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TOPIC PAPER

Randomized controlled screening trials for prostate cancer using prostate-specific antigen: a tale of contrasts

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Abstract
Objectives This article aims to review the merits of the use of prostate-specific antigen (PSA) as a screening tool in the detection of prostate cancer and the evidence presented by the US and European population-based, randomized controlled trials evaluating screening. Many studies have attempted to ascertain whether PSA screening is beneficial with respect to cancer-specific mortality. This report aims to clarify the issues specific to the PSA test, prostate cancer, sources of bias, and the future of screening.
Methods We performed an Ovid-Medline literature search for articles pertaining to the introduction of the PSA test, its use for screening for prostate cancer, confounders and biases specific to PSA and prostate cancer's natural history, and reports specific to the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO), and the European Randomized Study of Screening for Prostate Cancer (ERSPC). We reviewed these articles and present relevant data.
Results PSA emerged as one of the most-used serum tests to screen for cancer, particularly in the US, but in Europe as well. The PLCO trial showed no benefit to screening, and the ERSPC showed a 20% relative risk reduction of cancer-specific mortality. This translated to an absolute reduction of PCa-related deaths of 0.71 per 1,000. Each trial has criticisms that may or may not have affected power and outcome, although the rate ratios comparing screening to not screening are similar.
Conclusions Definitive evidence for or against screening is still lacking, as interim analyses from the ERSPC and PLCO await further follow-up in the years to come.

Keywords Prostate cancer · Screening · PSA · DRE · Biopsy

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Introduction

The history of prostate-specific antigen (PSA) as a screening tool to detect prostate cancer (PCa) is both storied and controversial, with various medical societies publishing contradictory recommendations for its use. Proponents point to earlier detection, stage migration to organ-confined disease allowing for interventions of curative intent, and decreased mortality since the introduction of PSA testing in 1987 as proof of its efficacy as a screening tool. Opponents note that lead-time bias in screen-detected cancers cannot have accounted for the decreases in PCa-related mortality seen only a few years after the test's introduction and widespread use, instead arguing that these declines in mortality may have been caused by advances in treatment, detection, or other unknown factors [1]. Prior to the widespread use of PSA, there had been no comprehensive assessment of the trade-offs between benefits and risks of a screening program.

Since the introduction of PSA, multiple studies have attempted to address the benefits of screening. However, most early studies were either observational in nature or suffered methodological flaws. Two large population-based randomized controlled trials (RCT), the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC), set out to definitively answer the

questions over the merits of PSA screening. This article will present a detailed review of the body of evidence surrounding the PSA test, discuss confounding factors with respect to screening for PCa, review and contrast the particular approaches used by these two PCa screening trials, and reflect on the future of PCa screening.

Characteristics of serum PSA as a screening tool

Discovery of PSA

PSA was first discovered in 1969 as part of a collection of antigens precipitated from prostate tissue with isolation 10 years later [2]. Some posited that measurement of serum PSA could be helpful to follow a patient's response and course after treatment for PCa. Multiple investigations took place during the 1980s to better understand normal and abnormal PSA levels, with some noting that it was not appropriate as a screening device [3]. Several case studies suggested that the upper limit of normal be set at 2.6 ng/ml, but concerns over the lack of specificity for PCa prompted others to recommend 10 ng/ml [4]. After several trials, a level of 4 ng/ml became the standard for diagnosing PCa [5, 6].

Detection of cancer

PSA is not cancer specific, and other conditions routinely cause PSA levels to be elevated, including benign prostatic hyperplasia, infection, and recent instrumentation. False positivity can lead to unnecessary biopsies, treatment, associated morbidities, and undue anxiety. PSA levels constitute a continuum of risk, and this was best demonstrated by a subset of the placebo arm of the Prostate Cancer Prevention Trial (PCPT) [7]. In this RCT, study participants were randomized to receive either finasteride, a 5α-reductase inhibitor, or placebo to determine whether the development of PCa could be prevented. A subset of those receiving placebo with negative PSA (<4.0 ng/ml) and negative DRE still underwent biopsy at the end of the trial. Surprisingly, 6.6% of men with the lowest levels of PSA, <0.5 ng/ml, were found to harbor PCa despite low PSA levels. Autopsy studies have also demonstrated that the background incidence of indolent, subclinical PCa is not small [8, 9]. That some PCa can be clinically insignificant further muddles the efficacy of PSA testing, as PSA cannot distinguish between clinically significant and insignificant disease.

