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Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Prepared by:
Kenneth Lin, MD
Jennifer M. Croswell, MD, MPH
Helen Koenig, MD, MPH
Clarence Lam, MD, MPH
Ashley Maltz, MD, MPH

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Structured Abstract

Background: In 2008, the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years. The USPSTF recommended against screening for prostate cancer in men aged 75 years or older.

Purpose: To update a previous systematic review performed for the USPSTF and evaluate new evidence on the potential benefits of prostate-specific antigen (PSA)-based screening for prostate cancer.

Data Sources: English-language articles identified in PubMed and the Cochrane Library (search dates January 2007 to July 2011), reference lists of retrieved articles, and expert suggestions.

Study Selection: Randomized controlled trials, systematic reviews, and meta-analyses were selected to determine whether PSA-based screening decreases prostate cancer-specific or all-cause mortality. Where available, information on the potential harms of screening for prostate cancer was also extracted from included studies.

Data Extraction: Studies were reviewed, abstracted, and rated for quality, using predefined USPSTF criteria.

Data Synthesis: Five randomized controlled trials (two fair- and three poor-quality) and two meta-analyses evaluating the impact of PSA-based screening on prostate cancer mortality were identified. A report describing results from a single center participating in one of the fair-quality trials was also identified. Of the two highest-quality trials, the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found no statistically significant effect of PSA-based screening on prostate cancer mortality after 10 years (rate ratio [RR], 1.11 [95% CI, 0.83–1.50]). The European Randomized Study of Screening for Prostate Cancer also found no statistically significant effect in all enrolled men (ages 50–74 years) after a median followup of 9 years (RR, 0.85 [95% CI, 0.73–1.00]), but reported a 0.07% absolute risk reduction in a prespecified subgroup of men aged 55 to 69 years (RR, 0.80 [95% CI, 0.65–0.98]). Neither meta-analysis indicated a reduction in prostate cancer mortality with the use of PSA-based screening. When a benefit was found, PSA-based screening resulted in an estimated 48 additional men being treated for each prostate cancer death that was averted. Twelve percent to 13% of screened men had false-positive results after 3 to 4 screening rounds, and clinically important infections, bleeding, or urinary retention occurred after 0.5%–1.0% of prostate biopsies.

Limitations: Evidence was conflicting regarding the effect of screening on prostate cancer mortality in the highest-quality trials; they also represented interim results. We restricted the search on the potential harms of PSA-based screening to information available from randomized efficacy trials.

Conclusions: After about 10 years, PSA-based screening results in the detection of more cases of prostate cancer, but small to no reduction in prostate cancer-specific mortality.

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Chapter 1. Introduction

Purpose of the Review

The American Cancer Society estimates that in 2011, about 241,000 men will be diagnosed with prostate cancer and 34,000 men will die from it, making it the most commonly diagnosed nonskin cancer and the second leading cause of cancer death in men.[1] Prostate-specific antigen (PSA)-based screening programs have been advocated as a possible means to reduce the mortality rate, as the test can detect asymptomatic, early-stage tumors. Beginning in the 1990s, utilization of the PSA test became widespread in U.S. clinical practice; data from nationally representative surveys[2,3] and community primary care clinics[4] consistently show that the majority of American men aged 50 years and older receive regular PSA tests.

Prior USPSTF Recommendation

In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against screening for prostate cancer in men aged 75 years and older.[5] It concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years, due to a lack of evidence that screening reduced mortality. The subsequent publication of initial mortality results from two large, randomized controlled trials of prostate cancer screening (the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCO][6] and the European Randomized Study of Screening for Prostate Cancer [ERSPC][7]) prompted the USPSTF to request an updated systematic evidence review of direct evidence on the benefits and harms of PSA-based screening for prostate cancer. The USPSTF commissioned a separate report examining the benefits and harms of treatment for localized prostate cancer,[8] given that the overall outcomes of early detection are intrinsically tied to the subsequent use of therapies.

Chapter 2. Methods

Key Questions and Analytic Framework

This evidence update summarizes new and previously reviewed randomized controlled trials, systematic reviews, and meta-analyses to answer the following key questions: 1) Does PSA-based screening decrease prostate cancer-specific or all-cause mortality? and 2) What are the harms of PSA-based screening for prostate cancer? **Figure 1** provides the analytic framework that guided both this and the related treatment review.

