EDITORIAL

Prostate-Specific Antigen (PSA) Screening for Prostate Cancer
Revisiting the Evidence

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Prostate-specific antigen (PSA)–based testing for detection of prostate cancer has remained controversial since its widespread adoption by clinicians in the United States in the late 1980s. Although measurement of PSA blood levels was approved in 1995 by the US Food and Drug Administration for early detection, PSA levels are not specific for prostate cancer or the more aggressive forms of the disease, which include approximately 1 in 3 newly diagnosed prostate cancers. In a randomized screening trial that included 162 388 patients, low specificity resulted in prostate biopsies in 20% of men screened,[1] cancer was not detected in 3 of every 4 biopsies performed,[2] and 70% of cancers detected in the screening group were found to be low grade (nonaggressive form).[3] Prostate biopsies carry the risk of bleeding and infection requiring hospitalization in from 0.5% to 6.9% of men.[4] However, these harms are less concerning than the rates of overdiagnosis (ie, detection of cancers that would not have been detected during life in the absence of screening), estimated to be from 23% to 42% in the US population and as high as 67% in a randomized screening trial conducted in Europe.[5] If treated, these men risk a reduction in quality of life in urinary, sexual, and bowel domains[6,7] without the benefit of extending life, because they would not have known about their cancer in the absence of screening.

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A decade ago, 90% of men diagnosed with low-grade screen-detected prostate cancers were treated with curative intent[8] by urologists and radiation oncologists because of the perception that given time, these cancers inexorably progressed from low- to high-grade disease. Without high-quality studies to assess the benefits of screening, in 2008 the US Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to make a recommendation on PSA-based screening for prostate cancer in men younger than 75 years (I statement) but recommended against use of the PSA test for men 75 years and older (D recommendation).[9]

In 2012, the USPSTF assigned a D recommendation to PSA-based screening for prostate cancer (ie, discouraged use of this service) for all men, irrespective of age, family history, and race, concluding that "there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms."[10] The evidence review on which this recommendation was based included the harms of biopsy, overdiagnosis, and treatment, as well as initial reports from the 2 largest randomized trials of screening, which reached opposite conclusions regarding benefits.[11] The US trial (PLCO) was launched after widespread adoption of PSA testing in the population, was limited by high rates of PSA screening in the control group, and found no reduction in prostate cancer mortality. During the 6-year screening phase of the PLCO trial, patients in the screening group received an average of 5 PSA tests, compared with 3 in the control group.[12] Thus, the findings in the PLCO trial do not exclude the possibility of a reduction in prostate cancer mortality with screening. In the European trial (ERSPC) with less prescreening in the population and less screening in the control group, there was a 20% relative reduction in prostate cancer mortality with screening (29% after adjustment for nonadherence) and an absolute reduction of 7 prostate cancer deaths per 10 000 men in the core age group aged 55 to 69 years at a median of 9 years of follow-up.

In this issue of *JAMA*, the USPSTF has revisited the evidence[13] and concluded "with moderate certainty that the net benefit of PSA-based screening for prostate cancer in men aged 55 to 69 years is small for some men," justifying the offer of PSA testing selectively to men in this age group based on the judgment of the physician and the values of the patient (C recommendation).[14] For men 70 years and older, the USPSTF recommended against routine testing (D recommendation). A multidisciplinary panel in 2013 reached a similar conclusion, albeit more nuanced with respect to men at higher than average risk (eg, positive family history and African American race), to engage in shared decision making on screening for men aged 55 to 69 years at average risk.[15] That panel assessed an independent evidence review for the American Urological Association but did not consider the PLCO trial to be informative with respect to the benefits of screening because of contamination in controls. What has changed since 2012 that led the USPSTF to modify this important change in their recommendation from D to C for men aged 55 to 69 years?