Overdiagnosis and biases of screening

The benefits of a screening program should be aimed at early detection to allow earlier intervention when cure is more possible. When PSA screening was introduced in the late 1980s, there was a large increase in the incidence of diagnosed PCa for a number of years before levels dropped. Ideally, for a new screening program, the increase in early-stage disease should be mirrored by a 1:1 decrease in late-stage disease as a population is screened over time. Based on SEER data, the incidence of PCa increased from 184/100,000 in 1983 to 416/100,000 in 1992. This subsequently dropped to 352/100,000 in 2006. As latent cancers were pulled into the present, there was not a notable offset in the number of late-stage cases. The number of late-stage cases has declined with time, but this reduction only accounts for a fraction of the increase in early-stage disease [10]. Still, improvements in the effectiveness of treatments and timing and sequencing of treatment may have contributed to the overall decline in prostate cancer mortality, which has fallen about 4% per year in the United States after 1992, according to data from the Surveillance, Epidemiology and End Results (SEER) database.

The difference between the substantial increase in early-stage PCa and the smaller decline in late-stage disease translates to overdiagnosis and subsequently, overtreatment. While exact definitions vary, overdiagnosis is generally the number of cancers detected in the course of screening that would not have otherwise been found in the absence of screening. These are diagnoses of tumors that are clinically silent, indolent, and progress so slowly they would not adversely affect the patient. Generally, overdiagnosis is expressed as a percentage of screen-detected cancers and has been previously estimated between 25 and 84% [11]. For an excellent review of overdiagnosis and overtreatment, please refer to the reference by Bangma et al. [12].

To date, the data largely agree that the introduction of PSA screening led to an increased incidence of PCa diagnoses and a stage migration toward early-stage disease [13]. However, the impact of screening on PCa mortality, and the overall risk–benefit ratio, is less clear. These controversies form the basis of the need for large, population-based RCTs to ascertain the true effect of PSA screening on disease outcome, the two largest, most comprehensive trials of which we will review here.

Randomized controlled trials of PSA screening

PLCO cancer screening trial

The PLCO Cancer Screening Trial randomized 76,693 men 55–74 years of age at ten US study centers to annual screening with PSA for 6 years and DRE for 4 years or to usual care between 1993 and 2001 [14]. The screening group consisted of 38,343 men, and the control group

consisted of 38,350 men. PSA levels greater than 4 ng/ml were considered positive, and treatment choices were left to patient and clinician. Screening compliance was 85% for PSA and 86% for DRE. In the control arm, a substantial number of subjects did undergo PSA testing after enrollment, increasing from 40% at baseline to 52% in the sixth year.

74.2% of subjects with PSA >4 ng/ml or abnormal DRE underwent additional PSA and DRE testing, and 31.5% ultimately underwent biopsy. Men with a positive DRE and a PSA level less than 4 ng/ml had a biopsy rate of 19.1%, whereas men with a positive DRE and a PSA level higher than 10 ng/ml had a biopsy rate of 85%. Conversely, biopsy rates dropped as age increased (33.2% for men aged 55–59 years and 27.1% for men aged 70–74 years) [15].

At 10 years (follow-up complete for 67% of subjects), diagnoses numbered 3,452 versus 2,974 in the screening versus control (rate ratio 1.17, 95% CI 1.11–1.22). Through year 10, PCa deaths were 92 in the screening group and 82 in the control group (rate ratio 1.11, 95% CI 0.83–1.50). These differences were not significant at any time point.

The number of subjects with advanced tumors (stage III/IV) was also similar in the two groups (screened 122, control 135). Overall mortality rates were also the same between the two study arms. Study investigators plan to continue follow-up in the PLCO trial until all subjects reach at least 13 years. At the time of the interim report, investigators noted that about 23% of deaths from any cause in both arms, excluding prostate, lung, colon, and ovarian cancers, were from other cancers; 21% were from heart disease, 3% stroke, 18% circulatory disease, and 10% respiratory disease.

ERSPC trial

The ERSPC study used data from 7 different European countries, with a total of 162,243 men between the core ages of 55 and 69 years undergoing randomization. Men outside these ages were also randomized and analyzed separately. Of these, 72,890 men were assigned to the screening group and 89,353 men were assigned to the control group [16]. Randomization was 1:1 in all countries except Finland, where a ratio of 2:3 for the screening group to the control group occurred. In Finland, Sweden, and Italy, informed consent occurred after randomization, whereas in Netherlands, Belgium, Switzerland, and Spain, informed consent preceded randomization. PSA cutoffs varied from 2.5 to 4.0 ng/ml. Contamination of the control group by PSA screening was only reported for 1 of the 7 centers, Rotterdam; however, overall contamination was estimated at 15.2% [17]. Intervals for the screening group were much larger than the PLCO—between 2 and 7 years (4 years for 87% of patients). Belgian and Dutch centers used a combination of DRE, ultrasound, and PSA as the primary screening approach until 1997. Biopsy methodologies were different between the various countries, ranging from 6 to 12 cores, and either transrectal or transperineal in approach.

