Screening for Prostate Cancer
Is the Third Trial the Charm?

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In this issue of JAMA, Martin and colleagues report the results of the third, and with more than 400,000 participants by far the largest, randomized trial of prostate-specific antigen (PSA) screening for prostate cancer. The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) joins the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial (about 77,000 participants) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (about 162,000 participants) in attempting to settle the question of the balance of benefits and harms from PSA screening. In this cluster randomized trial, 573 primary care practices in the United Kingdom offered men aged 50 to 59 years a single PSA screening test or usual care. The mean age of the 419,582 participants was 59 years and about 40% of the participants treated at the practices randomized to the intervention group accepted the invitation to be screened, a degree of dilution of the intervention consistent with the prediction of screening uptake included in the trial’s power calculation.

This screening trial was the front end of the Prostate Testing for Cancer and Treatment (ProtecT) trial. Men in the CAP trial diagnosed with prostate cancer were offered randomization to radical prostatectomy, external beam radiotherapy, or active monitoring in the ProtecT trial. Prostate cancer–specific mortality over 10 years was low (about 1%) in the ProtecT trial and not significantly different across the 3 treatment groups; however, treatment with either surgery or radiotherapy was associated with a significantly lower cumulative risk of metastases during follow-up compared with observation, with an absolute difference of about 3% (6.3 events per 1000 person-years with active monitoring, 2.4 events per 1000 person-years with surgery, and 3.0 per 1000 person-years with radiotherapy).

The CAP trial reported by Martin and colleagues has many remarkable strengths, including 85% of men in the intervention group with a PSA level between 3.0 and 20 ng/mL undergoing a 10-core biopsy, a standard approach to diagnosis and treatment of prostate cancer for participants in both groups, and near-complete follow-up for study outcomes. Although the degree of PSA testing in the control group (a major concern in the PLCO trial) was not directly measured, it was estimated at a relatively low 10% to 15% over 10 years based on epidemiological data on PSA testing from the United Kingdom. Empirical confirmation of this estimate would be valuable. In the CAP trial, the cumulative risk of metastases was not reported (in the ERSPC trial, cumulative risks of metastases have been reported from a subset of 4 of the 8 centers).

The results of the CAP trial reported in this issue of JAMA do not provide compelling support for PSA screening. At a median follow-up of 10 years, the number of men diagnosed with prostate cancer was higher in the intervention group (with an offer of 1-time screening) (n = 8054; 4.3%) than the control group (n = 7853; 3.6%), which is about 0.65 new diagnoses per 1000 person-years. Most of this difference is attributable to the increased detection of tumors with a Gleason grade of 6 or lower (n = 3263 [1.7%] vs n = 2440 [1.1%]). Not surprisingly, with a mean of 2.1 screening tests (generally 4 years apart) per intervention group participant, as opposed to the offer of just 1 test, the cumulative risk of prostate cancer was much higher with screening in the ERSPC trial, which found 3.4 more diagnoses per 1000 person-years over 13 years of follow-up. In the CAP trial, the offer of 1-time screening was not associated with a significant difference in cumulative prostate cancer mortality either in the primary analysis (549 deaths [0.30 per 1000 person-years] in the intervention group vs 647 deaths [0.31 per 1000-person years] in the control group; rate difference −0.013 per 1000 person-years [95% CI, −0.047 to 0.022], P = .66) or in a preplanned instrumental variable analysis adjusting for adherence (adjusted rate ratio, 0.93 [95% CI, 0.67 to 1.29], P = .66).

A key question is whether the findings from the CAP trial should swing the pendulum further in the direction of not offering screening PSA tests. Based on the CAP results, an offer of a single PSA screen in a population of men aged 50 to 59 years is ineffective, and given the higher risk of a prostate cancer diagnosis this approach engages, likely does more harm than good. Further follow-up, as the authors suggest, might uncover some additional benefit, but with the intervention being a single screen at the beginning of the study, and with the prostate cancer cumulative incidence curve for the intervention group coming closer to the control group curve over time, that eventuality seems unlikely.

Further follow-up from the ERSPC trial has seen an increase in the absolute benefit of periodic screening over time, although a modest one. The point estimate of the absolute risk reduction in the screening group compared with the control group in the ERSPC trial increased after 9 years of follow-up from 0.71 fewer prostate cancer deaths per 1000 men randomized to 1.28 fewer prostate cancer deaths per 1000 men randomized after 13 years. The relative rate reduction remained stable, 20% as initially reported after 9 years and 21% at 13 years. Although initiating screening at an earlier age has been
suggested as a strategy to increase screening benefits, stratification by age in both the CAP trial and the ERSPC trial populations did not find significantly larger benefits for men in their 50s compared with older men.

In contrast to the findings from the CAP trial based on an offer of a single screening PSA test, the ERSPC trial likely provides the best direct estimate of the benefits and harms of periodic (every 2-4 years) PSA screening. High levels of contamination of the PLCO trial control group with usual care PSA tests make its negative result difficult to interpret. However, a recent modeling effort suggests the results of the PLCO trial may not be all that different from the ERSPC trial when differences in mean lead times in the intervention and control groups are used to adjust for differences in study characteristics. However, the absolute prostate cancer mortality benefit in the ERSPC trial (but like the CAP trial, without any evidence of an overall mortality benefit) comes at the cost of a considerably higher risk of being diagnosed with prostate cancer. The ERSPC authors estimated that 27 additional men were diagnosed with prostate cancer at 13 years for every man who avoided a prostate cancer death through screening.

In a biological sense, of course, screening does not cause prostate cancer, but in a practical sense, it does. More men must be told they have prostate cancer when screening PSA tests and follow-up biopsies are performed, and hence are at risk for anxiety and the harms related to further interventions. So, who should decide whether the ERSPC trial estimate of prostate cancer mortality reduction, which appears rather small, is worth the higher risk of being diagnosed with prostate cancer? Informed men should share in this decision. How they feel about the trade-off between risks and benefits is important, particularly because they must live with the consequences, good or bad, of the decision about PSA screening. A previous study found that men (n = 1041) who were provided with information about the pros and cons of PSA screening, and who could pass a knowledge test about the key issues, still wanted a PSA test about one-third of the time. Those results will need to be updated when the newest data from the CAP trial and the other trials are incorporated into PSA decision support materials, and tested in broader populations.

Can prostate cancer screening strategies be modified to provide a better balance of benefits and risks from an individual perspective, and greater efficiency from a societal perspective? Efforts to uncouple the risk of overtreatment from the higher risk of diagnosis may help mitigate the harms of PSA screening for men who decide to be screened. Active surveillance programs appear to be helpful, yet the concern about allowing even a few prostate cancers to escape from possible cure during surveillance may be leading to more and more intensive surveillance, including frequent biopsies and now, magnetic resonance imaging scans. How “active” active surveillance needs to be and which men are candidates requires further research. More selective treatment, including avoiding overtreatment of men with low-risk cancer cases but also avoiding undertreatment of men with high-risk cancer cases, combined with offering screening to men aged 55 to 69 years (the core group in the ERSPC trial), even has the potential to make PSA screening cost-effective.

**ARTICLE INFORMATION**

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**REFERENCES**


