Insights From the PLCO Trial About Prostate Cancer Screening

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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 that PSA screening has played in reducing mortality remains uncertain. Changes in patient management, including the increasing use of surgery, higher doses 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 for providing insights into 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 quantifies the serum concentration of PSA from a blood draw at a single point in time. A high concentration (eg, >50 ng/mL) is strongly indicative of prostate cancer; a low number (eg, <2 ng/mL) suggests the absence of clinically significant disease.4 Beyond the choice of a trigger for prostate biopsy based on the continuum of PSA concentrations from 1 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 on a patient’s age or life expectancy. The implementation of a PSA screening program can, therefore, involve an infinite number of permutations.

Even if we confirm that 1 approach to PSA testing can lower prostate cancer mortality, an equally important question is whether we have identified a sufficiently effective approach. Furthermore, 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 set in the context of competing demands for scarce health care resources.

In this issue of Cancer, Pinsky et al5 report updated results from the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Starting in 1993, the PLCO trial randomized 38,340 men to 4 to 6 annual PSA tests and 4 rectal examinations and 38,343 men to usual care, which involved PSA testing for most men. All men were aged 55 to 74 years at randomization. PSA concentrations higher than 4 ng/mL were considered suspicious, but decisions about biopsying or further workup were left to the physician and the 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 nonsignificant 4% increase (95% confidence interval, 13% decrease to 24% increase) in the risk of prostate cancer death in the intervention arm versus the control arm. These results are similar to those of 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 PSA tests (biennial in Sweden) 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 to 69 years at randomization. In most centers and trial rounds, PSA concentrations higher than 3 ng/mL were considered suspicious, but decisions about biopsying or further workup were left to the physician and the patient. After a median of 15 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%-31%) in the risk of prostate cancer death in the intervention arm versus the control arm.9 These results are also similar to those of earlier reports.10,11

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See referenced original article on pages 000-000, this issue.

DOI: 10.1002/cncr.30472, Received: October 31, 2016; Accepted: November 2, 2016, Published online Month 00, 2016 in Wiley Online Library (wileyonlinelibrary.com)
Although these trial results appear to conflict, the disagreement is resolved when we focus on the questions being addressed. Because of the modest amount of screening in the ERSPC control arm, this trial demonstrates that at least 1 screening strategy can reduce prostate cancer mortality in comparison with 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 (age range, 50-64 years), the Netherlands (age range, 55-74 years), and Finland (ages 55, 59, 63, and 67 years) showed a significant 44% reduction, a significant 20% reduction, respectively, in prostate cancer mortality due to screening. A detailed accounting of differences in protocols, disease prevalence rates, and background clinical practice may help to explain the variation in findings.

The next question is whether there are better ways to screen. The high rates of screening in both the intervention arm and the control arm place the PLCO trial in a unique position to address this question. On the basis of responses to regular questionnaires given to trial participants, Pinsky et al estimate that on average 84% of the participants from either arm were screened each year during the 6-year screening phase of the trial, and approximately 45% of the 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 in comparison with the screening conducted in the control arm. Thus, there is at least 1 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,” although certain ways of organized screening may be superior to certain ways of opportunistic screening.

One possibility is that the screening frequency may have reached a saturation point in the PLCO trial. Even with relatively frequent screening (eg, biennial screening), some prostate cancers will progress too quickly to be caught. The additional number of cancers that can be netted with still more frequent screening (eg, annual screening) is likely to be small, and only a fraction of these might have a lower 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 the mortality benefit against the number of tests, the risks of overdagnosis and overtreatment, or costs. There is a general consensus that screening men with a life expectancy of less than 10 years is unlikely to provide a benefit. There also appears to be agreement that limiting screening ages (eg, 55-69 years), testing less frequently (eg, biennially or quadrennially), or adopting age-adjusted thresholds is necessary for a population-based PSA screening program to be cost-effective. Others have argued for individualized screening strategies based on a baseline PSA test result around the age of 50 years, increased PSA screening specificity through the use of additional markers, early cessation for men with low PSA levels, and/or strategies that screen more intensively according to 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 ways in which the 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 Prostate Testing for Cancer and Treatment (Protect) study showed similarly low prostate cancer mortality rates among men with screen-detected localized disease who had been randomized to definitive treatment or active monitoring after a median of 10 years of follow-up. However, the risk of metastasis was higher for men randomized to active monitoring, underscoring the need for caution with this approach. Longer follow-up is needed, but this trial shows that the 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. Although trials in Europe have estimated that certain screening protocols can reduce prostate cancer mortality in comparison with no screening, there is gold-standard evidence in the US setting showing 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.
FUNDING SUPPORT

This work was supported by award U01 CA199338 (to Roman Gulati) from the National Cancer Institute. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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