Prostate cancer screening using prostate-specific antigen (PSA) testing has been a contentious subject. With the advent of results from several completed randomized controlled trials (RCTs), concern for the efficacy of PSA screening and subsequent overtreatment of prostate cancer has arisen. Croswell et al present a detailed review of these studies and build their arguments around five RCTs. They argue that although PSA screening has increased the detection of early-stage prostate cancer, the decline in incidence of late-stage prostate cancer has been less impressive. They also note that PSA screening has not resulted in a reduction in deaths due to prostate cancer. In addition, they highlight the potential harms associated with PSA screening, including aggressive overtreatment and associated toxicities. However, there are a number of issues that we believe are worthy of additional comment.

As Croswell et al point out, the available RCTs have significant potential biases and limitations. For example, the Quebec trial showed a mortality benefit for PSA screening, but due to a high cross-over rate in the randomized arms and subsequent as-treated analysis, Croswell et al considered the randomized Quebec trial equivalent to an observational study. Interestingly, the Prostate, Lung, Colorectal, and Ovarian (PLCO) study, which showed a mortality detriment for PSA screening, also had a high cross-over rate of > 50% in the control group. However, the authors use the PLCO trial as one of the primary studies supporting the argument against PSA screening, despite its limitations. In contrast, the largest RCT, the European Randomized Study of Screening for Prostate Cancer (ERSPC), did show a significant relative risk reduction in mortality of 20% with PSA screening in the prespecified “core” group. There was a contamination level of only 20%, and after adjusting for noncompliance and contamination, the adjusted relative reduction in prostate cancer mortality was even larger. Although the number needed to screen to prevent one prostate cancer death was large at 1410, this is similar to the numbers involved in screening for breast cancer and colorectal cancer.[1] Adding to the evidence for PSA screening, the randomized Gteburg trial also showed a significant reduction in the prostate cancer death rate of 0.56. The trial had a higher rate of biopsy with positive screening results than that seen in the PLCO trial. There was also a lower rate of contamination and a lower rate of PSA testing prior to the start of the study than were seen in the PLCO trial.[2] In addition, the Gteburg trial had much longer follow-up than the PLCO trial. Therefore, of the recent randomized trials, the largest and better controlled RCTs appear to argue for PSA screening rather than against it.

Croswell et al also suggest that more invasive or aggressive treatments result in increased mortality risk. However, the authors fail to mention evidence from multiple phase III randomized trials, including Radiation Therapy Oncology Group (RTOG) trials 8531, 9202, 9408, and European Organisation for Research and Treatment of Cancer (EORTC) trial 22961, that show overall survival advantages for patients who receive aggressive treatment for clinically localized prostate cancer. More recently, the Scandinavian Prostatic Cancer Group (SPCG)-7 RCT found that patients receiving androgen suppression and external beam radiotherapy (EBRT) for locally advanced prostate cancer had improved 10-year overall survival of 70% compared with 61% with androgen suppression alone.[3] Thus, the fact that aggressive treatment of clinically localized disease can result in a survival benefit should give pause to those arguing against screening.

Another point of contention is the suggestion that treatment causes significant morbidity. Sanda et al highlight toxicity rates, including rates for erectile dysfunction (ED), following surgery or radiotherapy for prostate cancer.[4] However, a significant proportion (~ 20% to 30%) of patients in that study had baseline ED. Of those patients receiving EBRT or brachytherapy, the incidence of sexual dysfunction did not differ much from baseline after 2 years. As for long-term outcomes,
sexual dysfunction is multifactorial, and over time sexual function can decline.[5] The Massachusetts Male Aging study demonstrated that the prevalence of ED increases to almost 70% in men at age 70 years.[6] Therefore, the magnitude of morbidity that can be directly attributed to treatment can be difficult to assess.

The authors allude to recommendations by various organizations, including the American Cancer Society, that emphasize the need for informed consent and discussion of the uncertainties, risks, and benefits of PSA screening and of potential treatment modalities. However, the recommendation for premature discussion of the risks and benefits of potential treatment modalities is unlike the recommendations associated with informed consent for most other screening procedures. For example, informed consent for colorectal cancer screening involves discussion of the accuracy and risks of the different screening tests but not of the risks and benefits of potential treatment modalities that may be involved if colorectal cancer is indeed found.[7] Why then should informed consent for PSA screening involve discussion of the risks and benefits of potential treatment modalities, particularly when the majority of men will have a normal test result? In addition, such complicated informed consent requirements may lead to unwillingness by physicians to spend adequate time explaining consent to the uninsured and thus may worsen health disparity. Instead, we argue for a more appropriate discussion timeline whereby only men with abnormal PSA test results would be asked to give their consent to the risks associated with biopsy. If the biopsy is positive, then the informed consent discussion would be expanded to include the risks and benefits associated with various treatment modalities.

Overall, the role of PSA screening remains controversial. However, the best evidence from the largest and best controlled RCT appears to argue for PSA screening, since it shows that the test can lead to a mortality benefit. Many of the other RCTs that argue against PSA screening have significant flaws and limitations. With further follow-up and careful consideration of the merits and limitations of the available and ongoing RCTs (eg, the ProtecT trial), the benefits and harms of PSA screening may be better elucidated. Until then, recommendations to stop all PSA screening efforts may need to be tempered.

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