First, with longer follow-up in the ERSPC[2]—the only randomized trial of periodic PSA screening that informs benefits—the absolute reduction in prostate cancer mortality has increased from 7 per 10 000 men at 9 years to 13 per 10 000 men at 13 years. Estimated benefits from mathematical modeling suggest that the absolute reduction in mortality, and thus the number needed to diagnose to prevent a prostate cancer death, will decline further with longer follow-up.[16] In the ERSPC, the reduction in prostate cancer deaths was attributable to a reduction in the rate of metastatic disease that preceded the mortality reduction on average by 3 years.[17] Thirty percent fewer men developed metastatic prostate cancer, an absolute reduction in the cumulative incidence of metastatic disease of 31

cases per 10 000 men at a median of 12 years of follow-up.[18] The treatment morbidity associated with metastatic disease is often overlooked when assessing the benefits of PSA-based screening.[19] Second, after accounting for differences in the PLCO and ERSPC trials, including protocol adherence and contamination, there was a consistent 25% to 30% relative reduction in deaths from prostate cancer.[20]

Third, even though there was no difference in prostate cancer mortality at 10 years after an invitation to attend a single PSA screening vs standard practice for men aged 55 to 69 years,[21] adherence to screening was 40%, and a single screen is not likely to be optimal for identifying harmful disease. Fourth, morbidity associated with prostate cancer remains substantial, despite claims that technological advances have improved quality-of-life outcomes,[22] although the harms of screening have been reduced.[23] For example, clinicians are increasingly using reflex tests (follow-up tests after PSA testing) that combine multiple PSA isoforms to improve the specificity of PSA and decrease the number of unnecessary biopsies in men with elevated PSA levels. Furthermore, the uptake of active surveillance—an alternative management option that involves careful monitoring rather than immediate treatment—for men with favorable-risk prostate cancers has reduced the overtreatment of prostate cancer that occurs with screening.

The USPSTF has provided a timely and careful approach to reassessment of the benefits and harms of PSA-based screening for prostate cancer. Patients, together with their physicians, should decide whether prostate cancer screening is right for the patient. In this regard, primary care physicians have an important role in reducing the harms associated with screening and could consider a number of factors in this decision process.

First, physicians should offer screening primarily to patients for whom the evidence of benefit is strongest (ie, those aged 55-69 years)[2] and avoid testing men with multiple comorbidities, especially those at an older age unlikely to gain life-years from treatment of prostate cancer. However, population-based data show that approximately half of the metastatic cases and deaths from prostate cancer occur in men diagnosed at 75 years and older—a group that represents less than 30% of the overall population.[24] Older age is associated with more aggressive prostate cancer[25]; thus, a very healthy older man with the prospects of extended life might benefit from PSA testing. Nevertheless, routine screening of average risk men 70 years and older should be rare, because older men are more likely than younger men to experience the harms of screening, diagnosis, and treatment. Second, a 2- to 4-year PSA testing interval, rather than annual testing, could reduce false-positive test results and overdiagnosis without substantially sacrificing the benefits of screening.[26]

Third, a family history of cancer mortality related to adenocarcinoma (including prostate cancer) and African American race may identify men with more to gain from screening compared with a man at average risk. The presence of a hereditary form of prostate cancer is more likely among men with a family history of metastatic or lethal adenocarcinomas (eg, prostate, male and female breast cancer, ovarian, pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.[27,28] Furthermore, African American men are more likely to harbor the aggressive form of prostate cancer and have twice the risk of death from disease compared with men of European American ancestry.[29] The ratio of benefit to harm could be higher compared with the average-risk man, and these men may benefit from PSA testing that begins before age 55 years. Fourth, by virtue of their relationship with patients, primary care physicians are in a unique position to help ensure that men diagnosed with favorable-risk disease (Gleason score 6 cancer grade on biopsy, and PSA level <10 ng/mL) are presented a balanced message regarding management options. This message should emphasize that active surveillance, not surgery or radiotherapy, is the preferred option for most men with favorable-risk prostate cancer.[30,31]

PSA-based screening for prostate cancer will continue to evolve as more data emerge from the pivotal screening trials; new measures are developed to identify men at risk of developing an aggressive phenotype who could then be targeted for screening; staging of disease evolves; and treatment for prostate cancer improves. It is incumbent on patients and physicians to be informed of these changes as they become available.

ARTICLE INFORMATION

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