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EDITORIAL

# Prostate Cancer Screening: Time to Question How to Optimize the Ratio of Benefits and Harms

Screening for prostate cancer with prostate-specific antigen (PSA) testing has been widespread in the United States since the late 1980s. Remarkably, it was not until 2009 that good evidence was published on the effectiveness of PSA screening, when the results of the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) and the ERSPC (European Randomized Study of Screening for Prostate Cancer) appeared together in the *New England Journal of Medicine* (1, 2). Their findings seemed contradictory: The PLCO found low rates of prostate cancer death that did not differ significantly between groups (1), whereas the ERSPC suggested that screening reduced prostate cancer mortality by 20% (2).

One response to these divergent results is to conclude that we don't really know the answer. An editorial published with the trials described PSA screening as "the controversy that refuses to die" (3). Others have assumed that the truth might be a reduction in mortality of 10% (roughly speaking, the average of the 20% reduction in the ERSPC and the 0% reduction in the PLCO) (4). In 2012, the U.S. Preventive Services Task Force concluded that if the benefit was small in the ERSPC and nonexistent in the PLCO, the true effect was probably very small (5).

Yet, these approaches ignore the elephant in the room: contamination. About 50% of PLCO control patients had PSA testing before enrollment, and of the remainder, close to 90% had PSA measured during the trial (6). The PLCO researchers described the trial as comparing "opportunistic versus systematic screening" rather than screening versus no screening. This has led many commentators, myself included, to see different study questions as the explanation for the conflicting results. Comparing the PLCO and ERSPC is like comparing a trial of 1000 mg of aspirin versus placebo with a trial of 1000 mg versus 900 mg of aspirin.

Tsodikov and colleagues apply a mathematical framework to make this same argument (7). They demonstrate that "the effects of screening on prostate cancer mortality [did not differ] between the ERSPC and PLCO after differences . . . were [mathematically] accounted for." They conclude that "the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer mortality" (7).

I hope that Tsodikov and colleagues have finally put to rest the question of whether PSA screening reduces prostate cancer mortality. I say this not to close debate but to refocus it. Screening with PSA testing does good by saving lives, but it also causes harm in terms of overdiagnosis and overtreatment. Thus, we need to determine how to screen so that the benefits outweigh the harms. We can begin by addressing the following issues.

First, shared decision making should be encouraged. Although there is widespread agreement that men should not undergo PSA testing without consent, how best to involve patients is an open question. Many complex, quantitative decision aids are available, but whether they result in better decisions is uncertain. My colleagues and I have proposed a simpler decision architecture that considers the possibility that PSA testing will identify indolent disease and then assesses risk for overtreatment (8).

Second, we should stop screening men who have little to gain. Men older than 70 years are unlikely to benefit from screening, but they remain the most commonly screened group.

Third, biopsy should be done only in men who screen positive and are at high risk for aggressive disease. The incidence of aggressive disease in most men with elevated PSA levels is moderate. Several reflex markers are available to aid the decision of whether to perform biopsy (9).

Fourth, men who are unlikely to benefit should not be treated aggressively. At least 50% of men found to have cancer after a moderately elevated PSA level have low-grade disease (2) that is unlikely to lead to morbidity or mortality and can be managed conservatively.

Finally, effective treatment should be used. Far too many patients with aggressive localized prostate cancer are treated by inexperienced surgeons, with inadequate doses of radiotherapy, or with ineffective primary androgen deprivation therapy.

The effects of these commonsense strategies are not trivial. A back-of-the-envelope calculation estimates that stopping screening at age 70 years and adopting reflex biomarkers before biopsy could reduce overdiagnosis by at least 70%. A modeling study indicated that the number of quality-adjusted life-years gained by screening would increase 4-fold if U.S. clinicians implemented all 5 of the aforementioned practices (10).

In summary, PSA-based screening does reduce prostate cancer mortality, but whether this benefit outweighs the harms of overdiagnosis and overtreatment depends on how screening is implemented. Unfortunately, the way screening has been implemented in the United States leaves much to be desired. The controversy about PSA-based screening should no longer be whether it can do good but whether we can change our behavior so that it does more good than harm.

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