early identification of second malignancies in patients cured of a low-stage malignancy by surgery or more complex multimodality approaches.

The emphasis of the current paper is on screening for malignancies in asymptomatic individuals.

Why Is It So Difficult to Prove That Screening for Cancer Actually Accomplishes What It Is Supposed to Do?

The formalistic aspects of screening and its underlying scientific principles have been widely presented and discussed. The principles and general concepts involved in screening are relatively simple, but biases and confounders make execution of an interpretable screening trial very difficult. Screening trials demand considerable financial and personnel resources and the participation of large numbers of essentially well people. The key general concepts in evaluating a screening test have been discussed in detail elsewhere; a particularly well-done and comprehensive presentation has been provided by Kramer and Brawley [4•]. As they so aptly summarize, “The logic of cancer screening represents a clash of medical science and intuition.” Or, to cite Ogden Nash, as they do: “I believe that people believe what they believe they believe.”

The overriding goals of screening should encompass the following principles:

- Not only early case detection as such but also reduction of overall mortality should be part of screening.
- Cancer survival is not an adequate surrogate for reduction in cancer mortality.
- The natural history of screen-detected cancers cannot be extrapolated from the natural history of clinically detected disease.
- Both efficacy and morbidity of screening are inseparable from subsequent therapy.

These important principles are frequently ignored or glossed over in the contentious debates surrounding the

Table 1. US Preventive Services Task Force recommendations

Study	Organ	Recommendation
Humphrey <i>et al.</i> [10] and Mandelblatt <i>et al.</i> [11]	Breast	Recommends screening mammography (with or without clinical breast examination) every 1–2 years for women aged 40 years or older; evidence is insufficient to recommend for or against routine clinical breast examination or for teaching or performing routine breast self examination
Pignone <i>et al.</i> [12]	Colon	Colorectal cancer screening reduces death from colorectal cancer and can decrease the incidence of disease through removal of adenomatous polyps; several available screening options seem to be effective, but the single best screening approach cannot be determined because data are insufficient
US Preventive Services [13]	Cervix	Regular Papanicolaou testing is recommended for all women who are or have been sexually active
US Preventive Services [14]	Skin	Found insufficient evidence to recommend for or against routine counseling by primary cancer physicians to prevent skin cancer
Harris and Lohr [15]	Prostate	The net benefit of screening cannot be determined; although potential harms of screening for prostate cancer can be established, the presence or magnitude of potential benefits cannot
US Preventive Services [16]	Lung	Evidence is insufficient to recommend for or against screening asymptomatic individuals for lung cancer with CT, chest radiography, sputum cytology, or a combination of these approaches

value of screening. In addition to these general principles, a number of biases and confounders exist in the evaluation of screening: The major biases include screenee selection and length and lead-time biases. All levels of evidence, except evidence from randomized, controlled trials in which cause (disease-specific mortality) is the endpoint, can lead to spurious conclusions about the value of screening. Recently, a careful comparison of disease-specific and all-cause mortality in randomized trials of cancer screening revealed a significant discordance: Seven of the 12 trials examined were inconsistent in their direction or magnitude, thereby raising concern about even the time-honored endpoint of disease-specific mortality [5,6].

Medical decision making involves two main steps [7]: 1) “facts” and the analysis of this evidence and 2) personal judgments about the importance of the outcomes and risks of each option (*ie*, values). The issues affecting the second step are much less straightforward and include individual and societal perception of risk, benefits of screening to the individual, relative role of physicians and patients in decision making, and cost-effectiveness in policy decisions. Single-issue advocacy and gender politics also may play a role in decisions at the individual and sociopolitical levels. Each one of these issues merits a lengthy discussion, as done by Ransohoff and Harris [8••], but probably the most important variable for the practitioner to appreciate is that false-positive results are high for even the best screening test. The morbidity from testing and follow-up can be high, although physicians and patients tend to discount this parameter in decision making. However, the overwhelming enthusiasm of participants (and most of the medical profession) for screening obscures this important consideration in an individual’s decision to proceed with a screening test.

Even when a large body of high-quality evidence has been obtained, the debate about the value of screening may be contentious. Screening mammography in women aged from 40 to 49 years remains an archetypal situation despite the completion of many randomized, controlled trials. The issues surrounding the debate about mammographic screening have recently been analyzed and discussed and are applicable to any organ site [8••,9].

