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Targeted Cancer Screening in Average-Risk Individuals

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Abstract

Targeted cancer screening refers to use of disease risk information to identify those most likely to benefit from screening. Researchers have begun to explore the possibility of refining screening regimens for average-risk individuals using genetic and non-genetic risk factors and previous screening experience. Average-risk individuals are those not known to be at substantially elevated risk, including those without known inherited predisposition, without comorbidities known to increase cancer risk, and without previous diagnosis of cancer or pre-cancer. In this paper, we describe the goals of targeted cancer screening in average-risk individuals, present factors on which cancer screening has been targeted, discuss inclusion of targeting in screening guidelines issued by major U.S. professional organizations, and present evidence to support or question such inclusion. Screening guidelines for average-risk individuals currently target age; smoking (lung cancer only); and, in some instances, race; family history of cancer; and previous negative screening history (cervical cancer only). No guidelines include common genomic polymorphisms. RCTs suggest that targeting certain ages and smoking histories reduces disease-specific cancer mortality, although some guidelines extend ages and smoking histories based on statistical modeling. Guidelines that are based on modestly elevated disease risk typically have either no or little evidence of an ability to affect a mortality benefit. In time, targeted cancer screening is likely to include genetic factors and past screening experience as well as non-genetic factors other than age, smoking, and race, but it is of utmost importance that clinical implementation be evidence-based.

Introduction

Cancer screening, the routine testing of asymptomatic individuals without a history of the disease of interest,¹ is an important approach to cancer prevention and control. There is compelling evidence that screening for at least four cancers extends life,²⁻⁵ but population-based cancer screening also leads to unfavorable events.⁶ Only a minority of those screened will benefit, and many will have false-positive exams. Some screenees will experience undesirable sequelae, ranging from minor inconveniences to serious adverse events due to the exam itself or diagnostic evaluation.

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Targeted cancer screening attempts to segregate those who will benefit from screening from those who will not through use of information on disease risk. The practice is not new: Screening guidelines always have been age-dependent, and lung cancer guidelines restrict screening to those with substantial smoking history.⁵ In the past decade, advances in genomics have led to identification of many common polymorphisms associated with modest increases in risk, but when examined together, identify people at quite elevated risk.⁷

The success of targeted cancer screening among average-risk individuals depends on the ability to predict individuals' risk of cancers that would result in premature death without early intervention. By "average risk," we refer to people not known or suspected to be at drastically increased or decreased risk due to highly penetrant genetic mutations (e.g., Lynch syndrome); comorbidities known to increase risk (e.g., inflammatory bowel disease); and without previous diagnosis of cancer or pre-cancer (e.g., colonic polyps).

Of course, risk varies meaningfully among those defined to be at average risk. For those at so-called average risk, targeted cancer screening aims to identify those at the higher end of the risk distribution as well as those at the lower end, with an eye toward examining whether standard screening regimens can be modified. In this paper, we review three topics of relevance: classes of factors used to determine risk, guidelines from professional organizations, and availability of evidence to support such guidelines. We present examples from breast, cervical, colorectal, lung, and prostate cancer.

Classes of Factors Used to Determine Risk

We define three classes: genetic, non-genetic, and previous screening experience. Family history of cancer is classified as a genetic risk factor even though it can reflect a shared environment. Classes should be considered simultaneously when exploring targeted strategies (as in Dunlop et al.⁸ and Wacholder and colleagues⁹), but we treat them separately for ease of discussion.

Genetic Risk Factors

Genomewide association studies (GWASs) lead to identification of relatively common polymorphisms that on their own confer statistically significant but small increases in risk, yet when examined together, identify people at substantially increased risk of specific cancers. The strongest risk discrimination has been seen for prostate cancer. GWASs suggest that men of European descent in the top 1% and 10% of prostate cancer risk distributions have about a fivefold and threefold increased risk, respectively, of the disease, relative to average population risk.¹⁰ GWASs of breast cancer also suggest increases in risk, albeit more modest than in prostate cancer, for those at the top of the risk distributions.¹¹ Targeted screening based on polymorphisms has yet to be used in routine clinical practice, however.

GWASs also identify individuals without known high-risk allelic combinations. Although it is probable that some are at inconsequential risk, it is premature to exclude them from screening, as our understanding of genomic influences on cancer is incomplete.

