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The new data on prostate cancer screening: What should we do now?

THIS EDITION of the *Cleveland Clinic Journal of Medicine* includes a timely update on prostate cancer screening and prevention by a leading international expert, Dr. Eric Klein.¹ At long last, 2009 brought the publication of two large prostate cancer screening trials.^{2,3} Randomized controlled trials had been needed to discover whether screening had a benefit.

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Now that we have the data, was it worth the wait? Do we know the answer? Should our male patients, our male loved ones, and those of us who are men have prostate-specific antigen (PSA) tests?

■ DOES EARLIER DIAGNOSIS HELP OR HARM?

Over the past 20 years, PSA screening and other developments have transformed the presentation of prostate cancer in regions where PSA testing is common. The incidence of prostate cancer that was metastatic at the time of diagnosis fell by 56% between 1985 and 1995.⁴ The proportion of cancers that were localized in the mid-1980s was 58%, compared with 80% now, while only 4% now have metastases at diagnosis.⁵

This early detection had a predictable effect on 5-year relative survival, which increased from 69% in the mid-1970s and 84% in the late 1980s to 99.9% in the early 21st century.⁵ Prostate cancer now has the highest 5-year relative survival of any cancer except non-melanoma skin cancer.

This doesn't mean that prostate cancer doesn't kill men, but only that it almost always takes longer than 5 years from diagnosis. More than 27,000 Americans die of prostate cancer annually—lung cancer is the only malignancy that kills more men. Nonetheless, that 27,000 is a small fraction of the 192,000 men diagnosed with prostate cancer each year. And it is worth keeping in mind that autopsy studies show that most men have cancer in their prostates by the time they reach age 70, while the Prostate Cancer Prevention Trial reported that 24% of men at least 55 years old have prostate cancer detectable by biopsy, including 15% of men who have a serum PSA less than 4.0 ng/mL and a normal digital rectal examination.^{6,7}

Prostate cancer is thus highly prevalent, usually indolent, but sometimes deadly. Over-treatment of indolent disease and ineffective treatment of aggressive disease continue to represent major challenges.

As prostate cancer survival has lengthened, the prostate cancer death rate has declined, although to a lesser extent. The death rate from prostate cancer per 100,000 US males was 31 in 1975, climbed to 39 in 1990, and then declined to 25 in 2005, a 19% reduction over 30 years. Viewed differently, the lifetime risk of being diagnosed with prostate cancer increased from 13% in 1990 to 16% in 2006, while the risk of dying from it declined from 3.2% to 2.8%.⁵

This reduction in death rate was interpreted by some as evidence that PSA screening is effective, but it was impossible to control for confounding variables such as improvements in treatment. It was clear that PSA testing provided earlier diagnosis and hence longer

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doi:10.3949/ccjm.76a.09079

survival from the time of diagnosis, but it was not clear whether it resulted in men living longer. Given the numerous kinds of serious harm that can follow from a diagnosis of prostate cancer in the form of anxiety, treatment side effects, and medical expenses, early diagnosis could easily represent a net harm.

■ THE EUROPEAN PROSTATE CANCER SCREENING TRIAL

To address the question of whether prostate cancer screening with PSA testing lowers a man's risk of dying of prostate cancer, Europe and the United States each initiated randomized controlled trials.

The European study² randomized 162,000 men, age 55 to 69 years, to one of two groups. One group was offered PSA screening, the other was not. In those screened, PSA testing was repeated once every 4 years on average. Most centers participating in the trial used a PSA above 3.0 ng/mL as the threshold for biopsy. In the screening group, 82% of the men had at least one PSA test, 16% of all PSA tests were positive, and 86% of men who had an elevated PSA value underwent a biopsy. Of those undergoing biopsy for an elevated PSA, 76% had benign results, which shows that PSA as a test for cancer has a high false-positive rate.

As expected, screening increased the rate of prostate cancer detection. The rate was 70% higher in the screening group: 8.2% of men in the screening group were diagnosed, compared with 4.8% in the control group. Men undergoing screening were more likely to have localized disease and 41% less likely to have metastatic disease. The increased number of cancers detected by screening were predominantly less-aggressive tumors: the incidence of low- and intermediate-grade cancers (Gleason score 2 to 6) was 4.8% in the screened group vs 1.7% in the control group. Screened men had a lower proportion (28% vs 45%) but a higher incidence (1.9% vs 1.4%) of high-grade cancers (Gleason score 7 or higher). It is this tendency of screening to preferentially detect indolent cancers that results in length-time bias.

