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Insights from the PLCO trial about prostate cancer screening

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Abstract

The potential for prostate-specific antigen (PSA) testing to reduce prostate cancer mortality has been uncertain despite its common use in the United States starting in the early 1990s. Updated results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial after a median of 15 years of follow-up continue to show no reduction in prostate cancer mortality due to annual PSA testing for 4–6 years relative to usual care, which included less frequent PSA testing. In contrast with trials in Europe, which showed that certain PSA testing protocols can reduce prostate cancer mortality relative to not screening, the PLCO trial provides durable evidence of no benefit to screening more frequently than historical practice. Whether a limited population-based screening program can achieve an acceptable balance of benefit and harm remains to be determined.

Keywords

early detection; prostate-specific antigen; prostatic neoplasms; randomized controlled trials; screening

Prostate cancer mortality rates have fallen by approximately 2.5% each year since the early 1990s when prostate-specific antigen (PSA) screening entered routine practice in the United States.[1] However, the role PSA screening has played in reducing mortality remains uncertain. Changes in patient management—including the increasing use of surgery, higher doses utilized in intensity-modulated radiation therapy, and advances in the treatment of metastatic disease—have all contributed to lowering mortality rates during this period.[2, 3] Even if treatments had not changed, the potential for biases in observational analyses of epidemiological trends cannot be avoided. Randomized trials are essential to providing insights as to whether PSA screening can reduce prostate cancer mortality.

Many patients and clinicians evaluate the efficacy of PSA testing through a simple lens: does it work or not? The appropriate interpretation of available data is more nuanced. The reason for this is simple: PSA screening can be implemented in many different ways. A PSA test

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quantifies the serum concentration of PSA from a blood draw at a single point in time. A high concentration (e.g., >50 ng/mL) is strongly indicative of prostate cancer; a low number (e.g. <2 ng/mL) suggests the absence of clinically significant disease.[4] Beyond choosing a trigger for prostate biopsy based on the continuum of PSA concentrations given one or more tests, testing can be conducted with different starting and stopping ages and may be more or less frequent. Furthermore, biopsy thresholds and testing frequencies may depend upon patient age or life expectancy. The implementation of a PSA screening program can therefore involve an infinite number of permutations.

Even if we confirm that one approach to PSA testing can lower prostate cancer mortality, an equally important question is whether we have identified a sufficiently effective approach. Further, any benefit must be weighed against the known harms of screening, including the risks of unnecessary diagnosis and treatment of indolent disease, and possible tradeoffs placed in the context of competing demands for scarce health care resources.

In this issue of *Cancer*, Pinsky et al. report updated results from the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.[5] Starting in 1993, the PLCO trial randomized 38,340 men to 4–6 annual PSA tests and 4 rectal exams and 38,343 men to usual care, which involved PSA testing for most men. All men were aged 55–74 years at randomization. PSA concentrations above 4 ng/mL were considered suspicious, but decisions about biopsy or further work-up were left up to the physician and patient. After a median of 15 years of follow-up, the investigators report 255 and 244 prostate cancer deaths in the intervention and control arms, respectively, for a non-significant 4% increase (95% confidence interval 13% decrease to 24% increase) in the risk of prostate cancer death in the intervention arm relative to the control arm.[5] These results are similar to earlier reports.[6, 7]

In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC) involved 7 centers in 7 Western European and Scandinavian countries, each with slightly different protocols. Starting in 1991, the ERSPC randomized 72,891 men to quadrennial (biennial in Sweden) PSA tests and 89,352 men to usual care, which involved minimal PSA testing for most men.[8] The primary analysis was based on a core group of men aged 55–69 years at randomization. In most centers and trial rounds, PSA concentrations above 3 ng/mL triggered referral to biopsy, though other centers and rounds used higher or lower PSA thresholds with or without rectal exams or other ancillary tests. After a median of 13 years of follow-up, the investigators reported 265 and 415 prostate cancer deaths in the intervention and control arms, respectively, for a significant 21% reduction (95% confidence interval 9% to 31% reduction) in the risk of prostate cancer death in the intervention arm relative to the control arm.[9] These results are also similar to earlier reports.[10, 11]