"PSA-based screening" is defined as a screening program for prostate cancer in asymptomatic men that incorporates one or more PSA measurements, with or without additional modalities such as digital rectal examination or transrectal ultrasonography. "Asymptomatic" is defined as without symptoms that are highly suspicious for prostate cancer. Many older men have chronic, stable lower urinary tract symptoms (e.g., due to benign prostatic hyperplasia) that are not generally associated with an increased risk for prostate cancer.[9] As in a previous review for the USPSTF,[10] a broad definition of PSA-based screening was utilized that includes traditional single-threshold PSA testing as well as other PSA-based prognostic measures, such as age-adjusted thresholds, velocity, and doubling time.

Search Strategy

PubMed was searched for English-language randomized controlled trials, systematic reviews, and meta-analyses indexed between January 1, 2007 and July 1, 2011, using combinations of the MeSH terms and key words "prostate neoplasms," "screening," "prostate-specific antigen," "early diagnosis," "PSA velocity," "PSA doubling time," and "prostate specific antigen doubling." The exact strategy is described in **Appendix 1**. Additional articles were identified through a search of the Cochrane Database, hand searches of reference lists from included studies and review articles, and recommendations of experts.

Study Selection

Four contributors independently reviewed title lists, abstracts, and full articles using predetermined inclusion and exclusion criteria. At each point, articles selected for retention by at least one contributor advanced to the next stage of review. Eligible studies were randomized controlled trials, systematic evidence reviews, or meta-analyses that compared PSA-based screening with no screening or usual care in asymptomatic general primary care populations and that reported prostate cancer or all-cause mortality as an outcome. Information about the harms of screening reported in trials meeting the above criteria was included for key question 2.

Data Abstraction and Quality Assessment

For all citations that met the eligibility criteria, two contributors reviewed the full articles and independently rated their quality using previously published USPSTF criteria.[11] Disagreements

were resolved through consensus. The quality assessment included the following items: initial assembly and maintenance of comparable groups, absence of important differential loss to followup or overall high loss to followup, use of equal, valid, and reliable outcome measurements, clear definition of interventions, and appropriateness of outcomes. **Appendix 2** describes more thoroughly the criteria and definitions for USPSTF quality ratings.

Data Analysis and Synthesis

The data was synthesized qualitatively in narrative and tabular formats. Information from randomized controlled trials, systematic reviews, and meta-analyses on the direct effect of PSA-based screening on prostate cancer mortality, as well as the harms of screening and diagnostic procedures reported in these trials, were included. Data from the 2008 review[10] were included to facilitate an overall assessment of the body of evidence.

Role of the Funding Source

The general work of the USPSTF is supported by the Agency for Healthcare Research and Quality. This review did not receive specific funding.

Review of Draft

The draft report was peer reviewed by content experts, USPSTF members, and collaborative federal partners.

Chapter 3. Results

A total of 379 potentially relevant articles were identified; of these, two fair-quality trials,[6,7] two poor-quality trials,[12,13] and two meta-analyses[14,15] met inclusion criteria (**Figure 2**). Additionally, we included a report that describes results from a single center participating in one of the fair-quality trials.[16] For completeness, we also included one poor-quality randomized trial that was previously considered by the USPSTF.[17] **Table 1** summarizes key characteristics of all of these studies. A list of excluded studies can be found in **Appendix 6**.

Key Question 1. Does PSA-Based Screening Decrease Prostate Cancer-Specific or All-Cause Mortality?

In 2008, the USPSTF considered two poor-quality randomized controlled trials and one meta-analysis that addressed this question. The first trial, by Labrie et al,[17] randomized 46,486 men to PSA-based screening versus usual care and showed no statistically significant difference in prostate cancer mortality between screening-invited and control groups when data were analyzed via intention-to-screen (risk ratio [RR], 1.09 [95% CI, 0.82–1.43]). The second trial, by Sandblom et al,[18] involved 9,026 men and also found no statistically significant difference in prostate cancer mortality between screening-invited and control groups (RR, 1.04 [95% CI, 0.64–1.68]). A 2007 Cochrane meta-analysis[19] of these two trials found no statistically significant difference in prostate cancer mortality in men randomized to screening versus controls (RR, 1.01 [95% CI, 0.8–1.29]); however, the authors concluded that due to the methodological limitations and high risk for bias inherent in both trials, the evidence was insufficient at that time to support or refute the use of screening to reduce prostate cancer mortality.

New evidence, along with updated results from the Cochrane meta-analysis and the Sandblom trial, is summarized below.