What Screening Tests for Organ Site Cancers Have Sufficient Evidence to Suggest That Screening Is Worthwhile?

Many groups recommend various screening tests, resulting in confusion among the public and medical practitioners. Perhaps the most objective analysis of the evidence is provided by the US Preventive Services Task Force (USPSTF). This group is an independent panel of private-sector experts in primary care and prevention that systematically reviews the evidence for effectiveness of a wide range of clinical preventive services, including screening tests, counseling, and chemoprevention. Members of the USPSTF represent the fields of family medicine, gerontology, obstetrics and gynecology, pediatrics, nursing, and prevention research. A summary of their conclusions regarding evidence for screening for specific organ-site cancers is provided in Table 1. It should be noted that this group deals mostly with the first step of medical decision making. Only those organ sites that are sufficiently common to merit consideration for generalized screening are listed, including breast, colon, cervix, skin, prostate, and lung. USPSTF recommendations do not, in general, factor in important personal and societal issues of costs and benefits and competition for scarce

resources that policy makers need to address, and which represent the second stage in medical decision making.

Breast

Screening tests include self-breast examination, clinical breast examination administered by health-care professionals, and mammography. The USPTF has carefully considered the issues and recommends a screening mammography every 1 or 2 years for women aged 40 and older [10,11], a position I favor. Randomized, controlled trials of a large number of women from several countries have unequivocally demonstrated a 30% to 40% decrease in mortality from breast cancer in women who have annual mammograms beginning at the age of 50 years [17]. However, the opinion on routine screening in women between the ages of 40 and 49 and after age 65 to 69 is mixed. Successful implementation of large-scale screening programs incorporating these techniques, followed by treatment of detected lesions, is probably responsible for most of the decline in the overall death rate from breast cancer that occurred in American women from 1989 through 1993 [18]. This decline continues and probably represents both the increased use of mammography and the effectiveness of systemic adjuvant therapy. Five-year survival rates for all women diagnosed with breast cancer have increased to over 90%.

New areas being evaluated for the enhancement of primary and secondary prevention strategies include the use of optical scanning, nipple aspirates, blood and urine assays for growth factors, and autoantibodies to oncoproteins and to tumor DNA. Validated biologic markers of breast cancer risk and more sophisticated screening modalities may well increase our ability to detect lesions in high-risk populations; however, these newer modalities need to be validated.

Colon

Everyone aged over 50 years needs to be screened for colon cancer [19•]. The USPSTF has concluded that several available screening tests seem to reduce death from colon cancer, although it is unclear which test is the best [12]. Yet, surprisingly, less than 50% of people who should be screened are evaluated by FOBT, digital rectal examination (DRE), or sigmoidoscopy [20,21]. Recently attempts have been made to improve participation in FOBT screening. The simple expedient of direct mailing and timely follow-up has led to a marked increase in the use of FOBT and doubled the increase in overall rate of adherence to colorectal screening guidelines [22]. Numerous studies have validated the use of DRE, FOBT, and sigmoidoscopy as effective screening tools, provided that regular screening is performed (to detect lesions in this disease with a long pre-invasive phase) [23,24]. This concern is particularly important with the FOBT because reported sensitivities are low, ranging between 22% and 92%.

Regular screening with sigmoidoscopy in patients aged over 50 years lowers mortality from colorectal cancer as well

as prolonging survival [25]. More frequent screening may be needed in certain individuals who are at increased risk for the development of adenomatous polyps or colorectal cancer. A particularly important group is made up of those who have been treated for a primary colorectal cancer. Recent studies indicate that evaluation of this high-risk group has been inadequate. Other high-risk conditions requiring close surveillance include individuals with a high familial or genetic history of colon polyps or cancer, a longstanding history of inflammatory bowel disease, a prior history of polypectomy or ureterosigmoidoscopy, and a personal history of ovarian, endometrial, or colon cancer.

Cervix

The Papanicolaou (Pap) smear is the most successful screening test in medicine. The USPSTF recommends regular Pap testing for all women who are or have been sexually active [13]. Current screening guidelines of the American College of Gynecologists and the American Cancer Society include annual Pap smear and pelvic examinations for any woman who is sexually active and/or 18 years of age. Despite the profound impact that the Pap test has had on decreasing the incidence of cervical cancer by facilitating early detection of preinvasive lesions, its validity has been questioned periodically. General misperceptions by the media, public regulatory agencies, plaintiffs, physicians, and the community at large exist regarding the role of this screening test.