So did PSA testing lower the risk of death from prostate cancer? In the European trial it did, and by 20% (95% confidence interval

5%–33%, $P = .01$). This study thus provided level-1 evidence that PSA testing to screen for prostate cancer reduces prostate cancer mortality rates.

However, more than 1,400 men needed to be screened and 48 needed to be treated for each death prevented. Moreover, because fewer than 3% of men die of prostate cancer, lowering the risk of death from prostate cancer does not result in an appreciable effect on all-cause mortality or on life expectancy. We cannot say that men live longer as a result of prostate cancer screening—only that they are less likely to die of prostate cancer.

■ THE US SCREENING TRIAL

What about the US trial? Unfortunately, it was beset by limitations that make its interpretation extremely difficult.³

Between 1993 and 2001, 76,693 men were randomized to prostate cancer screening with PSA testing and digital rectal examination, or else to usual care.

The problem is that in the United States “usual care” often includes PSA testing. Thus, 34% of men participating in the trial had had a PSA test within 3 years prior to enrolling on the trial, and 52% of the control group had PSA testing during the trial. In the group randomized to screening, 85% complied with PSA testing. This trial thus compared one group in which most were screened at least once against another group in which 85% were screened regularly. Rather than asking whether screening is effective, the trial compared two different PSA screening schedules.

Thus, it was no surprise that there was less than a 25% increase in the cancer detection rate and less than a 30% reduction in the likelihood of having detectable metastatic disease at the time of diagnosis. And after 7 years of follow-up, the two groups showed no statistically significant difference in the likelihood of dying of prostate cancer.

■ SHOULD MEN BE SCREENED FOR PROSTATE CANCER?

The European trial provides strong evidence that PSA testing reduces prostate cancer mortality rates,² while the US trial

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sheds little light on the subject. But does this mean that men should be screened routinely?

It's not that simple. The 75% false-positive rate of PSA testing and the high number needed to treat ($n = 48$) to save one life represent significant harmful effects of prostate cancer screening that must be factored into the decision-making process. And we know from other studies that half or more of men undergoing prostate cancer treatment will report erectile dysfunction, while a smaller number will experience urinary incontinence. More and more men without detectable metastatic disease are being treated with medical or surgical castration, which is associated with loss of libido, osteoporosis, weight gain, loss of muscle, and an increased risk of diabetes and death from cardiovascular disease. Prostate cancer treatments also result in large medical bills, which are a source of hardship for the increasing number of Americans with inadequate health insurance.

The benefit of PSA testing is limited by several key facts:

- It is an inaccurate test with a high false-positive rate
- The treatment of prostate cancer results in serious adverse effects
- Most men will develop prostate cancer if they live into their 70s
- Most prostate cancers are not life-threatening.

Whereas cervical cancer screening typically detects precancerous lesions that can be treated superficially and colon cancer and breast cancer screening often detect precancerous lesions or small tumors that can be removed with relatively minor surgery, prostate cancer treatment is radical and often results in significant long-term adverse effects. The benefits of PSA screening must be balanced against the harm.

One way out of this dilemma, as discussed in Dr. Klein's article, is to eliminate the reflex progression from PSA elevation to biopsy and from positive biopsy to treatment. As Dr. Klein discusses, variables other than PSA help predict the likelihood that a biopsy would detect a clinically significant cancer and can reduce the likelihood of performing unnecessary biopsies.¹

Similarly, there is growing interest in active surveillance for clinically localized low- or intermediate-grade prostate cancers, thus sparing men unnecessary and aggressive treatment.⁸ The challenge is determining which cancers are indolent and which are aggressive. Until we have accurate tools to make such a distinction, overtreatment will remain a problem as men and their doctors opt for aggressive treatment in the face of uncertainty about a cancer's true danger.

MOVING FORWARD

This year has brought strong evidence that PSA screening lowers the risk of dying of prostate cancer, but at a cost of overdiagnosis, overtreatment, and a significant burden of treatment side effects and costs. Moving forward will depend on a more sensitive and specific screening test, tools for better predicting which cancers actually need treatment, and treatments that result in fewer long-term side effects. Progress on all these fronts can be expected in the future.

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