Nörrkoping Trial

In early 2011, longer-term results from the randomized trial by Sandblom et al became available.[13] In 1987, all male residents aged 50 to 69 years living in Nörrkoping, Sweden were identified in the National Population Register, and every sixth man (n=1,494) was invited to participate in a multiyear screening program. The remaining 7,532 men—who were not contacted—were treated as controls. Screening consisted of digital rectal examination in 1987 and 1990; this changed to digital rectal examination plus PSA testing in 1993 and 1996. Depending on the screening round, between 70%–78% of invited men received screening. A PSA cut-off point of >4.0 μg/L was used. A positive screening result led to biopsy, and confirmed prostate cancer was treated according to a standardized management program common to the southeast region of Sweden.

No statistically significant difference in prostate cancer mortality was seen between the screened and control groups after 20 years of followup (RR, 1.16 [95% CI, 0.78–1.73]).

This trial was rated as poor quality, as the method of randomization was inadequate, there was no information available on the baseline comparability of the screened and control groups or the degree of contamination in the control group, and there was insufficient information regarding outcome assessment. Additionally, the sample size was originally calculated to assess the acceptance and feasibility of a prostate cancer screening program rather than mortality outcomes. (See **Appendix 3** for additional information on quality ratings for included trials.)

Stockholm Trial

Kjellman et al[12] conducted a comparative study in which 2,400 male residents of Stockholm, Sweden aged 55 to 70 years were invited to a single prostate cancer screening in 1988 and followed for 15 years. Of the men invited, 74% attended the screening, which included a PSA test, digital rectal examination, and transrectal ultrasonography. A PSA threshold of 10 ng/mL triggered prostate biopsy, while a measurement of 7–10 ng/mL led to repeat ultrasonography. Death rates from prostate cancer and all causes other than prostate cancer in the screening-invited group were compared with death rates in the remaining 24,804 men in the source population.

Neither the relative risk of death due to prostate cancer (RR, 1.10 [95% CI, 0.83 to 1.46]) nor the relative risk of death from other causes (RR, 0.98 [95% CI, 0.92 to 1.05]) was statistically significantly different in the screening-invited group compared with the controls. Only three of the 65 cases of prostate cancer found during screening were detected by an elevated PSA level alone.

This trial was rated as poor quality because of uncertainty about initial comparability of the screening and comparison groups and the potential for attribution bias in outcomes assessment, as it is not clear if the review committee was blinded to group allocation. The trial also has internal discrepancies about the total number of participants because the file containing the registration numbers of the original cohort could not be retrieved. This trial's findings are poorly generalizable to the United States due to the high PSA cut-off points and probable outdated treatments used.

PLCO Cancer Screening Trial

In the prostate cancer component of the PLCO trial,[6] 76,693 U.S. men aged 55 to 74 years were randomized to annual PSA-based screening for 6 years in combination with digital rectal examination for 4 years or to usual care. Randomization occurred after consent. Abnormal screening results, defined as a PSA level of ≥4.0 ng/mL or suspicious digital rectal examination findings, were made known to the patient's primary care clinician, and further diagnostic testing and treatment were based on patient and physician preferences.

After 7 years' (complete) followup, there was a statistically significant increase in prostate cancer incidence in men assigned to the screening group (RR, 1.22 [95% CI, 1.16–1.29]), but no difference in prostate cancer mortality (RR, 1.13 [95% CI, 0.75–1.70]) compared with the usual care group. Similar findings were observed after 10 years (67% complete followup). There was no difference in all-cause mortality in the screened versus usual care arms (10-year RR, 0.97

[95% CI, 0.93–1.01]) based upon an analysis that excluded lung and colorectal cancer deaths. Eighty-nine percent of men in the screen-invited group and 90% of men in the control group who received a prostate cancer diagnosis chose active treatment (surgery, radiation, and/or hormonal therapy). Treatment choices stratified by prostate cancer stage were similar between the screening and control groups.

The PLCO trial was rated fair quality because of contamination; up to 52% of men assigned to usual care received a PSA test at some point during the trial. Contamination could have compromised the ability of the trial to detect a positive effect of screening on prostate cancer mortality; in order to maintain 90% power at 7 years of followup, the relative prostate cancer mortality reduction from screening would have had to be 40%, according to the group's baseline calculations.[20] However, contamination does not explain the (nonstatistically significant) trend toward increased mortality in the screened arm. Forty-four percent of the men in both the screening and usual care groups had undergone PSA screening prior to entry. Subgroup analyses stratified by a history of PSA testing at baseline did not reveal differential effects on prostate cancer mortality rates between the screen-invited and control arms,[6] but the high rate of prescreening affects the ability of the study to be generalized to a screen-naive population.