82.2% of the screening cohort were ultimately screened. Compliance with biopsy recommendations on the basis of the screening PSA was relatively high at 85.8%. Investigators detected 5,990 cancers in the screening group and 4,307 in the control group (cumulative incidences of 8.2 and 4.8%, respectively).

As of December 2006, there were 214 PCa deaths in the screening group and 326 in the control group. For the screening group, this results in an adjusted rate ratio of 0.80 (95% CI 0.65–0.98, $P = 0.04$). To prevent 1 death from PCa, 1,410 men needed to be screened and 48 men treated. The absolute reduction of PCa-related deaths was 0.71/1,000 men after 8 years. This benefit was restricted to men 55 to 69 years of age.

Discussion

When polled, people support the idea of screening for cancer even when they are given information about the trade-offs associated with said screening [18]. Although at face value, screening makes intuitive sense, the compounding factors surrounding PSA screening, including lead-time bias, false positives, large proportion of latent, indolent disease, morbidity, overtreatment, unknown mortality benefit, attribution bias, render the situation far less clear to the informed clinician.

While both trials have the same endpoints, with regard to design and implementation, the PLCO and ERSPC are very different and each can be faulted for particular aspects. The PLCO, for example, noted that 44% of patients were prescreened, that is, underwent PSA testing prior to randomization, versus only 3% in the Swedish arm of the ERSPC. This could have removed high-risk cancers from the available pool prior to enrollment, diluting the power of the study. PLCO participants were older than those in the ERSPC. Finally, the PLCO showed a smaller proportion of PCa-related deaths than the ERSPC. PLCO follow-up at 10 years has only been reported as about 70% complete. Given long lead times, longer follow-up may show a small benefit to screening. More screened men opted for active surveillance in the ERSPC than the PLCO (18.6% vs. 11%). Finally, the number of advanced cancers found at interval screenings for both trials was equivalent to those found at initial screening rounds, indicating that screening did not find the ideal 1:1 ratio of increased early-stage cancers to decreased late-stage cancers [19].

With respect to the ERSPC, several centers enrolled control subjects who were unaware they were participating in a

trial. When diagnosed, they received treatment at their usual point of care. Participants in the screening arm, however, tended to receive treatment from high-volume tertiary referral centers, which may have been provided by urologists of different expertize. All men in both arms of the PLCO were consented prior to randomization, and stage-specific therapies were equivalent for both arms. Overall, the risk ratio confidence intervals between the two trials are not grossly different.

While the ERSPC did report a 20% relative reduction in the death rate from PCa in men 55-69 years of age at a median follow-up of 9 years, the absolute reduction of about 7 PCa deaths per 10,000 men screened begs the question of risk versus benefit. How many cancers will be overdiagnosed to achieve this benefit? While the risk of complication from screening (PSA and/or DRE) and diagnosis (biopsy) is fairly low (reported at 26/10,000 for PSA and 68/10,000 for biopsy from PLCO data), adverse effects from subsequent treatment are not trivial: incontinence, erectile dysfunction, anxiety, decreased quality of life, and cost to healthcare systems at large [20]. Indeed, PLCO investigators chose to publish interim results early not for reasons of crossing a futility boundary, but rather because data showed no mortality benefit to screening and began to suggest potential harm. Interestingly, after results from these trials were released, the discoverer of PSA, Dr. Richard Albin, published a statement describing the widespread use of PSA as a screening tool as a "public health disaster" in the *New York Times* in [21].

Cancer-specific mortality statistics make a statement, but they do not necessarily reflect the quality of those lives affected by screening programs, which for now, has not been reported. Further, subsequent analyses have posted more results surrounding the number of false positives in both the PLCO (10.4% of those with positive PSA) and the ERSPC (75.9% of those who had positive PSA) and noted that the cumulative risk of false positives increases with each subsequent round of screening of which clinicians and patients alike should remain cognizant [22]. The large difference in false positivity rate between the two trials may largely stem from differences in the proportion of men who underwent biopsy, which was far higher (85.8%) in the ERSPC than the PLCO (31.5%). While the low follow-up biopsy percentage has been a staunch criticism of the PLCO, further testing prior to diagnostic biopsy may have contributed to greater overall clinical sensitivity, limiting unnecessary biopsies. Certainly, the power to detect any benefit from screening was reduced by the high contamination rate in the PLCO, although it remains difficult to compare without reported contamination rates from all 7 sites of the ERSPC.

