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## Screening for Prostate Cancer — The Controversy That Refuses to Die

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In the United States, most men over the age of 50 years have had a prostate-specific antigen (PSA) test,<sup>1</sup> despite the absence of evidence from large, randomized trials of a net benefit. Moreover, about 95% of male urologists and 78% of primary care physicians who are 50 years of age or older report that they have had a PSA test themselves,<sup>2</sup> a finding that suggests they are practicing what they preach. And indeed, U.S. death rates from prostate cancer have fallen about 4% per year since 1992, five years after the introduction of PSA testing.<sup>3</sup> Perhaps the answer to the PSA contro-

versy is already staring us in the face. At the same time, practice guidelines cite the unproven benefit of PSA screening, as well as the known side effects,<sup>4,5</sup> which largely reflect the high risks of overdiagnosis and overtreatment that PSA-based screening engenders.<sup>6</sup>

The first reports from two large, randomized trials that many observers hoped would settle the controversy appear in this issue of the *Journal*. In the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Andriole et al.<sup>7</sup> report no mortality benefit from combined screen-

ing with PSA testing and digital rectal examination during a median follow-up of 11 years.<sup>8</sup> In the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, Schröder et al.<sup>8</sup> report that PSA screening without digital rectal examination was associated with a 20% relative reduction in the death rate from prostate cancer at a median follow-up of 9 years, with an absolute reduction of about 7 prostate cancer deaths per 10,000 men screened.<sup>8</sup> The designs of the two trials are different and provide complementary insights.

First, one must ask, "Why were these results published now?" Neither set of findings seems definitive; that is, there was neither a clear declaration of futility in the PLCO trial nor an unambiguous net benefit in the ERSPC trial. Both studies are ongoing, with future updates promised. The report on the ERSPC trial follows a third planned interim analysis, which found a marginally significant decrease in prostate-cancer mortality after adjustment of the P value for the two previous looks in an attempt to avoid a false positive conclusion (yet apparently preserving no alpha for the planned final analysis). On the other hand, the investigators in the PLCO trial made the decision to publish their results now because of concern about the emerging evidence of net harm compared with potential benefits associated with PSA screening. Both decisions to publish now can be criticized as premature, leaving clinicians and patients to deal with the ambiguity.

The ERSPC trial is actually a collection of trials in different countries with different eligibility criteria, randomization schemes, and strategies for screening and follow-up. The report by Schröder et al. is based on a predefined core group of men between 55 and 69 years of age at study entry. Subjects were generally screened every 4 years, and 82% were screened at least once. Contamination of the control group with screening as part of usual care is not described. Biopsies were generally recommended for subjects with PSA levels of more than 3.0 ng per milliliter. It is unclear whether the clinicians and hospitals treating patients with prostate cancer differed between the two study groups.

Adjudications of causes of death were made by committees whose members were unaware of study-group assignments, though not of treatments. This point is important, since previous research has suggested that the cause of death is

less likely to be attributed to prostate cancer among men receiving attempted curative treatment.<sup>9</sup> Misattribution might then create a bias toward screening, since the diagnosis of more early-stage cancers in the ERSPC trial led to substantially more attempted curative treatments.

The ERSPC interim analysis revealed a 20% reduction in prostate-cancer mortality; the adjusted P value was 0.04. The estimated absolute reduction in prostate-cancer mortality of about 7 deaths per 10,000 men after 9 years of follow-up, if real and not the result of chance or bias, must be weighed against the additional interventions and burdens. The 73,000 men in the screening group underwent more than 17,000 biopsies, undoubtedly many more than did men in the control group, though the latter is not reported. Men had a substantially higher cumulative risk of receiving the diagnosis of prostate cancer in the screening group than in the control group (820 vs. 480 per 10,000 men). Diagnosis led to more treatment, with 277 versus 100 per 10,000 men undergoing radical prostatectomy and 220 versus 123 per 10,000 undergoing radiation therapy with or without hormones, respectively (tentative estimates given the unknown treatments in both groups).

