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What do the screening trials *really* tell us and where do we go from here?

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Synopsis

Publication of apparently conflicting results from two large trials of prostate cancer screening has intensified the debate about PSA testing and led to a recommendation against screening from the US Preventive Services Task Force. In this article we review the trials and discuss the limitations of their empirical results in informing public health policy. In particular, we explain why harm-benefit tradeoffs based on empirical results may not accurately reflect the tradeoffs that might be expected under long-term population screening. This article should be useful to clinicians attempting to reconcile the studies and understand their implications regarding the value of PSA screening in the population setting.

Keywords

Prostate cancer; mass screening; clinical trials; Prostate-Specific Antigen; simulation modeling; public health policy

Introduction

The prostate screening odyssey has captivated researchers, policymakers and clinicians since the late 1980s when the PSA test was approved by the FDA for monitoring prostate cancer progression. The test was rapidly adopted for screening in the US (1) even as clinical trials to evaluate its efficacy in early detection were just beginning in the US and Europe.

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While the US and European trials were ongoing, routine PSA screening became the standard of care in the U.S., dramatically changing the profile of prostate cancer and prompting concerns about overdetection and overtreatment of the disease. As prostate cancer death rates declined after the inception of screening, it became clear that policies for prostate screening would have to carefully navigate the harm-benefit tradeoffs of PSA testing. The results of the two large, randomized screening trials were eagerly awaited for what was hoped would be the final word regarding the lives saved and the price that would have to be paid for any screening benefit.

Five years after the publication of the primary trial results, there remains a vigorous debate about whether and how best to screen for prostate cancer. The randomized trial results were the basis for revised prostate screening recommendations from all of the major policy panels including the US Preventive Services Task Force (USPSTF) (2), the American Cancer Society (3) and the American Urology Association (4). While the USPSTF has recommended against PSA screening at all ages, the other panels have generally recommended shared decision making except for men with a limited life expectancy.

In this article we re-examine the trials and their findings in light of what we need to know to develop policies for population screening. We first review the empirical results from the trials and ask what they tell us about (a) screening benefit, (b) screening harms, particularly overdiagnosis, and (c) the harm-benefit tradeoffs of screening. We then consider statistical and modeling analyses that go beyond the trial results and consider how these results may modify perceptions of the aforementioned outcomes. All screening outcomes depend on the screening strategy employedl, including the screening ages, intervals and cutoffs for biopsy referral. Varying these parameters can dramatically alter the balance of harm and benefit; unfortunately, the two randomized trials are inherently limited in their ability to compare alternative screening strategies. We conclude that screening trials in general, and the PLCO and ERSPC studies in particular, provide information that is critical for screening policy development but cannot provide all information needed for developing sound population screening policies.

The Large Randomized Prostate Cancer Screening Trials

The two large screening trials, the US-based Prostate, Lung, Colon and Ovarian (PLCO) cancer screening trial (5, 6), and the European Randomized Study of Screening for Prostate Cancer (ERSPC) (7, 8) have been previously described in detail.

Several measures of screening benefit and harm are presented in the trial reports. We briefly review these here as the manner by which harm and benefit are measured will significantly influence the perception of the value of screening. Several definitions are important to understand screening outcomes. The *relative screening benefit* is expressed by the (prostate cancer) mortality rate ratio which is the ratio of the risk of prostate cancer death in the screened relative to the control group over the follow-up period. The *absolute screening benefit* is expressed by the difference between the cumulative incidence of prostate cancer deaths in the two groups and may be thought of as an estimate of the lives saved by screening over the follow- up period. Both relative and absolute benefits are time-sensitive and generally increase with follow-up time (9-11). *Overdiagnosis* is the detection by

screening of cases that, in the absence of screening, would not have caused morbidity or mortality in the patient's lifetime. Overdiagnosis may be expressed as an absolute number of overdiagnosed cases, as a fraction of the number screened, or as a fraction of screen-detected cases. Depending on how overdiagnosis is estimated, the results may also be highly time-sensitive. Finally a measure of *harm-benefit tradeoff* that has become fairly standard is the (additional) number needed to detect (NND) to prevent one prostate cancer death, defined as the estimated overdiagnoses divided by the estimated lives saved by screening. The NND has been referred to as the additional number needed to treat to prevent one prostate cancer death but this is not, strictly speaking, accurate, because not all newly diagnosed prostate cancers receive immediate treatment. The concept of the NND, a harm-benefit tradeoff measure pertaining specifically to screening that carries the possibility of overdiagnosis, should be distinguished from the similarly-named NNT or number needed to treat, which is a concept of benefit most commonly used in analysis of treatment trials.

