Prostate-Specific Antigen Testing: Good or Bad?

PETER C. ALBERTSEN

Division of Urology, University of Connecticut Health Center, Farmington, Connecticut, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

The authors of the recent 13-year update of the European Randomised Study of Screening for Prostate Cancer (ERSPC) claim that testing for prostate-specific antigen (PSA) at least once every 4 years reduces prostate cancer mortality by as much as 27% among men aged 55–70 years [1]. This interpretation of the data is probably the most optimistic but is often quoted by the media or prostate cancer screening enthusiasts. The recent statement by the U.S. Preventive Services Task Force (USPSTF) takes the opposite position [2]. The USPSTF stated that the harms associated with PSA testing far outweigh the benefits and argued that PSA screening should not be done. What should patients be told regarding these seemingly contradictory statements concerning PSA screening? Several factors affect PSA testing outcomes including how the data are accrued and analyzed, the prevalence of prostate cancer among the men being tested, the natural history of prostate cancer progression, and the impact of treatment interventions. This commentary will review these factors with the goal of assisting the practicing oncologist in counseling patients appropriately.

A careful review of the abstract of the ERSPC 13-year update reveals several numbers summarizing the trial results [1]. What do they all mean? The “rate ratio of prostate cancer incidence” between the intervention and control groups was 1.57 after 13 years. This means that one and a half times as many cancers were identified in the screening arm as in the control arm. Many people assume that it is good to find more cancers, but unfortunately, with prostate cancer, this may not be so. In the screening arm, more than half of the cancers identified were categorized as Gleason 6 tumors. In the control arm, less than one-third of the tumors were classified this way. Gleason 6 tumors are usually associated with an excellent prognosis; therefore, many men tested for PSA now carry the burden of a prostate cancer diagnosis without obvious benefit. Epidemiologists describe this problem as overdiagnosis. The ERSPC investigators estimate that almost half of the men diagnosed with screen-detected cancers have disease that will probably never cause morbidity.

The abstract states that the “rate ratio of prostate cancer mortality” was 0.79 at 13 years [1]. What does this mean? This means that 21% fewer men died in the screening arm than in the control arm. Although this number may sound impressive, it is actually difficult to interpret in isolation because it is a relative rate. The percentage depends not on the number of

men who died but simply on the *ratio* of deaths in the two arms of the trial. The next sentence states that the “absolute risk reduction” was 0.11 per 1,000 person-years or 1.28 per 1,000 men randomized. This means that the difference in prostate cancer deaths between the screening arm and the control arm was fairly modest. The authors note that for every 781 men invited for PSA testing, 1 prostate cancer death is averted. More important, for every 27 prostate cancers diagnosed by screening, 1 prostate cancer death is averted. Presenting the outcomes in relative terms versus absolute terms can influence how PSA testing is perceived. The editorial that accompanied the publication of the ERSPC update suggests that the absolute risk reduction will increase with longer follow-up [3]. This may or may not be true. The absolute risk reduction did not change when follow-up was extended from 11 to 13 years.

The authors of the update end the abstract by stating that “after adjustment for nonparticipation,” the rate ratio of prostate cancer mortality in men screened was 0.73 [1]. What does this mean? This is an attempt to estimate the maximum possible impact of screening. Men participating in the screening arm of the ERSPC study, for example, were supposed to be screened every 4 years, to undergo a prostate biopsy if PSA was elevated, and to undergo treatment if they were found to have cancer. Conversely, men participating in the control arm should not have had any PSA screening. Unfortunately, in the real world, not every man actually does what he is supposed to do. To avoid selection biases that might occur by reclassifying men, researchers conducting a randomized trial usually perform an “intent-to-screen” analysis. Patients who do not complete their assigned intervention are considered not to have participated. By adjusting for nonparticipation, the authors are trying to calculate the maximum possible impact of PSA testing in a perfect world. As noted in the editorial, “such adjustments are not a precise science” [3]. Most epidemiologists usually quote the more conservative rate ratio derived from the unbiased intent-to-screen approach.