Although estimates of the benefit of screening were somewhat greater for men who actually underwent testing (taking into account noncompliance) than for those who were not tested, the side effects would be proportionately higher as well. Given these trade-offs, the promise of future ERSPC analyses addressing quality of life and cost-effectiveness is welcome indeed. The ERSPC results also reemphasize the need for caution in screening men over the age of 69 years, given an early trend toward higher prostate-cancer mortality with screening in this age subgroup, although this finding may well be due to chance alone.

A final point to make about the ERSPC trial is that to the extent that the diagnosis and treatment of prostate cancer in the screening group differed from those in the control group, it becomes difficult to dissect out the benefit attributable to screening versus improved treatment once prostate cancer was suspected or diagnosed. A similar distribution of treatments among seemingly similar patients with cancer is only partially reassuring in this regard.

Despite a longer median follow-up, the PLCO trial was smaller and therefore less mature than

the ERSPC trial, with 174 prostate-cancer deaths driving the power of the study, as compared with 540 such deaths in the ERSPC trial. The screening protocol was homogeneous across sites with an enrollment age of 55 to 74 years and annual PSA tests for 6 years and digital rectal examinations for 4 years, with about 85% compliance. Subjects in the screening group who had a suspicious digital rectal examination or a PSA level of more than 4.0 ng per milliliter received a recommendation for further evaluation. This strategy helped to ensure that any difference in outcome was attributable to screening, rather than downstream management. The effectiveness of screening, of course, will be determined by the effectiveness of subsequent "usual care," but this is the same usual care that many practitioners assume has been responsible for the falling U.S. death rate from prostate cancer. Adjudication of causes of death was similar to that in the ERSPC trial.

Though the PLCO trial has shown no significant effect on prostate-cancer mortality to date, the relatively low number of end points begets a wide confidence interval, which includes at its lower margin the point estimate of effect from the ERSPC trial. Other likely explanations for the negative findings are high levels of prescreening in the PLCO population and contamination of the control group. Contamination was assessed by periodic cross-sectional surveys, with about half the subjects in the control group undergoing PSA testing by year 5. It is unclear whether these estimates reflect testing that year or since trial inception; if the former, the cumulative incidence may be even higher. The smaller difference in screening intensity between the two study groups in the PLCO trial, as compared with the ERSPC trial, is reflected in a smaller risk of overdiagnosis (23% vs. more than 70%) and a less impressive shift in cancer stage and grade distributions. Given that study-group contamination from the use of digital rectal examination was less problematic (only about 25%), ongoing results from both of these trials may necessitate rethinking the role of digital rectal examination in cancer screening.

After digesting these reports, where do we stand regarding the PSA controversy? Serial PSA screening has at best a modest effect on prostate-cancer mortality during the first decade of follow-up. This benefit comes at the cost of sub-

stantial overdiagnosis and overtreatment. It is important to remember that the key question is not whether PSA screening is effective but whether it does more good than harm. For this reason, comparisons of the ERSPC estimates of the effectiveness of PSA screening with, for example, the similarly modest effectiveness of breast-cancer screening cannot be made without simultaneously appreciating the much higher risks of overdiagnosis and overtreatment associated with PSA screening.

The report on the ERSPC trial appropriately notes that 1410 men would need to be offered screening and an additional 48 would need to be treated to prevent one prostate-cancer death during a 10-year period, assuming the point estimate is correct. And although the PLCO trial may not have the power as yet to detect a similarly modest benefit of screening, its power is already more than adequate to detect important harm through overdiagnosis. However, the implications of the trade-offs reflected in these data, like beauty, will be in the eye of the beholder. Some well-informed clinicians and patients will still see these trade-offs as favorable; others will see them as unfavorable. As a result, a shared decision-making approach to PSA screening, as recommended by most guidelines, seems more appropriate than ever.

Finally, despite these critiques, both groups of investigators deserve high praise for their persistence and perseverance: to manage such monstrous trials is a herculean task, made no easier when so many observers think the results are self-evident. Further analyses will be needed from these trials, as well as from others — such as the Prostate Cancer Intervention Versus Observation Trial (PIVOT) in the United States (ClinicalTrials.gov number, NCT00007644)<sup>10</sup> and the Prostate Testing for Cancer and Treatment (PROTECT) trial in the United Kingdom (Current Controlled Trials number, ISRCTN20141297)<sup>11</sup> — if the PSA controversy is finally to sleep the big sleep.

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