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EDITORIALS

Serum Prostate-Specific Antigen for the Early Detection of Prostate Cancer: Always, Never, or Only Sometimes?

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See accompanying articles on pages 355 and 464

Few medical stories have attracted the interest of the media and generated as much confusion and controversy as the issue of prostate-specific antigen (PSA) testing for the early detection of prostate cancer. This story has been building for years, reflecting the widespread use of PSA testing in many developed countries, the ambiguity regarding its benefits, and the uncertainty as to what constitutes the best form of treatment (including nontreatment) for virtually all stages of disease. The recently updated best practice statement of the American Urological Association recommends that men be counseled regarding the option of PSA testing beginning at age 40 years.[1] Guidelines of other organizations vary markedly in their enthusiasm; the US Preventive Services Task Force guideline—which primary care providers consider the most influential[2]—is the most overtly hostile to screening.[3] The controversy reached a head in 2009 when two screening studies with disparate results were published simultaneously in the *New England Journal of Medicine*.

In the PLCO trial (Prostate, Lung, Colorectal and Ovarian Cancer Screening), men in the United States were randomly assigned to annual PSA screening or usual care; investigators reported that the cumulative risk of death as a result of prostate cancer at 7 to 10 years was low in both screened and unscreened men and did not differ significantly between them.[4] Seven years of follow-up (or even the 10 years of follow-up that two thirds of the cohort received) may still be too short a time to observe a difference, given the long natural history of prostate cancer. Moreover, the high prevalence of pre-enrollment screening and heavy contamination of the control group by PSA screening, together with a low rate of follow-up biopsies among men who crossed the predefined PSA threshold of 4.0 ng/mL,[5] severely limited the ability of this study to test the hypothesis fairly, even with longer follow-up.

In the ERSPC trial (European Randomized Study of Screening for Prostate Cancer), men in seven countries were randomly assigned to screening at 2- or 4-year intervals, with biopsy thresholds ranging from 2.5 to 4.0 ng/mL. This was a larger study than PLCO, with longer follow-up and much less contamination among control patients, and it demonstrated that screening was associated with a 20% relative risk reduction in prostate cancer–specific mortality.[6] Furthermore, a follow-up analysis demonstrated that with adjustment for compliance with screening in the ERSPC trial, the reduction in mortality rose substantially to 31%.[7] The hazard curves in the ERSPC trial only began to diverge approximately 7 years into the trial; thus, with longer follow-up, the observed benefit of screening would likely be additionally magnified. However, the risks of prostate cancer overdetection (ie, detecting a cancer that otherwise would not progress to clinically significant disease during the lifetime of an individual) are substantial and were well highlighted in the ERSPC trial. The authors estimated a number needed to screen (NNS) of 1,410 and number needed to treat (NNT) of 48 to avoid one death as a result of prostate cancer.[6] However, the NNT to avoid metastases was only 24. Because metastases are a harbinger of death resulting from prostate cancer, the absolute risk reduction in prostate cancer–specific mortality between the screened and control arms would presumably become more favorable with time.

Two articles in this issue of *Journal of Clinical Oncology* add some clarity to prostate cancer screening, although they do not resolve all the controversy. Crawford et al[8] reanalyzed the data from the PLCO study, stratifying the analysis by comorbidity and thereby testing the hypothesis that men in good health are those who benefit from early detection strategies. Although other comorbidity scales exist, the authors define a comorbid condition as one that could increase the risk of dying as a result of a cancer other than prostate or of cardiovascular disease (leading competing risks of death for US men between ages 55 and 74 years). Minimal comorbidity, according to the definition of Crawford et al, was observed in 35.7% of those in the trial. Consistent with current practice, healthier men were more likely to receive curative rather than noncurative treatment (including androgen deprivation therapy). Of note, the analysis did not adjust for this difference in treatment aggressiveness between groups. Perhaps not surprisingly, a significant decrease in the risk of prostate cancer–specific mortality was observed in those with few or no comorbidities (hazard ratio, 0.56; $P = .03$). The NNS and NNT were 723 and five, respectively. By contrast, among men with more comorbidities, there existed a trend toward an increase in prostate cancer–specific mortality with intensive screening compared with usual care (hazard ratio, 1.43; $P = .08$). The authors correctly point out that because analysis was performed post random assignment, the findings are hypothesis generating, and the risks of overdetection and overtreatment remain important issues.

