Controversies in Cancer Screening

David P. Miller Jr, Daniel S. Reuland

New studies raise concerns about whether screening for some cancers may cause more harm than good. This commentary reviews evidence relevant to current controversies in cancer screening, highlights why it is so difficult to formulate universal screening recommendations, and emphasizes the importance of informed and shared decision making.

Imagine that you are a physician attending a family reunion. Your long-lost cousins are fascinated to discover that you work in health care. Amid servings of barbecue and banana pudding, the conversation turns toward medicine. Francine, age 46 years, confides that she hates mammograms and wants to know whether she can postpone her next one for a few years. Doug, a 63-year-old mechanic without health insurance, casually mentions that he is considering attending a free prostate cancer screening event hosted by his local hospital. Judy, who is 58 years old and proud that she quit smoking last year, wonders whether she should get screened for lung cancer. You quickly realize that they want your advice on these topics. How would you respond?

These 3 scenarios highlight areas of recent controversy. Some well-respected clinicians will argue that all 3 individuals should receive cancer screenings immediately; others will argue that none should; and the majority likely will take positions somewhere in the middle. To understand the controversy, we need to understand the rationale for screening and the emerging evidence that raises questions about whether the balance of benefits and harms justifies screening in each scenario.

There is great enthusiasm for cancer screening in the United States. Widespread promotion of screening by the media, physicians, and advocacy groups has led to a predominant view that cancer screening is desirable in virtually all situations and that individuals have a moral obligation to receive screening. A 2004 national survey found that more than 40% of respondents believed that an 80-year-old woman who chooses not to have a screening mammogram is "irresponsible." In addition, 73% of respondents said that they would rather receive a total-body computed tomography (CT) scan than $1,000 in cash [1].

This enthusiasm for screening is based on the premise that identifying disease in its early, asymptomatic state improves health outcomes by allowing for more effective treatments. Controlled trials have demonstrated that screening specific populations can reduce mortality for certain cancers. However, new evidence suggests that the benefits associated with cancer screening are often very small, and the potential harms are often overlooked [2, 3].

When making screening decisions, physicians and patients should balance the potential benefits of early treatment against the potential harms of false-positive results and unneeded treatments. This balance depends on many factors, including a person's cancer-specific mortality risk, his or her life expectancy, and the likelihood that the screening test will find a cancer for which treatment is effective. Some cancers do not need to be detected and treated because they will never cause symptoms; researchers call detecting these inconsequential cancers "overdiagnosis." On the other hand, some high-grade cancers arise between interval screenings and are so aggressive that treatment is ineffective.

Controversies in Prostate Cancer Screening

In 1992 the American Cancer Society (ACS) recommended annual prostate-specific antigen (PSA) testing for men beginning at age 50 years [4]. Prostate cancer is the most common type of cancer diagnosed in men, which would seem to support the benefit of screening [5]. However, prostate cancer is often indolent, and the majority of men older than 85 years have prostate cancer on autopsy [6]. Therefore screening is likely to detect many clinically insignificant tumors, which increases the chance of unnecessary treatment and limits the effectiveness of screening in reducing mortality. Indeed, 20 years after the ACS's initial screening recommendation, recent evidence from 2 large trials [7, 8] suggests that screening asymptomatic men for prostate cancer has little to no effect on mortality.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomized more than 76,000 men aged 55–74 years to receive usual care or screening; the latter group received annual PSA testing for 6 years and annual digital rectal examination for 4 years. After 13 years, men in the screening group were 12% more likely to have been diagnosed with prostate cancer, but there was no signifi-

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Address correspondence to Dr. David P. Miller Jr, General Internal Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157 (dmiller@wakehealth.edu).

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cant difference in the cumulative prostate cancer mortality rate (3.7 deaths per 10,000 person-years in the screening group versus 3.4 deaths per 10,000 person-years in the control group) [7]. However, approximately half of men in the control group received at least 1 PSA test, which may have diluted the observed effect of PSA screening.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) randomized more than 162,000 men aged 55–69 years to receive PSA screening or no screening. In contrast to the PLCO trial, the ERSPC study observed a 21% reduction in the relative risk of death from prostate cancer after a median follow-up period of 11 years [8]. Despite this reduction in *relative* risk, screening resulted in an *absolute* reduction in prostate cancer mortality of only 0.1 deaths per 1,000 person-years, or 1.07 deaths per 1,000 men randomized. Translating this figure to a population, 1,000 men would need to be offered PSA screening for 10 years to avert 1 prostate cancer–related death.

