Efficacy vs Effectiveness in Prostate-Specific Antigen Screening

Peter C. Albertsen

The recent publication of interim analyses of two large randomized trials evaluating the impact of prostate-specific antigen (PSA) screening on prostate cancer mortality (1,2) has generated considerable controversy and analysis. On first glance, the conclusions from these studies appear to be contradictory. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (1) demonstrated no benefit from PSA testing, whereas the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (2) suggested that PSA testing reduces prostate cancer mortality by 20% but with the caveat that at least 48 men require treatment to prevent one prostate cancer death.

Closer inspection of the study designs of these two trials reveals that the PLCO trial evaluated the effectiveness of PSA screening, whereas the ERSPC trial primarily evaluated the efficacy of PSA screening. Although these words—effectiveness and efficacy—appear to describe similar concepts, an understanding of their distinct meanings will help clarify the basis of the differing conclusions about whether PSA screening reduces prostate cancer mortality. A clinical trial that evaluates the effectiveness of PSA screening tests whether PSA screening can lower prostate cancer mortality in routine clinical practice. A clinical trial that evaluates the efficacy of PSA screening tests whether PSA screening can lower prostate cancer mortality when compared with no screening in a clinical trial setting.

In the PLCO trial, men were recruited to study centers and randomly assigned to receive either annual PSA tests for 6 years and digital rectal examinations for 4 years or usual care. If a study participant was found to have an abnormal PSA test or digital rectal examination, study researchers referred him to his primary care physician or other health-care provider for further evaluation, a possible prostate biopsy, and treatment if the biopsy specimen was positive for cancer cells. In the ERSPC trial, potential study participants were identified from population registries and invited to participate in the study. Men who were found to have an abnormal PSA level were offered transrectal ultrasounds and biopsies. Men with positive biopsies were provided definitive treatment.

The distinction between PSA screening efficacy and effectiveness is not an academic one. When considering broad public health policies such as population-based PSA screening, this distinction helps determine clinical relevance. PSA screening must be efficacious if it is to be effective, but it may be not effective even when it is efficacious.

How can these concepts be explored and tested? The study by Wever et al. (3) in this issue of the Journal offers a prime example. The authors used computer models to simulate outcomes of various PSA screening scenarios. Specifically, they explored the performance of PSA screening by using a previously validated microsimulation screening analysis model for prostate cancer. The Rotterdam section of the ERSPC study was designed to test the efficacy of PSA screening; thus, it provided key data demonstrating that PSA screening can lower prostate cancer mortality in ideal situations. The authors first simulated prostate screening and progression in the Rotterdam section of the ERSPC study. They then adjusted the model results to US population data.

Wever et al. explored two scenarios. In model 1, they asked the question: What would happen if PSA screening was conducted as...
rigorously in the United States as was done in the Rotterdam section of the ERSPC trial? In model 2, they explored this problem from the opposite perspective. They assumed that the PLCO trial data reflected routine clinical practice and asked how much does PSA screening performance deteriorate when it moves from a trial environment to routine practice? Their findings are remarkable and very instructive. They report that to achieve the results reported in the Rotterdam section of the ERSPC trial, the intensity of PSA screening and prostate biopsy would need to increase by well more than 50% from the values recorded in 1992 when prostate cancer incidence rates were at their peak in the United States. Presumably, the rates of radical prostatectomy and radiation therapy among men aged 55–69 years would also need to increase by 50% to achieve the mortality reduction noted in the ERSPC trial. The consequences of such large increases in surgery and radiation are sobering.

When viewed from the opposite perspective, the public health implications are equally daunting. The authors estimate that, based on the PLCO trial data, the sensitivity of PSA testing in the United States is approximately 0.26. This sensitivity would need to increase to almost 0.94 to achieve the mortality reduction observed in the ERSPC trial. A public health campaign to increase PSA testing sensitivity by this magnitude would require considerable political support and would compete with other campaigns, such as smoking cessation, breast and colon cancer prevention, and efforts to curb drunk driving.

Finally, because the sensitivity of PSA testing in the United States is so modest, the computer simulation models developed by Wever et al. suggest that only a small component of the prostate cancer mortality decline noted in the United States during the past two decades can be attributed to the PSA screening effort. If this is so, what else could be driving the decline in prostate cancer mortality? Have environmental risk factors contributed to the increase in prostate cancer mortality observed during the 1970s and 1980s? If so, should prostate cancer prevention efforts be directed toward more epidemiological studies rather than toward funding screening and treatment efforts? Should we be investing scarce research dollars to identify these factors and their impact on the mechanisms of cellular replication?

ERSPC researchers in Rotterdam (2) have demonstrated the efficacy of PSA testing to lower prostate cancer mortality. Wever et al. are now exploring the magnitude of the effort needed to achieve the maximum effectiveness of PSA testing. Their report in this issue of the Journal (3) suggests that the health-care costs would be considerable and therefore need to be weighed carefully against alternative uses of increasingly scare health-care resources. Patients and those responsible for managing health-care expenditures need to know what tests and procedures work in the daily practice of medicine. Research efforts such as those conducted by Wever et al. provide critical insights into our understanding of the important differences between treatment efficacy and treatment effectiveness in the diagnosis and management of prostate cancer.

References


Affiliation of author: Department of Surgery (Urology), University of Connecticut Health Center, Farmington, CT.