Prior to genotyping, family history was the only information that could be used to gauge heritability of cancer. Etiologic research indicates that the presence of just one first-degree relative with a family history of breast, colorectal, prostate, or lung cancer is associated with modest increased risk. GWASs were expected to allow discrimination between heritability and shared risk factors among average-risk individuals, but to date the GWAS-identified risk loci can explain only about 30% of familial risk for prostate cancer,¹⁰ 14% for breast cancer,¹¹ and 6% for colorectal cancer.⁸ Family history continues to drive screening decisions, even for individuals with just one affected relative diagnosed at an older age.¹²

Non-genetic Risk Factors

Non-genetic risk factors include those that are modifiable (e.g., smoking) and not modifiable (e.g., age attained). Age attained is the most frequently stratified-upon risk factor for screening, as cancer risk changes drastically over a typical lifetime.¹³

Previous Screening Experience

Screening exam findings not suspicious for cancer but indicative of potentially elevated risk or reduced modality sensitivity drive future screening practices. A woman found to have dense breasts on screening mammography may receive ultrasonography in addition to mammography at future screening visits.¹⁴ Lack of findings can drive future practice as well. A current question in colorectal cancer screening is whether individuals with one negative colonoscopy require another 10 years later; proposed alternatives include longer screening intervals¹⁵ or screening with fecal immunochemical stool testing.¹⁶ Intensification of screening regimens because of positive findings on a screening exam, such as cervical dysplasia, actually represents surveillance rather than screening and is not discussed here.

Guidelines From U.S. Organizations and Other Recommending Bodies

We discuss guidelines from the U.S. Preventive Services Task Force (USPSTF)^{2-5,17}; American Cancer Society (ACS)¹⁸; and influential U.S. organ-specific societies: the American College of Obstetrics and Gynecology (ACOG; breast¹⁹ and cervix²⁰); American College of Gastroenterology (ACG; colorectal)²¹; American College of Chest Physicians (ACCP; lung)²²; and American Urologic Association (AUA; prostate).¹² We include lung cancer screening guidelines from the National Comprehensive Cancer Network (NCCN), as they vary somewhat from those of the other organizations.²³ We also discuss the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative.²⁴ EGAPP provides guidance on the appropriate use of genetic tests in clinical settings. Table 1 provides a summary of targeted guidelines.

Many organizations provide separate guidelines for people whom they consider to be at higher risk, typically owing to family history of cancer. The degree to which risk is higher varies by organization. We report those guidelines that are stated to be for those at average risk or are intended to apply to the population as a whole.

Genetic Risk Factors

No organizations include genomic information in screening guidelines. However, EGAPP currently supports a microsimulation modeling effort to evaluate the potential impact of including polymorphisms and family history in colorectal cancer screening guidelines.²⁴

The USPSTF does not modify screening guidelines for a family history of any of the five cancers. The ACS modifies its screening recommendations for individuals with a family history of breast, prostate, or colorectal cancer, but does not consider these individuals to be at average risk. ACOG does not modify its guidelines for family history of cervical cancer or for breast cancer per se: Breast cancer screening recommendations are modified for women at high risk, which could be because of family history. The AUA recommends shared decision making for men aged 40–54 years with any family history of prostate cancer. The ACG considers individuals to be at average risk of colorectal cancer in the instance of only one first-degree relative diagnosed with colorectal cancer or advanced adenoma at age 60 years or older; it does not modify guidelines for these individuals. The NCCN, but not the ACCP, modifies lung cancer screening guidelines for people with a family history of lung cancer; they recommend screening for those aged 50 years or older and have at least 20 pack-years of smoking history.

Non-genetic Risk Factors

Age is included in all cancer screening guidelines, although specific ages can vary. The USPSTF, ACS, and ACG recommend that colorectal cancer screening begin at age 50 years, but only the USPSTF recommends that screening cease after age 75 years. The USPSTF recommends that biennial breast cancer screening mammography begin at age 50 years, whereas the ACS and ACOG recommend that annual screening mammography begin at age 40 years. The ACS and AUA recommend shared decision making for prostate cancer screening for men aged 50 years and older, and those aged between 55 and 69 years, respectively. The USPSTF, ACS, and ACOG guidelines for cervical cancer agree with respect to age.

The USPSTF, ACS, ACCP, and NCCN recommend that lung cancer screening begin at age 55 years. The ACS, ACCP, and NCCN recommend that screening cease at age 75 years, but the USPSTF recommends age 80 years. The four organizations recommend screening for individuals who have at least 30 pack-years of smoking exposure; in addition, they only recommend screening for former smokers who quit within 15 years of the exam. The NCCN, but not the other organizations, modifies lung cancer screening guidelines for people with a history of chronic obstructive pulmonary disease or pulmonary fibrosis: They recommend screening for those aged 50 years or older and who have at least 20 pack-years of smoking history.