The PLCO Screening Trial

The PLCO trial randomized 76,693 men to screening or a control group managed according to community standards. Screening arm participants were given annual PSA tests for 6 years with concomitant digital rectal exams (DREs) for the first four. Diagnostic followup for positive test results was left to participants who were referred to their doctors for PSA above 4.0 ng/ml or a suspicious finding on DRE. Approximately 40% of participants referred to biopsy for an abnormal screening test underwent prostate biopsy within one year (12).

By the time the PLCO trial began randomizing participants, PSA screening was widespread (1). This had a critical impact on the trial and its outcomes. Briefly, 45% of participants had had at least one PSA prior to enrollment (6); moreover, over the course of the trial, approximately half of the control arm participants were screened every year, with 74% of the control group receiving at least one screening test during their participation in the trial (13). By contrast, 95% of the screened group was screened at least once during the course of the trial. The average number of screening tests was 5 in the screened group and 2.7 in the control group (13). Thus, screening in the control group was approximately half as intensive as that in the screened group

The empirical results from the PLCO after 11 and 13 years of followup clearly show no relative or absolute benefit of PSA screening (5, 6). Not only was there no statistically significant difference in prostate cancer mortality between screened and control groups after 11 and 13 years of follow-up but the cumulative incidence of prostate cancer deaths was slightly (but nonsignificantly) higher in the screened group than in the control group (mortality rate ratio 1.09, 95% confidence interval (0.87,13.6)).

In its recent recommendation against routine PSA screening, the US Preventive Services Task Force concluded that the benefit of PSA screening ranged from zero to one life saved per 1,000 men screened at 8-10 years, with the zero directly based on the results of the PLCO trial (2). However, it is clear that the trial did not compare screening with no screening; the trial investigators themselves note in their most recent report that the results pertain to annual versus ‘opportunistic’ screening in the US (6). By simulating a replication of the trial many times, we have shown that even if screening were to confer a clinically

significant reduction in prostate cancer mortality, it is quite unlikely (only 10-20% chance) that the trial would have produced a statistically significant benefit (14). In addition, we showed that the finding of zero lives saved (or, more generally fewer deaths in the control group than in the screened group) could reasonably have occurred in practice given that the numbers of deaths in both groups were considerably lower than expected. Thus, deeper analysis of the PLCO results indicates that the trial cannot be interpreted as a negative study regarding the benefit of PSA screening despite the empirical results concerning disease-specific deaths in the control and intervention arms. Similarly, meta-analyses drawing on the PLCO results that simply use the empirical trial findings as a data point comparable to the other trial results are not interpretable.

The PLCO trial does provide a great deal of information regarding the comparison of (approximately) annual versus opportunistic (approximately half as intensive) screening in the US. The trial also provides valuable information regarding the false positive properties of PSA testing as conducted in the trial; among men with a positive test who underwent biopsy, 35-45% had prostate cancer detected (15). Finally, the trial provides important data about the likelihood of compliance with a referral for prostate biopsy in the US population; only about 40% of participants underwent biopsy within one year after a positive test (12). However, the empirical results *do not* inform about the benefits of screening versus no screening, the likelihood of overdiagnosis, or the NND.

The ERSPC Screening Trial

The ERSPC was designed as a single trial to evaluate PSA efficacy in European countries that satisfied pilot study requirements and incorporated 60 percent of participants in a trial that had already been started in one center (Göteborg, Sweden) (16). The trial randomized 182,160 men with the largest number randomized in Finland and the smallest number in Spain. An age range of 55-69 was designated as the core age group and enrolled across all centers with some centers also including men age 70-74. Testing took place every four years in most centers, but every two years in Sweden. The criteria for biopsy referral varied across centers. Most centers used a PSA cutoff of 3 ng/ml while Finland used a cutoff of 4 ng/ml. In contrast with the PLCO trial, there was generally excellent compliance with screening and biopsy referral: on average 86% of participants complied with biopsy recommendations (8). An analysis of contamination across 5 centers of the ERSPC (17) reveals quite variable frequencies of opportunistic screening with annual rates of less than 10% in Finland, the Netherlands and Spain and higher rates (20-30% per year) in Italy and France.

