VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Evidence-Based Versus Personalized Prostate Cancer Screening: Using Baseline Prostate-Specific Antigen Measurements to Individualize Screening

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The prostate cancer screening controversy has reached a critical turning point. There has been a 50% reduction in prostate cancer mortality in the United States, and screening is estimated to account for 45% to 70%.[1] On the other hand, screening may result in significant harms, including unnecessary biopsies with potential associated adverse effects, overdiagnosis, and resultant overtreatment.

Where should we go from here? In 2012, the US Preventive Services Task Force issued a grade D recommendation against prostate-specific antigen (PSA) screening for men of all ages.[2] Early data suggest that this has been associated with a reduction in the diagnosis of low-risk disease but that the proportion of high-risk cases has increased.[3] Mathematical models project that abandoning screening altogether, as suggested, would eliminate overdiagnosis but also would result in a doubling of patients presenting with metastatic disease and a 13% to 20% increase in prostate cancer deaths by 2025.[4] Thus, completely eliminating screening is not a good option, because it will also reverse the substantial progress that has been made in reducing suffering and death from advanced disease.

Most other professional societies instead recommend a shared decision-making approach, including a discussion about the pros, cons, uncertainties, and patient preferences regarding PSA-based screening.[5-8] However, there continues to be disagreement between guidelines as to how screening should be implemented for men who opt to proceed, including the age to start and stop and the interval between tests.

The American Urological Association recommends offering PSA screening to men age 55 to 69 years, with individualized decisions in men age 40 to 55 years and screening intervals of $\geq$ 2 years to reduce harms.[5] The American Cancer Society recommends offering screening beginning at age 50 years for average-risk men and in their 40s for African American men and those with a positive family history, after which it recommends using PSA levels to determine the frequency of subsequent screenings.[7] The National Comprehensive Cancer Network and European Association of Urology recommend offering baseline PSA testing to men in their 40s and using PSA levels to determine subsequent screening intervals.[6,8]

A major reason for this disparity between guidelines is how strictly they adhere to the protocols from randomized trials. All of the major randomized trials of PSA screening were designed in the early 1990s, initiated screening in men in their 50s, and used predefined screening intervals and a single PSA cutoff to determine the need for prostate biopsy. These trials include the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial that randomly assigned 76,685 men age 55 to 74 years to annual screening versus usual care and recommended a prostate biopsy for a PSA $>$ 4 ng/mL or suspicious digital rectal examination. This study found no difference in prostate cancer mortality between the screening and usual care groups.[9] However, these results are not surprising, given that approximately 90% of men in the usual care arm had PSA testing (more than in the screening arm).[10] Therefore, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is not informative regarding the efficacy of screening versus no screening.

The European Randomized Study of Screening for Prostate Cancer randomly assigned 162,388 men age 55 to 69 years to screening and control arms.[11] This study reported a significant reduction in metastatic disease and prostate cancer death with PSA screening at 2- to 4-year intervals, primarily using a PSA threshold of 3 ng/mL.

The Goteborg population-based randomized trial in Sweden randomly assigned 20,000 men to PSA screening every 2 years beginning at age 50 years and found the greatest overall reduction in prostate cancer mortality reported to date.[12] This may imply that more frequent screening in younger men accounts for the better results observed in this population compared with the rest of the European trial. Indeed, a recent study comparing men age 50 to 54 years from this trial to age-matched Swedish men from the pre-PSA era found that screening in this age group was associated with a large reduction in metastatic disease (incidence rate ratio, 0.43; 95% CI, 0.22 to 0.79) and prostate cancer death (incidence rate ratio, 0.29; 95% CI, 0.11 to 0.67).[13]

However, since the time of these randomized trials, numerous studies suggest offering screening at an even earlier age. In a large prospective US screening study, our group reported that men with a baseline PSA level in their 40s above the age-specific median of 0.7 ng/mL had a significantly higher risk of future prostate cancer diagnosis and aggressive disease.[14] Conversely, among men with a baseline PSA level below the age-specific median in their 40s, only 0.3% reached the PSA threshold for biopsy of 2.5 ng/mL within the next 5 years, and only one was diagnosed with prostate cancer before age 50 years.[15]

Subsequent studies using stored serum samples from unscreened men in Scandinavia found that higher baseline PSA levels

predicted the long-term risk of metastatic disease and prostate cancer death.[16,17] Using stored serum samples provided in 1981 to 1983 as part of the Copenhagen Heart Study, Orsted et al[16] reported that in men younger than 45 years, the absolute 10-year risk of death from prostate cancer was 0.3%, 0.6%, 1.5%, 1.7%, 2.4%, and 9.8% for men with baseline PSA levels of 0.1 to 1.00, 1.01 to 2.00, 2.01 to 3.00, 4.01 to 10.00, and > 10 ng/mL. For men age 45 to 49 years, the corresponding 10-year risk of prostate cancer death by baseline PSA levels was 0.4%, 1.0%, 2.4%, 2.6%, 3.9%, and 16%, respectively.

