Prostate-Specific Antigen Screening: Time to Change the Dominant Forces on the Pendulum

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Whether prostate-specific antigen (PSA) screening prevents men from dying of prostate cancer has been the subject of debate for decades. Rather than resolve the controversy, two major randomized trials of PSA screening, with discrepant results, only further polarized the discussion. We recently showed that PSA testing in the control arm of the major US study, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, was substantially higher than previously recognized (approximately 90%), making the trial results uninterpretable. Here, we contextualize the debate about PSA screening and highlight the broad implications of our finding for prostate cancer care. Namely, we argue that the remaining singular randomized evidence shows that PSA testing does save lives and that screening should be an evidence-based recommendation.

PSA testing was widely adopted in the United States in the early 1990s on the basis of its ability to detect organ-confined prostate cancers. Although population-based screening with PSA clearly resulted in more prostate cancer diagnoses, the morbidity associated with the treatment of indolent disease and the associated costs were major concerns. Randomized controlled trials were therefore initiated in Europe and the United States to address the efficacy of PSA screening.

The European study found that PSA screening reduced prostate cancer–specific mortality, whereas the US study, the PLCO Cancer Screening Trial, found no difference in prostate cancer death between the intervention and control arms.¹⁻³ Based largely on the outcomes of the PLCO trial, several major US organizations have advised against screening, leading to declines in PSA screening rates nationally and a shift toward fewer prostate cancer diagnoses.⁴⁻⁶

The major criticism of the PLCO trial is the degree of PSA screening in the control arm, which was stratified by screening that occurred before (baseline contamination) and during the trial. Screening in the control arm was particularly problematic because of the rapid uptake of PSA testing that occurred nationally between the trial design phase and the initiation of recruitment (Appendix Fig A1, online only).^{6a} Moreover, the demographics of men who tend to have screening overlapped with those of men who entered the trial; namely, men enrolled in the trial were more likely to be married, have higher education levels, and (on the basis of recruitment strategies) have a preexisting relationship with a health care provider.⁷⁻¹⁰

The study designers were able to limit baseline contamination to 10% of the cohort by excluding men who had undergone two or more PSA tests within 3 years of study entry from the trial starting in 1995.³ To address the issue of PSA testing that occurred in the control arm during the trial, a survey termed the Health Status Questionnaire was sent to a random subset of subjects on the basis of baseline contamination status and trial arm.¹¹ When reporting the results of this survey, the authors of the initial trial stated that “In the control group, the rate of PSA testing was 40% in the first year and increased to 52% in the sixth year.”^{3(p1313)} A subsequent report in *Clinical Trials* in 2010 also discussed the results of the Health Status Questionnaire; however, this study was limited by low visibility relative to the initial trial report and a complex presentation of the relevant data in the body of the paper.¹¹ As such, although screening in the control arm during the trial has been widely viewed as the major limitation of PLCO, there are widespread discrepancies in the literature as to the actual rate of PSA testing. Not surprisingly, those who cite a lower testing rate in the control arm generally recommend against PSA screening,^{5,6,12} whereas those who quote a higher testing rate tend to be more favorable toward screening.^{4,13-15}

By analyzing the results of the survey, we recently demonstrated that the testing rate in the control arm of the PLCO trial is higher than any previous analysis has indicated.¹⁶ The contamination rate reported in the original 2009 trial report was limited to men reporting testing within the past year and did not include many of the men reporting having had a “PSA blood test for prostate cancer”^{16a} on the basis of a follow-up question regarding the reason testing was performed. The survey as it relates to PSA is shown in Appendix Fig A2. By analyzing the survey used to estimate PSA testing rates in the control arm of the PLCO trial, we found that the proportion of men who had PSA screening was much higher than previously recognized, with approximately 90% of men in the control arm reporting having undergone testing.¹⁶

We also found that when men in both the control and intervention arms were surveyed with the Health Status Questionnaire, men in the control arm reported having had more testing during the seventh through the thirteenth year of the trial than men in the intervention arm.¹⁶ Thus, while there is increasing evidence that the benefits of intermittent testing are equivalent to those of annual testing, as prior literature on self-reported PSA screening suggests underreporting is common,¹⁷ even the limited conclusion that the

intervention arm had more PSA testing than the control arm is uncertain. Based on these data, it is clear that comparing prostate cancer mortality between study arms is not a meaningful way to assess the value of PSA-based screening.

