Prostate Cancer Screening Did Not Reduce Deaths from the Disease in a Large Randomized Trial

Andriole GL, Grubb RL 3rd, Buys SS, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310–9.

Study Overview

Objective. To determine whether screening for prostate cancer with prostate-specific antigen (PSA) testing and digital rectal examinations (DREs) reduces mortality from prostate cancer.

Design. Randomized controlled screening trial (Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial).

Setting and participants. 76,693 men aged 55 to 74 years in 10 U.S. study centers were randomly assigned to receive screening or usual care as determined by their regular physician. Patients in the screening arm were offered annual PSA testing for 6 years and DREs for 4 years, and all results were sent to patients' health care providers. If the DRE was abnormal or if PSA was > 4.0 ng/mL, additional diagnostic testing was recommended and determined by the patient and his health care provider. Patients were excluded if they had a history of prostate, colorectal, or lung cancer or were undergoing current cancer treatment. The exclusion criteria were changed somewhat in 1995 to exclude any participants who had a PSA test in the 3 years prior to enrollment.

Main outcome measures. The primary endpoint was mortality related to prostate cancer. Secondary endpoints included cancer incidence, staging, and mortality from causes other than prostate, lung, or colorectal cancer. Event rates were calculated as the number of events per person-years at risk.

Main results. Baseline characteristics were equivalent in both groups. 63.6% of patients were aged 55 to 69 years in each group, and 86.2% in the screening arm and 83.8% in the control arm were white. In the 3 years prior to enrollment, 34.6% and 34.3% in the screening and controls arms, respectively, had a PSA test, and 32.8% and 31.9% had a DRE. Adherence to the screening protocol in the screening arm was 85% for PSA testing and 86% for DRE. PSA screening was reported by 40% of the control group in the first year of enrollment and 52% in the sixth year, with DREs ranging from 41% to 46%. Patients were followed for a mean of 11.5 years; 67% were followed for 10 years. Death rates from prostate cancer were similar between the screening and control groups at 7 years of follow-up (50 deaths, 2.0 per 10,000 person-years vs. 44 deaths, 1.7 per 10,000 person-years), with a rate ratio of 1.13 (95% confidence interval [CI], 0.75–1.70]). Prostate cancer incidence was higher in the screening group (rate ratio, 1.22 [95% CI, 1.16–1.29]). Mortality rates from causes other than prostate, lung, or colorectal cancer also were similar in both groups (rate ratio, 0.98 [95% CI, 0.92–1.03]). At 10 years of follow-up, findings were unchanged.

Conclusion. Prostate cancer screening with PSA testing and DRE was not effective in reducing mortality rates from prostate cancer.

Commentary

Prostate cancer screening has become routine practice

despite limited evidence of benefit. Some professional societies, including the American Cancer Society and the American Urological Association, have endorsed screening by recommending that physicians offer screening to patients starting at age 50 years after discussion about the associated benefits and harms [1,2]. Other societies have been more circumspect in their recommendations, including the American College of Physicians, which recommends that physicians have informed consent discussions with their patients regarding the potential benefits and harms of screening [3], and the U.S. Preventive Services Task Force (USPSTF), which recently reported that insufficient evidence was available to recommend prostate cancer screening in men younger than age 75 years [4]. The USPSTF recommended against screening men over the age of 75 years. The publication of mortality results from the prostate cancer screening component of the PLCO trial and the related European Randomized Study of Screening for Prostate Cancer (ERSPC) trial have been highly anticipated to provide some clarity to these somewhat divergent recommendations.

The PLCO trial found no difference in prostate cancer mortality between the screening and control arms. For the secondary endpoints, there was a slightly higher rate of tumors with Gleason scores of 8 to 10 in the control group (341 vs. 289 tumors in the screening group). However, there were no differences in rates of advanced stage tumors between the groups. Risks related to screening were minimal and included mild complications from the DRE (rate of 0.3 per 10,000 screenings) and from phlebotomy performed for the PSA test (26.2 per 10,000 screenings). Diagnostic evaluations performed after positive results on screening led to moderate complications that occurred at a rate of 68 per 10,000 tests.

The major limitation of this trial was the high contamination rate of the control group. By year 6 of the trial, over 50% of men in the control group received screening. Any mortality differences between the intervention and control groups in the study would therefore be biased toward a null finding. The large sample size does help to overcome this limitation.

The results of the PLCO trial partially contrast those of the ERSPC trial [5]. In the ERSPC trial, 162,243 men aged 55 to 69 years were randomized to receive screening or usual care, and patients were followed for a mean of 8.8 and 9.0 years in the screening and control groups, respectively. Screening generally included a PSA test every 4 years with diagnostic biopsies recommended for PSA values greater than 3.0 ng/mL. Some countries utilized additional testing procedures for borderline high PSAs, had different PSA cutoffs for diagnostic biopsies, or used different screening intervals. In total, 82% of men in the screening group were screened at least once (rates of screening in the control group are not reported but are assumed to be very low because PSA testing has not been routine across Europe). The incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65–0.98; $P = 0.04$), and the absolute risk reduction was 0.71 deaths per 1000 men in the screening group. According to these results, 1410 men would have to be screened and 48 cases of prostate cancer would need to be treated to prevent 1 death from prostate cancer. Limitations of the ERSPC study included a heterogeneous study design; each country involved in the study had somewhat different study procedures. Additionally, the ERSPC investigators have previously reported interim mortality results on 2 occasions, and the current results required adjustment of the statistical results for sequential testing.

Ultimately, the PLCO and ERSPC trials will likely create a temporary status quo in recommendations for prostate cancer screening. Both trials will soon report quality of life results that could speak to the issue of overtreatment of prostate cancer and morbidity resulting from treatment. If these results show a substantial negative impact on quality of life from prostate cancer screening and treatment, the balance could tilt away from prostate cancer screening, especially because the effect of prostate cancer screening on mortality is mild at best. Additionally, the PLCO trial will continue to follow patients through 13 years of complete follow-up, and any changes in the results would be revealing.

Applications for Clinical Practice

Prostate cancer screening had no impact on mortality from prostate cancer in a large-scale U.S. study; however, these results diverge somewhat from a simultaneously published European study. Clinicians should continue to have a thorough informed consent discussion with patients about the risks and benefits of prostate cancer screening. These discussions should include data on the numbers needed to screen and treat to prevent 1 prostate cancer death as well as any data that emerges regarding the potential impact of screening and treatment on quality of life.

—Review by Jason P. Block, MD, MPH

References

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