The primary outcome of the ERSPC differs from the PLCO: At 11 years of follow-up there was a statistically significant 21% relative reduction in the prostate cancer death rate in the intervention group (8). Since 5 men per thousand in the control group died of prostate cancer during the follow-up period, this relative reduction amounted to one life saved per 1,000 men screened. After accounting for non-compliance and contamination, the relative mortality reduction increased to 31% (18). Overdiagnosis was estimated as the excess cases of prostate cancer in the intervention relative to the control group (37 per 1,000 men screened). The corresponding estimate of the NND provided by study investigators was 37 at 11 years followup, given by the excess cases in the intervention group divided by the lives

saved. Table 1 summarizes the results of the trial at 11 years of follow-up and also the results of the Swedish (19), Finnish (20) and Dutch (21) trials, which have been reported in separate publications.

The ERSPC results have been interpreted as indicating that screening provides at best a very modest benefit at considerable cost in terms of overdiagnosis. Indeed, in the conclusion by US Preventive Services Task Force (2) that the absolute benefit of PSA screening ranged from zero to one life saved per 1,000 men screened, the upper limit was directly based on the results of the ERSPC trial after 9 years.

Both the estimate of lives saved (1 per 1,000 men screened) and the NND (37 excess cases per life saved) have been questioned in further analyses (22-25). First, when considered against a background mortality that is more reflective of the lifetime risk of prostate cancer death, the number of lives saved given annual screening of men aged 50-69 increases considerably, to 9 per 1,000 men screened in Europe (24) and 5-6 per 1,000 men screened in the US (25). Some of the differences between the US and European estimates of lives saved can likely be attributed to differences in background mortality, screening protocols (the European estimate used a PSA cutoff for biopsy referral of 3 ng/ml and the US estimate was based on a cutoff of 4 ng/ml) and biopsy compliance rates. It is noteworthy that, when considering these higher estimates of lives saved against the number of overdiagnosed cases in each setting, the NND is dramatically reduced to approximately 5 in both the European and the US settings (24, 25). Thus, deeper analysis of the ERSPC trial reveals a more favorable picture of both benefit and the harm-benefit tradeoffs of PSA screening than has generally been inferred from the empirical results.

Where do we go from here?

There is no question that the two randomized screening trials provide us with a wealth of information about PSA screening. However, they also present us with a fundamental question: do empirical findings from randomized trials adequately reflect the true harms and benefits of screening tests? Unfortunately, as illustrated in our review, these studies cannot answer this question and, focusing solely on empirical results, even from these very large high-quality trials, can lead to serious misperceptions regarding the value of prostate cancer screening.

With respect to benefit, results from a modeling analysis of the PLCO trial reveals that the empirical finding of no difference in prostate cancer mortality in this study could have easily occurred even if prostate cancer screening had a high degree of efficacy. The empirical result from the ERSPC trial regarding relative benefit is clinically significant (20-30% reduction in the risk of prostate cancer death) but the empirical findings concerning absolute benefit (lives saved) and the NND (harm to benefit ratio) appear to have eclipsed this finding to yield a general perception of modest benefit outweighed by harm. Statistical and modeling studies targeted at quantifying how these outcomes will likely change over longer followup (as would be expected with a policy of screening in clinical practice) (11, 22-25) reveal that the empirical results do not accurately reflect the lives saved nor the NND that would be expected under population screening. Even the reported mortality rate ratio may well underestimate the percent reduction over the longer term (9); this appears to be the case

as longer-term data are released from the ERSPC, showing greater relative mortality reductions with longer followup and an NND of 37 after 11 years compared to an NND of 48 after 9 years (8).