The ACG and AUA modify their screening guidelines for African Americans. The ACG recommends that colorectal cancer screening for African Americans begin at age 45 years, and the AUA recommends that shared decision making for prostate cancer screening occur between age 40 and 55 years. The ACS modifies its prostate cancer screening

recommendations for African Americans, but does not consider these individuals to be at average risk. No other guidelines are modified.

Previous Screening Experience

The USPSTF recommends that cervical cancer screening cease for women older than age 65 years who have had adequate screening and are not otherwise at high risk. The ACS and ACOG agree with the USPSTF, although they define women who can avoid screening as those who have had “3 consecutive Pap test or 2 consecutive negative co-test (Pap and [human papillomavirus] HPV) results within 10 years before cessation of screening, with the most recent test occurring within 5 years.”¹⁸ Negative screening experience is not considered in any other guidelines. No breast cancer screening guidelines are modified for women found to have dense breasts on previous screening.

Evidence in Support of Targeted Cancer Screening for Average-Risk Individuals

Cancer screening is considered to be of benefit if it leads to a reduction in mortality from the disease of interest. Intermediate endpoints, such as stage and changes in incidence, are considered when assessing screening’s impact, but cannot provide definitive evidence of a benefit owing to the introduction of lead-time, length biased sampling, and overdiagnosis bias.²⁵ Favorable changes in intermediate endpoints, such as down-staging, will exist when screening leads to a mortality benefit, however.

RCTs typically provide the strongest evidence of screening’s ability to reduce mortality from the cancer of interest. Other study designs, such as cohort and case–control studies, can be used to gauge possible benefit, but their results are subject to confounding by factors that could influence efficacy. The weakest evidence comes from case series, although these can be helpful in identifying modalities that warrant rigorous study.²⁵ Microsimulation modeling, which creates and analyzes hypothetical life experiences using assumptions,²⁶ and Markov modeling, which simulates the experience of cohorts,^{27,28} are being employed more frequently than in the past to assess cancer screening outcomes. The power of modeling is that screening parameters can be tweaked to gauge whether benefit might be possible under scenarios not tested or testable in RCTs. However, modeling is dependent on assumptions that often have limited data to support them.²⁶

Targeted cancer screening assumes that among people at average risk, those at the highest risk are most likely to benefit from cancer screening. That rests on the premise that a priori risk of diagnosis is strongly and positively correlated with screening efficacy and risk of death.

Genetic Risk Factors

No RCTs, cohort studies, or case–control studies assessing the impact of polygenic risk–stratified screening on organ site–specific mortality or intermediate outcomes have been conducted. Risk prediction models have been developed, though. Modeling for prostate cancer screening suggests that restricting screening to men of any age with a 10-year

absolute risk of at least 2% (assumed to be 53% of the male population) could lead to detection of 93% of cancers that are potentially screen-detectable in the absence of polygenic risk-based exclusions. Modeling for breast cancer screening suggests that restricting screening to women of any age with a 10-year absolute risk of at least 2.5% (assumed to be half the female population) could lead to detection of 73% of cancers that are potentially screen-detectable in the absence of polygenic risk-based exclusions.²⁹ These conclusions assume that exam sensitivity and specificity do not differ by polygenic factors.

Guidelines for men with a family history of prostate cancer to begin shared decision making at an early age are based on data suggesting that these men are at elevated risk.³⁰ No data have been published regarding the ability of screening these men at an earlier age to lead to a reduction in prostate cancer mortality.

Non-genetic Risk Factors

There is RCT evidence that screening for breast and colorectal cancer at certain ages, and screening for lung cancer at certain ages and smoking histories, reduces organ-specific mortality.^{2,4,5} However, because it is not feasible to conduct RCTs for every age (or smoking history for lung cancer), findings from RCTs have been extrapolated to other groups that are known or believed to have similar or stronger risk profiles. In these instances, observational data must be examined once screening moves into other risk groups to assess its impact.

Results from RCTs are often extrapolated to ages not examined in trials. For example, many women aged 75 years and older receive mammography, although there are insufficient RCT data to determine whether screening is efficacious at those ages. One case-control study suggests no benefit for women aged 75 years or older (relative risk for breast cancer mortality=1.05, 95% CI=0.27, 4.14), whereas a cohort study suggests benefit for women aged 75–84 years (hazard ratio for breast cancer mortality of mammography non-users versus users=2.47, 95% CI=1.70, 3.58).³¹

Microsimulation modeling was used to prepare the USPSTF lung cancer screening guidelines.³² Seven alternate screening strategies, created by varying minimum pack-years, age at onset of screening, and years since last smoked, were provided and compared to the eligibility criteria used for the National Lung Screening Trial (NLST; at least 30 pack-years of smoking history, age at onset of at least 55 years, no more than 15 years since last smoked).³³ The USPSTF used microsimulation modeling to inform the decision to continue screening to age 80 years, even though NLST participants completed screening by age 77 years. The NCCN lung cancer screening recommendation for people who are aged 50–55 years, have between 20 and 30 pack-years of smoking exposure, and one additional risk factor (such as family history) is based on observational data.²³ NCCN describes this evidence as “lower-level,” but states that there was consensus among panel members that these individuals should be screened.