While these trial results appear to conflict, the disagreement is resolved when we focus on the questions being addressed. Given the modest amount of screening in the ERSPC control arm, this trial demonstrates that at least one screening strategy can reduce prostate cancer mortality relative to not (much) screening. This question is not addressed by the PLCO trial because of the high rates of screening in both arms. Other trials, most notably individual ERSPC centers with more participants, wider age ranges, and/or longer follow-up, have also weighed in on this question. Individual reports from Sweden (ages 50–64 years), the

Netherlands (ages 55–74 years), and Finland (ages 55, 59, 63, and 67 years) showed a significant 40%,[12] a significant 20%,[13] and a non-significant 15%[14] reduction in prostate cancer mortality due to screening, respectively. A detailed accounting of differences in protocols, disease prevalence rates, and background clinical practice may help explain the variation in findings.

The next question is: are there better ways to screen? The high rates of screening in both the intervention and control arms place the PLCO trial in a unique position to address this question. Based on responses to regular questionnaires given to trial participants, Pinsky et al. estimated that an average of 84% of intervention arm participants versus 40% of control arm participants were screened each year during the 6-year screening phase of the trial, and about 45% of participants from either arm were screened each year thereafter. As a consequence, the PLCO results show that the increased frequency of screening in the intervention arm during the screening phase did not reduce mortality relative to the screening conducted in the control arm. Thus there is at least one way of screening that is not better than another way. Pinsky et al. summarize this result as showing “no benefit of organized over opportunistic screening”[5] although certain ways of organized screening may be superior to certain ways of opportunistic screening.[15]

One possibility is that screening frequency may have reached a saturation point in the PLCO trial. Even under relatively frequent (e.g., biennial) screening, some prostate cancers will progress too quickly to be caught. The additional number of cancers that can be netted under still more frequent (e.g., annual) screening is likely to be small, and only a fraction of these might have lowered risk of prostate cancer death due to early detection. One would not expect ever more frequent screening to consistently produce commensurate mortality reductions, but one can expect such a practice to produce more harm.

Numerous studies have investigated “smarter” ways of screening that attempt to balance mortality benefit against the number of tests,[16] the risks of over-diagnosis and over-treatment,[17] or costs.[18] There is a general consensus that screening men with a life expectancy <10 years is unlikely to provide benefit. There also appears to be agreement that limiting screening ages (e.g., 55–69 years), testing less frequently (e.g., biennial or quadrennial), or adopting age-adjusted thresholds is necessary for a population-based PSA screening program to be cost-effective.[18, 19] Others have argued for individualized screening strategies given a baseline PSA test result around age 50 years, increasing PSA screening specificity by using additional markers, early cessation for men with a low PSA, and/or strategies that screen more intensively depending on race or family history. The comparative effectiveness of these approaches has not yet been established.

It is also important to recognize that better ways of screening are intimately linked to the way that initial treatment and follow-up care are provided. For example, aggressive screening detects many slow-growing cancers that do not require treatment. Recently published results from the ProtecT[20] study show similarly low prostate cancer mortality rates in men with screen-detected localized disease randomized to definitive treatment or active monitoring after a median of 10 years of follow-up. However, the risk of metastasis was higher in men randomized to active monitoring, underscoring the need for caution with

this approach. Longer follow-up is needed, but this trial shows that evaluation of screening outcomes cannot be separated from associated treatment decisions.

Questions surrounding the potential value of PSA screening are complicated by the many ways of implementing a screening program. Insights from high-quality randomized studies such as the PLCO trial contribute foundational evidence about the relative efficacy of particular screening protocols. While trials in Europe have estimated that certain screening protocols can reduce prostate cancer mortality relative to not screening, there is gold standard evidence in the US setting that more frequent screening is not better than historical practice. Whether a limited screening and treatment approach can achieve an acceptable balance of benefit and harm remains an open question.

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