Invited Commentary

Prostate-Specific Antigen Testing for Prostate Cancer Screening—Is the Message Getting Through?

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Since the discovery of prostate-specific antigen (PSA) more than 40 years ago and its subsequent wide adoption for the detection of prostate cancer, screening for the disease has been plagued with continuing controversies that remain largely unresolved. There is a profoundly engrained public perception embraced by many professionals that cancer detection as early as possible saves lives and therefore should be promoted at any cost, be it financial or in kind, such as the inevitable adverse effects caused by radical treatments. Although this may be true for some cancers, more than 3 decades of PSA testing among asymptomatic men across the globe, particularly in the Western world, has proved otherwise. Leapman et al[1] illustrate this point in their article on the changes in the rates of PSA testing associated with recent updates in the US Preventive Services Task Force (USPSTF) recommendations on prostate cancer screening.

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Currently, the biggest challenges to making recommendations on PSA testing as a public health screening policy for prostate cancer are 3-fold: (1) the avoidance of overdetection of disease that would not otherwise manifest itself as clinically important during an individual's lifetime, (2) the subsequent inevitable overtreatment with potential unwanted adverse effects on quality of life, and (3) our inability to determine accurately the lethal potential of prostate cancer at diagnosis, resulting in undertreatment. It has been clearly demonstrated that screening by PSA testing saves lives, but at the unacceptable cost of overdetection and overtreatment, which has prevented many policymakers and organizations from recommending PSA testing as a public health policy for asymptomatic men in the general community.

Guidelines usually rely on evidence to make recommendations about any health intervention, but for prostate cancer screening, evidence has been scarce over decades. Two large randomized clinical trials of screening by PSA testing in the US and Europe have been major sources of high-level data on interval screening by PSA, complemented by the more recent Cluster Randomized Trial of PSA Testing for prostate cancer (CAP)[2] in the UK investigating the benefits of screening with a single PSA test. The Prostate, Lung, Colon and Ovary (PLCO) study in the US has ruled itself out as providing evidence because of heavy contamination and other unresolvable issues. The European Randomized Trial of Screening for Prostate Cancer (ERSPC) in Europe showed a benefit in favor of screening but at a high cost of overdetection,[3] and the UK CAP study showed no survival benefit with a single PSA test but increased detection of low-risk, low-volume prostate cancer.[2] At the same time, trials of the effectiveness in screening for disease, such as the ProtecT (Prostate Testing for Cancer and Treatment) study in the UK[4] and the Prostate Cancer Intervention vs Observation Trial (PIVOT)[5] in the US, showed no survival benefit in favor of early radical treatment, although ProtecT showed that early intervention reduced the rate of disease progression and metastasis in favor of radical interventions compared with active monitoring[4] and recent reports from PIVOT suggest a benefit of early treatment for intermediate-risk disease.[5] The most mature treatment effectiveness randomized clinical trial is the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial, which showed consistent benefits of radical treatments compared with watchful waiting in disease-specific, overall survival and progression, but approximately half of the SPCG-4 cohort already had nonorgan-confined disease, and most were not detected via PSA test, which largely explains the benefit patients received from early treatment.[6]

Based on emerging evidence from these few global randomized clinical trials, the USPSTF made recommendations in 2012 that PSA testing should not be offered to any man at any age with the purpose of prostate cancer screening (grade D recommendation). This recommendation has been associated with a notable reduction in indiscriminate PSA testing in the US but was deplored by many clinicians and institutions as in turn being associated with an increase in the number of men presenting with metastatic and advanced disease. As the trials matured, these recommendations were amended in 2018, suggesting that men between 55 and 69 years of age can be offered a PSA test but that men aged 70 years or older should not be tested.

Leapman et al[1] report the variations in PSA testing in a US cohort of men aged 40 to 89 years during 2 distinct periods associated with changes in the USPSTF recommendations in 2012 and 2018. The analysis was triggered because of the perceived increase in the presentation of late-stage disease, claimed by some as being caused by the reduction in PSA testing. The findings of the analysis are that there was a progressive and significant increase in PSA testing among men of all ages after the revision of the USPSTF grade C recommendation in 2018 for men aged 55 to 59 years, with particular concerns about the increase in testing for men aged 40 to 55 years and 70 years or older falling outside the age category in the USPSTF recommendations and causing potential harm. The findings are valuable, and the authors should be commended for undertaking this informative analysis, which reflects a flawed attitude toward PSA testing in the community.

Clinicians often advocate that the answer to the overdetection of prostate cancer is the adoption of safe active surveillance protocols. This is the incorrect approach. Whenever an asymptomatic man receives a diagnosis of prostate cancer, irrespective of its indolent nature, he is given a "new" identity of becoming a patient with cancer. A "cancer passport" is delivered, and its consequences may be far reaching. Men should therefore be counseled properly regarding the benefits and harms of screening before a decision is taken to mea-

sure their PSA level. Quality of life in the SPCG-4 randomized clinical trial of watchful waiting vs radical prostatectomy among a cohort of patients with prostate cancer was analyzed and compared with a matched cohort of men without cancer. It was revealing that the harm caused to quality of life was likely due to the diagnosis of cancer rather than the treatment administered.[7] Similar findings of anxiety were reported by the ERSPC, affecting men's mental health after PSA testing. In the ProtecT study, patient-reported outcomes showed no evidence of a difference in anxiety and depression levels between men who received active monitoring and men who underwent radical treatments.[4]

The prostate cancer screening landscape continues to evolve with the emergence of prebiopsy imaging using multiparametric magnetic resonance imaging of the prostate, which has transformed the diagnostic pathway in many countries but with slower uptake in the US. It is now evident that the long-term practice of a PSA test followed by systematic biopsies of the prostate is antiquated. In the CAP trial, for instance, a single PSA test missed more than one-third of lethal prostate cancers in men who underwent screening.[2] Although genomic testing and the use of other emerging risk calculators, such as polygenic hazard scores, have limited evidence to be adopted in a risk-stratification approach to screening, it is likely that with imaging and targeted biopsies, the field will progress further, minimizing the risk of overdetection and overtreatment and focusing on identifying early disease that warrants tailored treatments to improve outcomes and save lives. But when will the message get through to the public, clinicians, and health care professionals that inappropriate PSA testing outside evidence-based recommendations should cease?

ARTICLE INFORMATION

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