The only randomized evidence regarding PSA testing, therefore, comes from the European study, which found that randomization to PSA screening resulted in a 21% relative reduction in prostate cancer mortality.¹ In the European study there was likely less contamination; however, the frequency of PSA testing in the control arm is less clearly defined.¹⁸⁻²⁰ This study found that 781 men needed to be invited to screening to prevent one cancer death.¹ These numbers compare favorably to recent recommendations supporting breast cancer screening, which requires screening 1,339 women age 50 to 59 years to prevent one death.²¹

In the absence of additional data, the evidence supports that PSA screening prevents prostate cancer deaths. This mortality benefit is likely reflected in US epidemiologic data, which have shown dramatic and sustained decreases in prostate cancer mortality since the introduction of PSA screening.²² In addition, observational data demonstrate that the advent of PSA screening also coincides with fewer metastases and therefore likely reduces the morbidity and costs associated with metastatic and locally advanced cancers.

The relevant question then becomes whether the harms associated with the treatment of indolent disease justify these benefits. The European study found that 27 additional prostate cancers needed to be detected to prevent one death at 13 years. Although the number needed to diagnose to prevent a death from prostate cancer is projected to decrease with longer follow-up, the morbidity associated with cancer overdiagnosis is significant.⁴ Although further study is needed, there are reasons to be optimistic that this morbidity will be attenuated. The use of active surveillance, wherein men with low-risk prostate cancer are surveyed for progression of disease rather than pursuing immediate definitive therapy, is perhaps the most impactful and readily available approach to limiting overtreatment. Promisingly, active surveillance use has increased in recent years in the United States and is increasingly being incorporated into prostate cancer treatment guidelines.²³⁻²⁵ In addition, the incorporation of smarter screening strategies, supplemental biomarkers, and newer imaging techniques may also further limit this morbidity.

The rapid uptake of PSA screening followed by its equally rapid decline in the United States has been analogized to a pendulum swinging back and forth.⁴ Given the previously unrecognized degree of contamination in the PLCO trial control arm, the results of this trial should no longer guide policy. It therefore seems apparent that in light of the remaining evidence, the reversion back to the pre-PSA era in recent years will translate into more prostate cancer deaths in the United States.

Although additional work is needed to define the optimal frequency and age at which to begin screening, several organizations have developed approaches that may limit overdiagnosis.^{13,26,27} Shared decision making is no doubt important; however, a certain threshold of health literacy is needed to understand the benefits and limitations of PSA screening (including the concepts of overdiagnosis and false-positive and false-negative test results), and it may be impractical for primary care physicians to have detailed discussions about PSA when multiple other issues need to be addressed. In addition, the widespread misperception that PSA screening is proven to be ineffective likely can only be reversed by clear guidance

regarding whether the benefits of screening outweigh the risks. We therefore argue that all men, barring those with a limited life expectancy, should undergo at least baseline PSA testing in their 40s or early 50s, with subsequent screening tailored to individualized risk according to schedules put forth in newer screening guidelines.^{13,26,27} Rather than debating the utility of screening, future efforts should aim to further optimize the balance between the harms of overdiagnosis and a clear survival benefit to PSA screening.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Fig A1. Depiction of the increase in prostate-specific antigen (PSA) testing that occurred between the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial initial design and recruitment phases (modified from a depiction of men born from 1920 to 1924 in Mariotto AB et al: Cancer 109:1877-1886, 2007).

Men's Health Status Questionnaire (HSM)	
13a. Have you ever had a PSA blood test for prostate cancer?	1 ☒ Yes 2 ☐ No (GO TO ITEM 14) 3 ☐ Don't Know (GO TO ITEM 14)
13b. When did you have your most recent PSA blood test for prostate cancer?	1 ☒ Within the past year 2 ☐ 1 to 2 years ago 3 ☐ 2 to 3 years ago 4 ☐ More than 3 years ago 5 ☐ Don't Know
13c. What was the main reason you had this PSA blood test for prostate cancer?	1 ☐ Because of a specific prostate problem 2 ☐ Follow-up to a previous health problem 3 ☒ Part of a routine physical exam

Fig A2. Health Status Questionnaire as it relates to prostate-specific antigen (PSA) screening. Blue shading indicates responses that were counted as testing in the 2009 trial report. All other responses were not counted as testing. (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Men's Health Status Questionnaire. 2005. https://biometry.nci.nih.gov/app_media/cdas-bioshare/documents/studies/plco/forms/HSM.pdf).