A review of the entire paper reveals other important factors that have affected outcomes. Table 1 [1] lists all of the centers participating in the ERSPC trial. On quick inspection, one would assume that the trial was conducted in a similar fashion at each site, but this is not actually the case. Many epidemiologists look at this study as a series of seven separate screening trials, of which two are positive and the rest are negative. Each site had somewhat different accrual methods

and used different screening criteria and different screening intervals. From an absolute perspective, the number of cases randomized differs significantly by center. Finland enrolled >80,000 men; the Netherlands enrolled 35,000; Italy enrolled almost 15,000; and Sweden enrolled almost 12,000. I mention these four sites because the trial showed no advantage for PSA testing in Finland or Italy but showed a statistically significant decline in prostate cancer mortality in the Netherlands and Sweden. Finland had the largest number of men randomized but did not show a positive outcome, whereas Sweden had the smallest number of men among these four centers but showed the most dramatic outcome. Why were findings so different among these sites? This question raises concerns about whether the results can be generalized to other nations and other populations. Sweden is unusual in that it has much higher mortality from clinically significant prostate cancer than the other participating European centers. Prostate cancer mortality among men aged 65–74 years is twice as high in Sweden compared with the U.S. Consequently, screening is likely to be much more effective in identifying clinically significant disease in Sweden and less effective in the U.S.

A review of Table 4 [1] also raises concerns. This table lists prostate cancer mortality by age groups at the time of randomization. The results are statistically significant for the core age group of 55–69 years and for all ages from 54 to ≥ 70 years. A review by each age group, however, shows a more complex story. The results were dramatically positive for men aged 65–69 years at randomization but were not statistically significant for men aged 55–59 and 60–64 years despite comparable sample sizes and the fact that the men in the younger age groups were screened for a longer period of time. The positive findings of the entire trial are driven primarily by the older cohort of patients. Most screening advocates recommend that PSA testing start at age 50, but no evidence shows that more clinically significant cancers are found at this age.

The paper does not address two other issues that affect the screening debate and that led the U.S. Preventive Services Task Force to recommend against PSA testing: treatment efficacy and associated treatment complications. Screening works only if there is an effective treatment that alters the outcome of the disease. Fortunately, two randomized trials address these issues. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial was conducted by the U.S. Veterans Administration and enrolled 731 men with localized prostate cancer between 1994 and 2002 [4]. Men were randomly assigned to observation or radical prostatectomy and followed through January 2010. After a median follow-up of 10.0 years, 171 of 364 men assigned to radical prostatectomy died compared with 183 of 367 assigned to observation. Among men undergoing radical prostatectomy, 21 died of prostate cancer or treatment compared with 31 men assigned to observation. The authors concluded that radical prostatectomy did not provide a survival advantage for men identified with localized prostate cancer by PSA testing through 12 years of follow-up. Analysis by prostate cancer risk showed that observation was the preferred strategy for men with low-grade disease. There was a suggestion that surgery benefitted men with intermediate- or high-grade disease, but the sample size was too small to achieve statistical significance.

The other key trial, the Scandinavian Prostate Cancer Group 4 study, was recently updated in March 2014 [5]. This trial was conducted in Sweden and accrued patients between 1989 and 1999 and followed them until December 31, 2012. Although most of the patients were not identified by PSA testing, this trial provides important data concerning the efficacy of surgery to treat prostate cancer. After a median follow-up of 13.4 years, 200 of 347 men assigned to radical prostatectomy had died compared with 247 of 348 men assigned to observation. Among men undergoing radical prostatectomy, 63 had died of prostate cancer or treatment compared with 99 men assigned to observation. In this case, radical prostatectomy provided a survival advantage, but the primary beneficiaries were men aged <65 years with intermediate-grade disease. Relatively few men with low-grade disease succumbed to prostate cancer (11 and 20, respectively, in the surgery and observation arms), and surgery appeared to have no impact among men with high-grade disease (28 and 29 prostate cancer deaths, respectively, in the surgery and observation arms). The data surrounding the efficacy of radiation therapy is much less robust.