Conventional Pap smear screening has proven to be extremely effective. The success of this test and future screening modalities depends upon realistic expectations, continued quality assurance, improved sampling of cervical tissue, and incorporation of newer technologies to improve the accuracy of screening and interpretation of Pap smears. However, successful implementation needs to be cost-effective and lead to further declines in the incidence and mortality from cervical cancer. The recognition that human papillomavirus plays a critical role in cervical cancer pathogenesis has led to new approaches to the diagnosis of this disease and to the development of vaccines that appear to be effective [26,27•]. Projected clinical benefits from an effective vaccine should permit a later age of screening initiation, a less frequent screening interval, and considerable cost savings and cost-effective use of health-care resources [28]. The challenge of the next decade will be for cervical cancer screening to optimize the medical outcomes and economic costs in general, as well as in special high-risk populations. Visual inspection after an acetic acid wash of the cervix may be cost-effective in developing countries [29]. However, the relative value of visual inspection, cytologic evaluation, and human papillomavirus testing is a subject of intense debate [30].

Skin

Skin cancer is the most common cancer worldwide and is an important public health problem. Although no randomized, prospective studies have evaluated the efficacy of screening for skin cancer, nonrandomized studies support

its practice. Thinner melanoma lesions (stage I and II) are diagnosed more frequently with routine screening and intensive education programs. Screening for skin cancer, and in particular, for melanoma, is supported by a number of criteria. Melanoma is second only to leukemia in terms of years of potential life lost; it often affects younger people in the most productive period of their lives. Although basal and squamous cell cancers have a much better prognosis than melanoma, they cause considerable local disfigurement if they are not diagnosed and treated early. In addition, screening skin examinations are acceptable to patients and health-care providers. Premalignant cutaneous lesions tend to have long latency phases, making early diagnosis and treatment possible; however, the quality of the evidence supporting routine screening is low [31]. The USPTF has concluded that evidence is insufficient on whether to recommend routine counseling by primary-care physicians for prevention of skin cancer [14].

Prostate

The relative benefits and costs of screening for prostate cancer are among the most contentious issues in the medical community; two excellent balanced editorial commentaries on this issue have recently appeared [32,33]. The two most commonly used screening tests for prostate cancer are the prostate-specific antigen (PSA) and DRE, with transrectal ultrasound (TRUSP) reserved for patients with a positive PSA or DRE. Before the 1990s, yearly DRE in men after age 50 was the standard for detection of prostate cancer as well as for screening. Although many primary-care physicians use the DRE as part of the routine physical examination, assessment of its routine use indicates that DRE is performed in less than 50% of primary-care encounters in which one would expect it to be done. Many issues surround determination of the value of screening for prostate cancer. The following are some of the major concerns:

1. All available first-line techniques (DRE and serum PSA) have high false-positive rates. This leads to a relatively low positive predictive value and the unnecessary work-up of many normal individuals.
2. The natural history of prostatic IEN, the probable precursor of prostate cancer, is highly variable and cannot currently be predicted reliably in any one case or by any specific biologic or pathologic marker.
3. The work-up of abnormal screening tests is invasive, requiring multiple biopsies of the prostate.
4. The treatment of prostate cancer produces significant morbidity and measurable mortality.
5. The false-negative rate is also high, which can produce a false level of assurance about the reliability of the screening tests.

Equally important is the concern about how to identify and distinguish a biologically aggressive tumor in any one individual from those tumors that will remain latent for the life

of the individual. This is a very difficult problem to study, but an answer would greatly facilitate the conduct of screening for prostate cancer. The current consensus by the USPSTF is that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA [15].

Lung

Screening and early detection of lung cancer has not been an effective way to decrease morbidity or mortality [16]. Four large randomized trials of screening chest roentgenograms in smokers demonstrated no difference in survival between the randomized groups [34]. Various new approaches are being explored, including spiral CT, sputum screening by quantitative microscopy, measurement of a variety of molecular changes during malignant progression, and fluorescent detection of lesions during bronchoscopy. However, none of these approaches has been proved useful over the long term, nor have they decreased morbidity or mortality from lung cancer. A new large trial is attempting to determine whether spiral CT will improve outcome in high-risk smokers, but results are not expected until 2015 [35].