Loeb et al[9] reanalyzed the data from the ERSPC trial, noting that although NNS and NNT are useful statistics, they are time dependent; therefore, reporting values at one point in time can be misleading.

They aptly summarize the pitfalls in the calculation and interpretation of such statistics and concentrate on assessing their time-specific sensitivity. Their model yielded NNS and NNT at 9 years of 1,254 and 43, respectively, similar to the numbers quoted in the original article of 1,410 and 48.[6] However, with longer follow-up, the NNS and NNT dropped sharply to 837 and 29 at 10 years and 29 and 18 at 12 years, respectively.

The more favorable estimates of screening in these two articles are supported by the recently reported results of the Göteborg randomized population-based screening trial,[10] which received much less media attention than the PLCO and ERSPC trials. During a median follow-up of 14 years, the cumulative relative risk reduction of death as a result of prostate cancer in this trial was 50% in the screening group. To prevent one death resulting from prostate cancer, the number of men required to be invited for screening was 293, and 12 needed to be diagnosed. These numbers are more favorable than those initially reported in the ERSPC trial and are much more so than those reported in the PLCO trial. Why were these results different? Men were generally younger (median age, 56 years), the PSA threshold for biopsy was initially 3.4 ng/mL and subsequently lowered to 2.5 ng/mL (compared with 4 ng/mL in the PLCO study), the biopsy rate among those with an elevated PSA was high (93% *v* 30% to 40% in the PLCO study[5]), and PSA screening before the start of the study was much less common (3% *v* 44% in the PLCO study). In addition, at 14 years, median follow-up was the longest to date (compared with 9 and 11.5 years in the ERSPC and PLCO trials, respectively). Also critical in this trial was the fact that not all men in whom cancer was detected were treated, showing that screening can reduce mortality without requiring treatment of all diagnosed patients.

Indeed, active surveillance in lieu of immediate treatment is gaining popularity as centers have shown favorable outcomes in well-selected and carefully observed patients.[11-13] Overdetection may itself cause anxiety and lead to additional work-up and medical resource utilization, but it is primarily a problem to the extent that diagnosis is uniformly followed by treatment and thus by overtreatment. Unlinking detection and treatment is a high priority in efforts to improve prostate cancer management. Unfortunately, even those who are excellent candidates for active surveillance in the United States are most often treated.[14]

What should we conclude from contemporary studies of prostate cancer screening? First, PSA screening leads to reduced risk of death as a result of prostate cancer among selected men. Second, those men who are healthy and have a long life expectancy may benefit most from screening, because benefits of screening accrue over time. Third, screening in any patient is associated with significant risk of overdetection. Fourth, the impact of overdetection can be mitigated by selective treatment (ie, treating only those who are at risk of cancer-related morbidity and mortality as defined by tumor characteristics and competing risks[15]) and deferment of treatment in those with low-risk disease.

Debate and controversy will continue, but it is clear that the actual benefits and risks of screening are being elucidated with new information. There remain many unanswered questions. When should we start screening? Many recommend that it begin among men in their 40s, because baseline PSA in this age group is a strong predictor of future risk of advanced disease.[16] What are the optimal intervals for screening? Surely not all men require screening at yearly intervals. When do we stop screening? Emerging evidence suggests that older men with low PSA levels may not need to continue testing.[17] Can we supplement or even replace PSA with better markers of significant disease, thereby both improving the efficiency of screening and minimizing overdetection? What is the optimal role of chemoprevention, and which patients (eg, those with family history or other risk factors) will benefit most?[18,19]

Finally, despite mounting evidence in support of screening, it is important that the benefits not be overstated. Most men with prostate cancer—even those with high-risk disease—ultimately die as a result of other causes,[20] and fair consideration should be based on absolute rather than relative risk reduction (Fig 1).[21] Minds must remain open. Debate is welcome, but narrow opinions and facile guidelines should yield to fact and new information. Men worldwide deserve it.