Unfortunately, whether effective or not, treatment can be associated with morbidity. This has been well documented for both surgery and radiation [6]. The USPSTF estimated that PSA testing will prevent 1 prostate cancer death for every 1,000 men tested [2]; however, to achieve this outcome, approximately 100–120 men will undergo a prostate biopsy, with the associated risks of bleeding and infection. Approximately 110 men will be diagnosed with prostate cancer. A majority of these men will undergo treatment. Treatment is associated with at least 2 serious cardiovascular events, 1 serious deep vein thrombosis, 29 cases of erectile dysfunction, and 18 cases of incontinence. From the USPSTF's perspective, the ability to spare 1 prostate cancer death for every 1,000 men screened is not justified by the associated morbidity experienced by the 110 men undergoing treatment.

Is PSA testing good or bad? It clearly is not the panacea that PSA screening enthusiasts hoped for, but it is not worthless. The significant overdiagnosis and the modest number of deaths prevented over 13 years of follow-up raise major concerns from a public health perspective. Many patients, however, still want to be tested. They believe that early diagnosis can protect them from prostate cancer progression, and in some cases, it can. From a practical standpoint, screening makes the most sense for men in their 50s and 60s. Obtaining a series of PSA levels drawn annually or biannually allows a physician to monitor the growth of the prostate over time. PSA levels often rise with age as a consequence of benign hypertrophy. Elevated PSA values should always be repeated after a few weeks before proposing a biopsy. Many will return to baseline within 1 month. An increase of up to 0.75 ng/mL over a 3-year period is normal.

Those men who have elevated PSA need to be aware that a prostate biopsy can identify both clinically significant and insignificant cancers. Men found to have high-grade cancers will receive treatment, but this may improve outcomes for only a subset of patients. Men found to have low-grade cancers have a more difficult decision. Should they undergo treatment or active surveillance? Low-grade tumors usually do not progress for 10–20 years or longer. Patients must also

recognize that intervention can have a serious impact on their quality of life, although not always. The oncologist can provide expert guidance, but once a patient understands the risks and benefits, only he can make the choice to be screened or not.

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For Further Reading:

Controversies in Oncology - Breast Cancer

Daniel B. Kopans. Arguments Against Mammography Screening Continue to Be Based on Faulty Science. *The Oncologist* 2014;19:107–112.

Archie Bleyer. Were Our Estimates of Overdiagnosis With Mammography Screening in the United States “Based on Faulty Science”? *The Oncologist* 2014;19:113–126.

Martin J. Yaffe, Kathleen I. Pritchard. Overdiagnosing Overdiagnosis. *The Oncologist* 2014;19:103–106.

Excerpt:

There is solid evidence from both randomized trials and observational studies that screening mammography for women between the ages of 40–69 years contributes to a substantial reduction in mortality from breast cancer; however, mammography screening is far from a perfect test. Sensitivity is often reduced in women with very dense breasts, and lack of specificity results in recall of women who do not have breast cancer for further imaging investigation. In addition, concerns have been expressed regarding overdiagnosis and overtreatment. In this issue, Drs. Bleyer and Kopans express very strongly held differences of opinion regarding the degree of overdiagnosis associated with mammography screening. It is clear from their articles that some of the differences in their positions are based on acceptance of different data as being factually accurate, such as the level of mortality reduction attributable to screening. Other differences are related more to values, for example, the weight of the benefit of a life saved through earlier detection versus the harms caused by stress after having been called back after a positive screening examination when cancer is then ruled out or having treatment for ductal carcinoma in situ (DCIS) that may or may not eventually progress to become lethal.