On the other side of the equation, the potential harms of PSA screening are substantial. The ERSPC trial showed that 37 men will be diagnosed with prostate cancer for every death averted [9], leading to a large number of men undergoing unneeded treatment. Also, among those treated for prostate cancer, 20% to 40% will develop incontinence or erectile dysfunction [10] (Table 1). After reviewing the latest evidence in 2012, the US Preventive Services Task Force (USPSTF) concluded that these harms outweigh the potential benefits of PSA screening and reiterated its earlier recommendation against screening [10].

The ACS now recommends that health care providers inform men 50 years of age or older about the pros and cons of PSA screening so that patients can make an informed decision [5]. As additional years of follow-up accrue from the aforementioned trials, evidence regarding the benefits and harms of PSA screening may evolve, and recommendations may be changed. For now, it seems wise to simply inform men of the current evidence, which suggests that individuals who undergo PSA screening have a roughly 1 in 1,000 chance of averting a prostate cancer–related death, but their chance of experiencing urinary and/or erectile problems as a result of treatment is 20-fold to 30-fold greater than their chance of dying [10].

TABLE 1.
Expected Outcomes When 1,000 Men Aged 55–69 Years Are Screened With Prostate-Specific Antigen Testing Every 1–4 Years for 10 Years

100–120 men will have at least 1 false-positive result.
110 men will be diagnosed with prostate cancer.
29 men will develop erectile dysfunction as a result of treatment.
18 men will develop urinary incontinence as a result of treatment.
0–1 deaths from prostate cancer will be prevented.

Source: Adapted from the 2012 US Preventive Service Task Force recommendation statement [10].

Controversies in Breast Cancer Screening

In November 2009, the USPSTF made headlines when it recommended against routine screening mammography for women younger than 50 years [11, 12]. Instead, the USPSTF emphasized that the decision to start screening before age 50 years should be made on an individual basis, taking into consideration each woman's values regarding benefits and harms. However, not all groups agreed with the USPSTF recommendation. In reaction to the USPSTF's recommendation, the ACS stated that it was continuing to recommend routine screening mammography starting at age 40 years [13].

Both the ACS and the USPSTF agreed that available evidence indicated that mammography screening reduces a woman's relative risk of dying from breast cancer by approximately 15%, whether the screening is done when a women is in her 40s or her 50s. However, because breast cancer is less common before age 50 years, an additional 565 women need to be screened to save 1 life when screening is performed for women in their 40s, compared with screening women in their 50s. In addition, delaying the start of screening until age 50 years would decrease the number of false-positive results by 60% while still averting 85% of preventable breast cancer deaths [14]. The USPSTF concluded that the marginal benefit of screening women before age 50 years did not clearly outweigh the additional anxiety and potential harms that would result from investigation of numerous false-positive results (Table 2). The ACS disagreed.

A study published in February 2014 adds to the controversy. The 25-year follow-up results of the Canadian National Breast Screening Study reconfirmed its earlier results that annual mammography in women aged 40–59 years did not reduce mortality from breast cancer beyond what was accomplished by a clinical breast examination and usual care [15]. Screening trials vary in the strength of their methodology, which can contribute to differences in findings, but the Canadian study was randomized at the patient level and was judged to have a low risk of bias by the latest Cochrane systematic review [16]. The Canadian study also found that 22% of invasive breast cancers detected by screening were overdiagnosed and hence overtreated [15], a finding that is consistent with those of other studies [17]. Like prostate cancer screening, breast cancer screening identifies many clinically insignificant tumors; perhaps as many as 10 patients are unnecessarily diagnosed and treated per death averted [18]. Although we lack reliable predictors to know which tumors represent overdiagnoses and which are "true saves," there is an unsettling implication that the number of women who undergo unneeded treatments may be greater than the number who are helped by mammography.

Given the current data, what is the most appropriate recommendation? Only a fully informed woman who is considering screening can answer that question. In our view, health care providers should not attempt to convince a woman to

TABLE 2.
Expected Outcomes When 1,000 Women Aged 40–49 Years Are Screened Annually With Mammography for 10 Years

510–690 women will have at least 1 false-positive result.
60–80 women will have a false-positive result that leads to a biopsy.
23 women will be diagnosed with breast cancer.
11 or fewer women will be overdiagnosed with breast cancer.
0.1–1.6 deaths from breast cancer will be prevented.

Source: Adapted from Welch and Passow [18].

receiving screening (or not to receive screening); rather, women should be informed about the nature and magnitude of the benefits and harms of screening mammography. Some women will review the statistics and not hesitate to start screening early, while others will find that the same statistics reassure them in their decision to delay screening.