High-risk and special cases

Strictly speaking, screening is limited to normal individuals. Although early detection is formally defined as the evaluation of a symptomatic individual for cancer and is therefore different from screening, many of the caveats regarding evaluation of this approach are the same. The increasing ability to identify high-risk populations, either by phenotypic criteria or genetic analysis, had led to a running together of the classical divisions of screening and early detection. With the rapid advances in molecular diagnostics, routine genetic typing of individuals at risk for major tumor types should not be too distant in the future, and quantification and assessment of that risk, a concept we proposed quite some time ago [36], will become a major responsibility of primary-care physicians and probably oncologists. Identification and referral of families at high risk for cancer susceptibility should be an increasing emphasis of clinical oncologists, but participation in our discipline has been low [37•]. At the very least, the ability to downshift the stage of a disease at the time of detection should eventually lead to improved survival as new treatment approaches emanate from causative understanding of and intervention in a particular cancer.

Overenthusiasm for Screening

Overestimation of disease prevalence, along with the benefits of therapy driven by advances in diagnostic imaging, is a phenomenon present throughout medicine and not confined to cancer [38]. Because an increasing use of sophisticated diagnostic imaging promotes a cycle of increasing intervention that may not confer benefits, the issue of mass screening is a critical one to the public, the medical and public health professions, and policy makers. An important

recent study documents the enthusiasm of the public for "early cancer detection." The results from this study are well worth reviewing here [39••].

These investigators found that most adults (87%) believe routine cancer screening is almost always a good idea and that finding cancer early saves lives (74% said most or all the time). Less than one third believed that there would be a time when they would stop undergoing routine screening. A substantial proportion believed that an 80-year-old who chose not to be tested was irresponsible, ranging from 40% with regard to mammography to 32% for colonoscopy. Thirty-eight percent of respondents had experienced at least one false-positive screening test; more than 40% of these individuals characterized that experience as "very scary" or the "scariest test of my life." However, in retrospect 98% were glad they had had the initial screening test. Most had a strong desire to know about the presence of cancer regardless of its implications; two thirds said they would want to be tested for cancer even if nothing could be done, and 56% said they would want to be tested for what is sometimes termed "pseudodisease" (cancers growing so slowly that they would never cause problems during the person's lifetime even if untreated). Seventy-three percent of respondents preferred to receive a total-body CT scan instead of \$1000 in cash. The findings of this landmark study are remarkable.

As noted by these investigators, "This enthusiasm creates an environment ripe for the premature diffusion of technologies...placing the public at risk of overtesting and overtreatment" [39••]. Direct-to-consumer marketing of high-technology screening tests has become a great concern, a phenomenon driven by patients as well as physicians. Indeed, in Orange County, California, where I live, whole-body CT scanners are placed in shopping malls, and there are more cosmetic plastic surgeons than in all of the United Kingdom. However, the clinical, financial, and ethical implications of this level of screening are considerable. This author and others have serious reservations in the absence of proven benefits [40]. The atmosphere for a rational approach to screening has been further complicated by the highly litigious nature of US society, in which failure to diagnose breast cancer by mammography is the most frequent reason for medical malpractice litigation [41]. Finally, cancer needs to be placed in context as a cause of morbidity and mortality [42]. The absolute risk is relatively small for any one individual, particularly for nonsmokers. For example, a 60-year-old woman has a seven in 1000 chance of developing breast cancer and a man of similar age a six in 1000 chance of developing colon cancer. Resource limitations will inevitably lead to screening decisions using high technology based on risk from epidemiologic considerations; profiling health will be an increasingly important part of what primary-care physicians, and to some degree oncologists, will be doing in the future.

Conclusions

Screening for colon, breast, and cervical cancers has been shown to be effective in decreasing morbidity and mortality from these diseases. The long-term value of screening for prostate cancer using PSA remains problematic, and a wide range of opinions have been expressed. Screening for skin cancer, particularly melanoma, is probably worthwhile, and nonrandomized trials suggest benefit. Screening for lung cancer has not yet been found to reduce mortality from the disease. The enthusiasm for screening for cancer in the United States, by both the public and the medical profession, is high and out of proportion to its demonstrated efficacy. Physicians need to be informed interpreters of the data to provide a risk-benefit context that emanates from objective analyses because marketing of screening modalities directly to patients has intensified in the past few years. However, in the end, the decision to screen or not to screen will depend on policy implementations driven by a broad range of fiscal and other concerns, including personal interpretations of and biases toward screening and its relative value to the individual.

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