In conclusion, screening trial results are traditionally regarded as gold standard evidence but we must go beyond the empirical findings of the PLCO and the ERSPC to understand what these trials are really telling us. As deeper scrutiny of the trial outcomes using statistical and modeling analyses strongly suggests a clinically significant benefit from screening, a rational public health approach should be to determine optimal implementation of screening to minimize harm while maximizing benefit.

Recent observational and modeling studies provide some direction for a way forward. Vickers et al (26) studied the association of between PSA levels at ages 40-55 and the long-term risks of metastasis in an unscreened population. Their findings indicate a strong correlation between higher PSA levels at these ages and risk of future metastatic disease and prompt a suggestion to use early PSA testing to stratify men to more versus less intensive screening approaches. Gulati and colleagues (25) compared 35 different policies varying ages to start and stop screening, intervals between screens, and criteria for biopsy referral. Their results suggest that screening less intensively, particularly if PSA levels are low, and referring to biopsy less readily in men over 70 could substantially reduce overdiagnosis and false positive tests while preserving over 70% of the lives saved under annual screening. Heijnsdijk et al (24) compared fewer policies, also noting that less frequent screening (every 4 years) preserves the majority (two-thirds) of lives saved when compared with annual screening. However, the key conclusion of this study concerned the impacts of treatment and its consequences on the quality-adjusted life-years saved by screening. The specific quality weights used by the authors imply that screening benefit is highly sensitive to quality of life (quality-adjusted life-years saved were projected to be 23% lower than unadjusted life-years). However, as noted by an accompanying editorial (27), existing data on the distribution of utilities corresponding to key health states are far from adequate. This study therefore highlights the need for – and the challenge of – accurately quantifying harm-benefit tradeoffs when developing screening policies.

It is likely that the harms and benefits of screening will be valued differently by different individuals. The balance of harm to benefit will also be materially affected by patient decisions following diagnosis such as whether the patient selects aggressive curative treatment or active surveillance to reduce the chance of overtreatment. Ultimately, as acknowledged by current screening guidelines from national panels (e.g. 3, 28) that recommend shared decision making, the optimal approach to prostate cancer screening may well depend on the patient.

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Key Points

- Screening trials provide information that is critical for screening policy development but cannot provide all information needed for developing sound population screening policies.
- Results from a modeling analysis of the PLCO trial reveals that the empirical finding of no difference in prostate cancer mortality in this study could have easily occurred even if prostate cancer screening had a high degree of efficacy.
- The balance of screening harm to benefit will be materially affected by patient decisions following diagnosis such as whether the patient selects aggressive curative treatment or active surveillance to reduce the chance of overtreatment.

Table 1

Summary of published reports of primary outcomes from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colon and Ovarian (PLCO) trial. Also presented are reports from the three ERSPC sites that published results separately. Cum. Inc.: Cumulative incidence; the cumulative incidence of disease gives the fraction of participants on each arm diagnosed with prostate cancer during the course of follow-up. The similarity between the incidence on the screened and the control arms of the PLCO trial reflects the contamination by opportunistic screening among control group participants. The cumulative incidence of prostate cancer death gives the fraction of participants on each arm dying of prostate cancer during the course of follow-up. The lives saved is the difference between these fractions expressed relative to 1,000 men enrolled. The mortality rate ratio is the ratio of the risk of prostate cancer death on the screened arm relative to the control arm. The NND (additional Number Needed to Detect) should ideally reflect the ratio of overdiagnoses to deaths prevented however studies (11, 22) have shown that this is not accurately estimated by limited-term trial data.

Study	Age	N	Start year	Follow-up (median years)	Cum. Inc. of disease		Cum. Inc. of PC Death	Mortality Rate Ratio	Lives saved per 1,000	NND
					Control	Screened	Control			
ERSPC	55-69	162,388	1991	11	6.00%	9.60%	0.50%	0.79	1.07	37
Rotterdam	55-74	42,376	1993	12.8	6.84%	12.75%	0.90%	0.8	1.8	33
Finland	55-69	80,144	1996	12	6.90%	9.00%	0.55%	0.85	0.83	25
Sweden	50-69	20,000	1994	14	8.20%	12.70%	0.90%	0.56	4	12
PLCO	55-74	76,685	1993	13	9.95%	11.09%	0.38%	1.09	0	Inf

Data from Refs 6,8,19-21.