Controversies in Lung Cancer Screening

Results of the multicenter National Lung Screening Trial (NLST), which were published in 2011, show that screening using low-dose computed tomography (LDCT) reduces the risk of death due to lung cancer in high-risk individuals [19]. This was the first high-quality evidence that screening can reduce mortality from lung cancer, which is the leading cause of cancer-related death in the United States. Based on this evidence, the USPSTF [20] and other groups [21] issued new guidelines recommending that annual LDCT screening be offered to high-risk patients.

Despite its potential benefits, LDCT screening can also cause harms. In the NLST, 39% of screened individuals experienced at least 1 false-positive result after undergoing 3 scans, leading to costly and sometimes invasive procedures that did not find cancer [19, 21] (Table 3). Like screening for prostate and breast cancer, LDCT screening for lung cancer also likely leads to overdiagnosis and overtreatment of tumors that would never have affected patients. To prevent 1 lung cancer–related death, 320 people must be screened, which will result in 1.38 additional persons being diagnosed and treated unnecessarily [22].

In light of these data, it is reasonable to ask whether LDCT screening for lung cancer is appropriate for specific individuals. For example, consider Judy, the 58-year-old woman at the family reunion who quit smoking last year. If Judy smoked 1.5 packs per day for 35 years, or 52.5 pack-years, then her smoking history is similar to the average NLST participant, who smoked approximately 50 pack-years. In this case, she should be informed that the results of the NLST show that about 3 deaths from lung cancer will be prevented for every 1,000 individuals with a risk profile similar to hers who are screened annually. She should also be informed that for every 1,000 individuals screened, about 365 will experience at least 1 false-positive result during the first 3 rounds of screening, 25 of whom will have at least 1 invasive procedure, and 3 of these 25 individuals will experience a major complication [23]. Finally, she should know that 7.5% of all LDCT scans result in incidental findings [19], which could trigger additional workup that may or may not be beneficial.

However, if Judy smoked "only" 1 pack per day for 30 years, then her smoking history would be close to the minimum eligibility criteria for the NLST, and the chance that she would benefit from screening is considerably smaller. For participants in the NLST in the study's lowest quintile of lung cancer risk, 5,276 persons had to be screened to avert 1 death during 6 years of follow-up, and more than 30% of these individuals had a false-positive result, with its attendant costs and risks [24].

The Need for Informed and Shared Decision Making

We have focused on screening for prostate, breast, and lung cancer because these are areas of recent controversy. Navigating this confusing sea of information is a challenge, particularly when a patient asks, "What would you do?" The challenge is great in part because patients and providers may not share the same values or preferences. People vary in their risk tolerance, their willingness to undergo procedures, and the degree to which they can make peace with uncertainty. Given this variety, it would be inappropriate to make a blanket recommendation for all patients.

We believe that the best approach is to ensure that patients are well informed about the potential benefits and harms of screening, so that they can make the best decisions for themselves. Unfortunately, patients often lack the knowledge to make decisions about screening. In surveys, patients have reported that health care providers almost always discuss the pros of screening but seldom discuss the cons [25, 26]. Therefore, it is not surprising that US adults overestimate both their risk of cancer and the benefits of screening [26]. Decision aids can help address these shortcomings by giving patients knowledge and a better understanding of their options [27]. Some relevant online decision aids are listed in Table 4 (online version only).

Changes are needed to ensure that patients and health care providers are well informed. Reimbursement policies should reward clinicians who take the time to inform patients of the intricate risks and benefits involved in the decisions

TABLE 3.
Observed Outcomes After 6.5 Years of Follow-Up, per 1,000 Participants, Among Individuals Who Underwent 3 Annual Screenings with Low-Dose Computed Tomography

365 participants had at least 1 false-positive result.
25 participants had a false-positive result leading to an invasive procedure.
3 participants with a false-positive result experienced a major complication of a procedure.
3–5 participants were overdiagnosed with lung cancer.
Approximately 3 deaths from lung cancer were prevented.

Source: Data are from the National Lung Screening Trial Research Team [19] and Patz et al [22].

TABLE 4.
Online Resources for Shared Decision Making Regarding Screening for Breast, Lung, or Prostate Cancer

This table is available in its entirety in the online edition of the NCMJ.

they face. Screening trials should measure not only benefits but also harms, which have rarely been tracked in the past [3]. Researchers at the University of North Carolina at Chapel Hill are currently examining how potential harms are addressed in screening decisions and policy (http://smart-screening.org). We should also be wary of observational studies, which are prone to length and lead-time biases, and we should remain open to newer evidence showing that the net benefits of screening for some cancers are substantially smaller than we previously thought. Although medical knowledge is continually growing and changing, focusing on fully informing ourselves and our patients will always be helpful. NCMJ

David P. Miller Jr, MD, MS associate professor, Internal Medicine and Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina.
Daniel S. Reuland, MD, MPH associate professor, Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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