A subsequent study using stored serum samples from unscreened men from Sweden showed that higher baseline PSA levels at age 45 to 49 years predicted an increased long-term risk of metastases and prostate cancer death.[17] Overall, 44% of all prostate cancer deaths occurring within 25 to 30 years were in men within the highest 10th percentile of the PSA distribution (≥ 1.6 ng/mL) at age 45 to 49 years. Conversely, men with a baseline PSA level below the median of 0.68 at age 45 to 49 years had a < 0.1% risk of metastatic disease during the next 15 years.

In the article that accompanies this editorial, Preston et al[18] confirm in a large US population that baseline PSA levels at a young age predict the future risk of lethal prostate cancer. Compared with men with a baseline PSA below the age-specific median, men in the > 90th percentile at age 40 to 49 and 50 to 54 years had an 8.7- and 12.6-fold increased risk, respectively, of lethal prostate cancer. Overall, 92% of lethal events occurred in men with a PSA above the median at age 40 to 49 years. By contrast, men with baseline PSA levels below the median at age 40 to 44 and 45 to 49 years had a 0.19% and 0.51% absolute risk of developing lethal prostate cancer during the next 30 years.

Overall, these studies provide consistent and compelling data that baseline PSA levels are robust predictors of future life-threatening prostate cancer. Because the baseline PSA level is a stronger predictor of future prostate cancer risk than either race or family history,[14] it seems reasonable to use these values to tailor the screening protocol on the basis of the individual's level of risk. Men with PSA levels > 1 ng/mL in their 40s represent a high-risk population, for whom more frequent screening is justified. Conversely, men with a baseline PSA below the age-specific median represent a low-risk group, for whom more extended screening intervals are reasonable. It is noteworthy that the age at which screening is discontinued seems to have a larger impact on the rates of overdiagnosis than the age at which it is initiated,[19] and recent studies suggest that PSA levels may also inform the optimal age to discontinue screening.[20,21]

Although randomized trials provide the highest level of evidence, they are restricted to a specific study population and type of intervention. A one-size-fits-all approach to prostate cancer screening ignores the large variation in prostate cancer risk. This issue exemplifies the more global conflict of evidence-based versus personalized medicine, in which recommendations are tailored toward the individual.[22] Must we rigidly adhere to the protocols from randomized trials providing the highest level of evidence, or should we use other high-quality data sources to refine our protocols to provide a more nuanced approach on the basis of individual characteristics? Modeling studies suggest that a risk-adapted approach to prostate cancer screening can preserve benefits with fewer harms compared with fixed screening protocols.[23]

Improving the screening protocol is just one piece of the puzzle. In fact, significant progress has been made in reducing harms at each step of the path. For men with an elevated PSA, there are several new biomarkers with greater specificity that can be used to inform prostate biopsy decisions, such as the Prostate Health Index and 4K Score.[8] For men undergoing prostate biopsy, targeted prophylaxis on the basis of rectal swab cultures has been shown to reduce the frequency of infectious complications.[24] New techniques of prostate biopsy using magnetic resonance imaging targeting improve the yield for clinically significant tumors while reducing the detection of insignificant prostate cancer.[25] Finally, there has been a large reduction in overtreatment of low-risk disease through rapidly expanding use of active surveillance.[26]

Prostate cancer kills more than 26,000 men per year in the United States,[27] and there is significant morbidity in those who develop advanced disease. Only through the judicious application of screening, detection, and treatment can we further reduce morbidity and mortality from prostate cancer at a lower cost and without causing undue harm.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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DOI: 10.1200/JCO.2016.68.2138; published online ahead of print at www.jco.org on June 20, 2016.

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Acknowledgment

Supported by the Laura and Isaac Perlmutter NYU Cancer Center Grant P30CA016087 and the Louis Feil Charitable Lead Trust.