Interestingly, while the conclusions thus far from these two landmark RCTs are divergent, there are other very important, complementary data that have emerged. For one, investigators now have a much better understanding of PSA dynamics on a population-scale, where men with low baseline PSAs have a much reduced chance of progressing to higher PSAs, subsequent biopsy, and PCa diagnosis. In the PLCO, the proportion of men with initial PSA levels of 0–1.0 ng/ml who developed PCa with Gleason scores greater than or equal to 7 within 7 years of trial enrollment was only 0.14%. Data from the Baltimore Longitudinal Study of Aging, the Rotterdam Section of the ERSPC, Duke University investigators, and the Henry Ford Health System all corroborate that a man's first PSA is highly indicative of his subsequent 4- to 7-year risk of PCa diagnosis [23–25]. For example, the Henry Ford Health System data from 21,502 men greater than 40 years old revealed PCa rates were up to 19-fold higher in patients with a first PSA $\geq$1.5 ng/ml compared to patients with PSA <1.5 ng/ml. This prognostic information provided by the first or baseline PSA, however, was not suggested to dictate immediate biopsy.

Practical considerations

We and other have proposed that a risk-based approach to PCa screening may be prudent based on this data, where screening interval is individualized based on results after first round of PSA screening [25, 26]. Men with lower PSA might benefit from lengthened screening intervals while minimizing missed, clinically significant cancers, and men with higher baseline PSA should probably be screened more often. This approach has the greatest potential to mitigate cost, morbidity, and demonstrates a benefit for those choosing to undergo screening. Still, until trials demonstrate that such schemes are beneficial in terms of cost, quality of life, and mortality, they remain hypothetical.

For now, the American Urological Association (AUA) Prostate Specific Antigen Best Practice Statement recommends a baseline PSA at age 40, although neither the PLCO nor ERSPC included men ages 40 to 50. The National Comprehensive Cancer Network proposes similar screening guidelines, largely based on the Baltimore Longitudinal Study discussed earlier which provided no statement on patient outcomes. The American Cancer Society emphasizes the necessity of informed decision-making as a prerequisite to PCa screening. Controversially, the US Preventive Services Task Force, on the basis of the results of randomized controlled screening trials reviewed here, recommended again PSA screening altogether, citing either no benefit or potential harm to patients [27]. Finally, the American College of Preventive Medicine and American Academy of Family Physicians state there is insufficient evidence to recommend screening for PCa [28].

This diversity of practice statements and study data allows for some flexibility in the interpretation of the evidence for and against screening. Physicians and their

patients should be well informed of the risks of screening, risks of false positives with multiple rounds of screening, and take into account other clinical factors like age, expected ten-year mortality, comorbidities, and patient preferences. Anxiety can play a large component for clinician and patient alike, positively reinforcing the screening-diagnosis-treatment pathway.

Future of screening

The benefit of screening is largely dependent on downstream effectors like diagnosis and treatment. A UK trial has been set up to evaluate the merits of screening coupled with treatment. The Prostate Testing for Cancer and Treatment trial (ProtecT, NCT00632983) in the United Kingdom is a randomized treatment trial within a prostate cancer screening study [29]. More than 2,500 men with low-grade prostate cancer have been randomly assigned to prostatectomy, radiation therapy, or observation.

The Prostate Cancer Intervention versus Observation Trial (PIVOT; ClinicalTrials.gov number, NCT00007644) is a randomized trial comparing radical prostatectomy (RP) versus observation in men with low-grade prostate cancer. Results were recently released at the national AUA meeting in May 2011 [30]. Only in men with PSA >10 ng/ml did RP reduce cancer-specific mortality (hazard ratio 0.36, 95% CI 0.15–0.89, $P = 0.03$). This trial supports the use of active surveillance for low-grade PCa in men with PSA <10 ng/ml, what will certainly prove to be a controversial finding among some practitioners and patients alike.

Conclusions

The tradeoffs of the two largest RCTs evaluating the merits of PSA screening largely reflect different practice patterns of US and European counterparts, and the risk–benefit ratio remains uncertain. Definitive evidence for or against screening is still lacking, as these interim analyses await further follow-up in the years to come. For now, patients and clinicians should be well informed regarding the stated risks and benefits of PSA screening, subsequent diagnostic and therapeutic activities. In addition, long-term effects on quality of life have yet to be reported, and these may also serve to inform the ongoing debate over screening.

Conflict of interest Kyle O. Rove has no conflict of interest. E. David Crawford is a PLCO investigator.

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