The ACG guideline for African Americans to begin colorectal cancer screening at an earlier age is based on the fact that African Americans have higher colorectal cancer incidence and mortality, as well as younger age at diagnosis, than whites.^{34,35} There are no published data,

however, to support or refute a colorectal cancer mortality benefit of screening African Americans at an earlier age.

Previous Screening Experience

The USPSTF recommendation to cease cervical cancer screening for certain women older than age 65 years was based on results of Markov modeling and other information.³⁶ Modeling suggested that there is no substantial benefit, yet false positives and unnecessary colposcopies occur when screening continues. Also relevant was the fact that the rate of certain precursor lesions diagnosed by cytology was low among older women who had been previously screened. No data have been published to address whether cessation of screening beyond age 65 years leads to deleterious effects.

Conclusions

Cancer screening guidelines for average-risk individuals are made, for the most part, without consideration that no one is in fact average. As such, population-based screening casts a wide net, even with restrictions on age or other factors. The primary driver for that approach seems to be the desire to detect as many cancers as possible. An argument in favor of the wide net approach could be made if screening had no clinical, financial, or other non-trivial downsides, but that is not the case.

Targeted cancer screening may lead to a more efficient process, but evidence of benefits at both an individual and population level must be available before such approaches are employed in clinical settings. This is particularly true in the case of genomic targeting, as such information has never been considered in cancer screening RCTs, and it is unlikely that such efforts will be undertaken in the near future. In lieu of an RCT, established epidemiologic cohorts that contain banked biospecimens could be expanded by collecting detailed information on screening activities and outcomes. Another option is to establish cohorts with biospecimens that are designed specifically to assess targeted cancer screening rather than etiology.

For targeted screening approaches not tested in RCTs but already established in clinical practice, existing data sources, such as screening cohorts or those constructed using electronic medical records, should be explored to gauge if recommendations are appropriate. Established cohorts exist for mammography screening³⁷ and are under development for cervical and colorectal cancer screening,³⁸ which also could be used to examine the value of previous screening experience in guiding future screening regimens. These findings also could be used to upgrade risk prediction calculators so they can provide personalized screening information as well.

We expect that in time the marrying of genetic, non-genetic, and past screening experience data will be commonplace both in research and clinical screening settings. Of utmost importance, though, is that clinical implementation be driven by credible evidence. We recommend that targeted cancer screening, a strategy that may improve cancer screening in terms of both benefit and cost savings, becomes a primary research agenda as we contemplate how best to improve clinical cancer prevention.

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Table 1

Summary of Risk-Stratified Screening Guidelines for Persons at Average Risk of Breast, Cervical, Colorectal, Lung, and Prostate Cancer

Organ	Organization	Organization's guidelines include stratification for					
		Age	Family history	Genomic information	Previous screening experience	Race	Smoking history
Breast	USPSTF	✓					
	ACS	✓					
	ACOG	✓					
Cervical	USPSTF	✓			✓ (varies by age)		
	ACS	✓			✓ (varies by age)		
	ACOG	✓			✓ (varies by age)		
Colorectal	USPSTF	✓					
	ACS	✓					
	ACG	✓				✓ (varies by age)	
Lung	USPSTF	✓					✓ (varies by age and general health)
	ACS	✓					✓ (varies by age and general health)
	ACCP	✓					✓ (varies by age and general health)
	NCCN	✓	✓ (varies by smoking history and age)				✓ (varies by age, general health, family history, and medical conditions)
Prostate ^a	USPSTF						
	ACS	✓					
	AUA	✓	✓ (varies by age)				

ACCP, American College of Chest Physicians; ACG, American College of Gastroenterology; ACOG, American College of Obstetrics and Gynecology; ACS, American Cancer Society; AUA, American Urologic Association; NCCN, National Comprehensive Cancer Network; USPSTF, U.S. Preventive Services Task Force.

^aUSPSTF does not recommend prostate cancer screening in any instance; ACS and AUA recommendations are for shared decision making regarding screening.