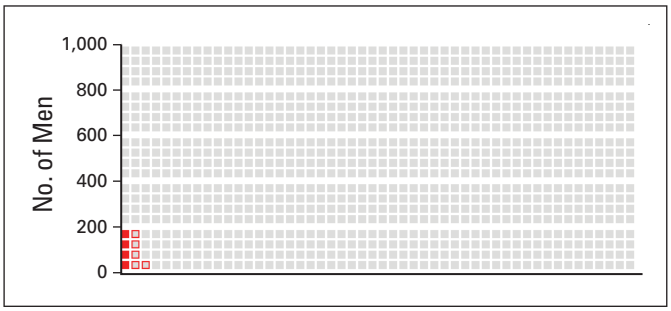

Fig 1. Absolute reduction in prostate cancer mortality. According to data from the Göteborg trial,[10] screening would reduce prostate cancer mortality from nine to four men per 1,000 at 14-year follow-up. Gray boxes indicate men who would not die as a result of prostate cancer in this time period, regardless of screening. Solid red boxes indicate men dying as a result of prostate cancer despite screening. Open red boxes indicate those among whom prostate cancer–specific mortality would be prevented by screening.

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Simple Rules Can Improve Prognostic Accuracy

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A new decision aid, a clever mnemonic, or simple rules of thumb can add precision, clarity, and focus to clinical dialogue. Computer-based decision tools that provide reliable estimates of risk reduction with adjuvant therapy help to anchor difficult conversations in solid statistical estimates of benefit.[1,2] Adjvuvant! Online[3] was quickly adopted by oncologists in the United States and abroad because it is simple, clear, and readily available. Colorful bar graphs provide visual estimates of risk reduction with various adjuvant therapies; these estimates are dramatically contrasted with the natural history without intervention. The program enables the clinician to show both relapse and mortality figures and to help a patient understand how source data was used to generate the estimate. It can strengthen the collaborative nature of the physician-patient relationship by modeling how we routinely sort through statistics and can provide a useful platform for deliberation in search of the best treatment for an individual patient. Numeric estimates and diagrams assist clinicians in their efforts to find the language to convey important information and diminish the anxiety experienced by both the physician and patient when discussing uncertain outcomes.[4] Similarly, simple communication skills, tasks, and protocols improve clinical performance and may contribute to better outcomes overall. More than 10 years ago, Baile and Buckman[5] introduced a catchy mnemonic known as SPIKES to provide a cognitive road map for discussions of difficult news. Six easy steps were presented in a straightforward manner that was designed to minimize the physician's anxiety by directing the physician's focus to what is best for the patient. Both of these tools, Adjuvant! Online and SPIKES, were designed to respond to real clinical concerns and have continued to prove useful after years of scrutiny and critique.

There is less agreement and perhaps greater variation in practice with respect to the communication of prognostic information and estimates of life expectancy. Philosophic arguments for and against complete disclosure and patient surveys shed some light on this challenging issue, and there are helpful suggestions to improve communication.[6-8] Clearly, new research and insight are needed to help oncologists work through these difficult conversations and optimize both the quantity and delivery of such vital information. The fact remains that many patients with incurable cancer live for months or years, but it is also true that most eventually die of their disease. Without realistic expectations and time frames, some patients may underestimate or overestimate their life expectancy and make poor choices that they may live to regret or that result in a complicated bereavement for their loved ones.[9]

The desire to protect patients by limiting prognostic information is not driven by available evidence. On the contrary, it is a gut reaction. The literature suggests that there is a large variability in the frequency of prognostic discussions in the metastatic setting.[10] We know little about how the information is conveyed and how it is received and processed by patients and families. An interesting study of parents of dying children showed that they remained more hopeful if fully informed, even though the information itself was devastating.[11] Perhaps this reflects the degree of support provided by multidisciplinary teams and the importance of recognizing the varying and multiple needs of family members who support the patient. In the world of adult oncology, most patients welcome prognostic estimates when the information is good, but when the news is less favorable, many prefer to know as little as possible. Decision aids such as computer-generated bar