Data Are Mixed on Prostate Screening Benefits

BY MICHELE G. SULLIVAN

Two large prostate cancer screening trials led to different conclusions about the disease's impact on mortality: One found that screening reduces prostate cancer deaths by 20%, and the other found that it makes no difference at all.

The results were published online to coincide with a press briefing at the European Association of Urology Annual Congress in Stockholm.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial followed 77,000 men for up to 10 years and found similar rates of prostate cancer death among those randomized to regular screening with prostate-specific antigen (PSA) testing or to usual care (50 vs. 44 deaths).

Conversely, the European Randomized Study of Screening for Prostate Cancer (ERSPC), which included 182,000 men, found that routine PSA screening significantly reduced the rate of prostate cancer mortality, compared with usual care. But the savings come at a price, admitted primary investigator Dr. Fritz Schroder and his colleagues: More than 1,400 men would need to be screened and 48 additional cancers treated to save one life.

After reading the two studies, physicians and patients may be as confused as ever about balancing the risks of longstanding adverse treatment effects with the benefits of early diagnosis and treatment, Dr. Philip W. Kantoff said in a discussion sponsored by the New England Journal of Medicine.

"The deceptively simple PSA test inevitably leads to a cascade of biopsies, which lead to prostate-cancer diagnoses, leading to aggressive treatments for those prostate cancers, leading to men having substantial side effects from those treatments [including] urinary incontinence and sexual dysfunction," said Dr. Kantoff, director of the Lank Center for Genitourinary Oncology at the Dana Farber Cancer Institute, Boston.

"And many of these men suffer those downstream troubles for a cancer that was never, ever destined to cause them harm in their lifetime," he noted.

Dr. Michael J. Barry, who wrote an editorial that accompanied the papers, concurred. "The trade-offs reflected in these data, like beauty, will be in the eye of the beholder," wrote Dr. Barry of Massachusetts General Hospital, Boston.

"Some well-informed clinicians and patients will still see those 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" (N. Engl. J. Med. 2009;360:1351-4).

From 1993-2001, PLCO randomized 77,000 men aged 55-74 years to either annual screening (PSA testing for 6 years and digital rectal exam for 4 years) or usual care, which sometimes included screening. The PSA cutoff for biopsy was 4 ng/mL.

Dr. Gerald Andriole and his colleagues reported outcomes after 7 and 10 years of follow-up (N. Engl. J. Med. 2009;360:1310-9). At 7 years, prostate cancer had been diagnosed in 2,820 in the screening group and 2,322 in the control group, a significant difference. At 10 years, there were still significantly more cancers diagnosed in the screening group (3,452 vs. 2,974).

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DR. SCHRODER

At 7 years, 50 men had died from prostate cancer in the screening group and 44 in the control group—a nonsignificant 13% difference. By year 10, with data in for 67% of the subjects, 92 in the screening group and 82 in the control group had died—also a nonsignificant difference. The difference stayed nonsignificant when the data were analyzed by tumor stage or previous screening at baseline.

Although treatment-related complications arose, those data were not included. Instead, they are being analyzed as part of an upcoming quality of life study.

The authors noted that the lack of mortality reduction could be caused by improved prostate cancer treatment over the trial period or by the short follow-up time, which might not have been enough for all cancers to develop. "However," wrote Dr. Andriole of Washington University, St. Louis, "We now know that prostate-cancer screening provides no reduction in death rates at 7 years and no indication of a benefit … by 10 years."

ERSPC examined outcomes in 162,000 men aged 50-74 years who had been included in seven European health registries, wrote Dr. Schroder of Erasmus Medical Center, Rotterdam. Subjects were randomized to PSA screening once every 4 years or to no regular screening. The screening protocol varied by country; PSA cutoffs triggering more investigation ranged from 2.5-4 ng/mL (N. Engl. J. Med. 2009;360:1320-8).

Overall, screening nearly doubled the number of prostate cancers diagnosed (5,990 in the screening group vs. 4,307 in the control group). But the increased diagnoses carried a price. Of those who underwent biopsy for an elevated PSA, 76% had a false-positive result. The positive predictive value of a biopsy was also low—just 24% on average.

In a preselected core group of men aged 55-69 years, there were significantly more prostate-cancer deaths in the control group (326 vs. 214; odds ratio 0.80). In the intent-to-screen analysis, which included all subjects, the absolute difference between the screening and control groups was 0.71 deaths per 1,000 men, yielding 1,410 screenings and 48 cancers to prevent one prostate cancer death.

The study did not report data on cost effectiveness, adverse treatment effects or quality of life issues. "The ratio of benefits to risks that is achievable with more frequent screening or a lower PSA threshold than we used remains unknown," the authors wrote. ■

GENOMIC MEDICINE

Prostate Cancer Screening

Thanks to public health programs aimed at stepping up screening efforts, considerable progress has been made in the United States regarding the early detection of prostate cancer, and our 5-year survival rates are among the best in the world.

BY GREG FEERO, M.D., PH.D.

There is, however, a dark side to this apparent success story. We are taking biopsies from and subsequently treating lots of men who will never develop clinical disease. This has real consequences for patients and society. These invasive procedures frequently induce considerable morbidity (occasionally mortality) and are costly.

If it weren't for having a physician in his family looking over his shoulder, my 70-year-old father would have had a radical prostatectomy 3 years ago for a "midgrade" cancer. The surgery was planned in a reputable community hospital by a well-meaning surgeon who was following guidelines and who was convinced he was doing the right thing. Today my father is hale and hearty without having gone through a life-altering intervention.

Ideally, we would develop prostate cancer screening methods that have a high sensitivity and specificity for identifying potentially lethal prostate cancers. There have been several advances toward that end. Genomewide association studies have identified well over a dozen genetic markers that are associated with prostate cancer risk. At least a few of these markers appear to be associated with more aggressive forms of the disease.

This has led to several lines of investigation, including a reexamination of genetic marker associations with prostate cancer biopsy results in previously collected patient cohorts.

In addition, studies are being launched to look at how a combination of genetic markers and clinical risk information might enhance the performance of prostate-specific antigen testing.

Investigation of biomarkers for prostate cancer has also accelerated. Recently, attention has focused on the development of screening panels using metabolic markers, including the molecule sarcosine, which appears to be associated with more advanced disease.

PCA3 is a somatic (non–germ-line) DNA marker that when elevated in the urine is specific but not highly sensitive for prostate cancer. It seems likely that, over time, a panel of tests will emerge that provide enhanced prostate cancer screening.

On the disease prevention front, a reanalysis of data from the Prostate Cancer Prevention Trial, suggests a possible role for finasteride in chemoprophylaxis. In the initial analysis, it appeared that the drug actually increased the risk of more aggressive cancers. However several recent reanalyses of the data, with proper corrections for the study design, suggest that the drug could reduce prostate cancer risk by as much as 25%. However, this preventive strategy would be costly if untargeted, both in terms of dollars and side effects.

The next big advance will occur when we are able to harness the effectiveness of prevention and screening strategies based on the individual's genomic profile.

It is plausible, for example, that individual genotypes might predict the benefits or side effects of preventive measures such as the daily use of finasteride. The cost of genotyping is no longer the barrier that it was 5 years ago.

One might argue that a genomic profile was not needed in my father's case since it appears that the right call was made without any high-tech testing. However, genomic discoveries that promise to reduce the uncertainty in the decision making process are being made on a daily basis, and I for one sleep better for it. ■

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