ERSPC

The ERSPC trial[7] randomized 182,000 men from seven European countries aged 50 to 74 years to be invited for PSA testing every 2 to 7 years—depending on center and year—or to usual care. PSA cut-off points for diagnostic evaluation ranged from 2.5 to 4.0 ng/mL (one center used the cut-off point of 10 ng/mL for several years). Recruitment and randomization procedures and age eligibility for enrollment also varied substantially among study centers. **Appendix 4** provides details about the exact differences between study centers. Treatment of prostate cancer was performed according to each center's local policies and guidelines.

After a median followup of 9 years, the cumulative incidence of prostate cancer diagnoses in men in the screened arm was higher than in the usual care arm (8.2% vs. 4.8%, respectively, or a net increase of 34 additional cases per 1,000 men). There was no statistically significant difference in the risk for prostate cancer death for the entire population of men assigned to screening invitation (ages 50 to 74 years) compared with men assigned to usual care (RR, 0.85 [95% CI, 0.73–1.00]). A prespecified subgroup analysis of 162,243 men aged 55 to 69 years found a statistically significant absolute risk reduction in prostate cancer mortality of 0.071% (RR, 0.80 [95% CI, 0.65–0.98]). Prostate cancer mortality rate ratios were greater than 1 for screen-invited men aged 50 to 54 years (RR, 1.47 [95% CI, 0.41–5.19]) and 70 to 74 years (RR, 1.26 [95% CI, 0.80–1.99]), although these were not statistically significant findings and the confidence interval in the younger age group is very wide. Using the 0.071% risk difference in the subgroup of men aged 55 to 69 years, the authors estimated that 1,410 men would need to be invited to screening and 48 additional men would need to be treated to prevent one prostate cancer death.

Sixty-six percent of men in the ERSPC trial who received a prostate cancer diagnosis were initially managed with surgery, radiation therapy, or hormonal therapy, while 15% chose active surveillance or watchful waiting (specific treatment information was not available for 19% of

diagnosed participants). Treatment choice varied by trial arm; participants in the control arm with high-risk prostate cancer were statistically significantly more likely than screen-invited men to receive radiotherapy, expectant management, or hormonal therapy than radical prostatectomy. This may have been because the major screening centers were large university hospitals, and once diagnosed, screen-invited participants tended to also receive treatment from these centers. In contrast, control subjects were not invited to screening centers, and as such, were more likely to be diagnosed and receive treatment at their usual place of care. However, on regression analysis, the association between treatment choice and study arm was weaker than other factors such as age, PSA level, and Gleason score.[21]

The ERSPC trial was rated fair quality due to the inconsistencies in screening intervals and PSA cut-off points among study centers, differences in exclusion of eligible and randomized men by age between centers, and exclusion of data from two study centers (Portugal and France, which would bring the total number of original participating countries to nine). Contamination was not systematically or uniformly evaluated at all centers for the duration of the trial. According to an earlier publication, PSA testing in men assigned to usual care varied widely by study center, from 8.6% (Spain) to 36.6% (Italy)[22]; however, based upon the Rotterdam center, contamination was extrapolated to be about 20% for the overall trial.[23]

Göteborg center. After the publication of the ERSPC results, a single center from within this larger trial chose to report data separately.[16] The center designed its protocol independently, but became associated with the ERSPC trial after 1 year. A total of 20,000 men in Göteborg, Sweden aged 50 to 64 years were randomized to PSA screening every 2 years versus usual care. The PSA threshold for additional evaluation varied during the course of the study from 3.0 ng/mL to 2.5 ng/mL. Followup testing included digital rectal examination, transrectal ultrasonography, and prostate biopsy, with treatment choice left to the discretion of the patient's physician.

Seventy-six percent of invited men attended screening. After a median followup of 14 years, there was a statistically significant increase in prostate cancer incidence in the screen-invited versus control arm (hazard ratio, 1.64 [95% CI, 1.50–1.80]; 11.4% of screening-invited vs. 7.2% of usual care group diagnosed). There was an absolute risk reduction of 0.34% for prostate cancer death in the screen-invited arm compared with controls (RR, 0.56 [95% CI, 0.39–0.82]). The authors estimated that 293 men would need to be invited to screening and 12 additional men would need to be treated in order to prevent one prostate cancer death.

In screening-invited men, 56% chose radical prostatectomy, radiation, or hormonal therapy as a primary treatment strategy, while 42% initially chose surveillance. Primary hormonal therapy was more commonly used in men diagnosed with prostate cancer in the usual care compared with screen-invited arm (22.6% vs. 7%, respectively), but for low- or moderate-risk tumors, curative treatment was applied similarly between the screening (49.2%) and usual care (50.8%) groups.

This study was rated fair quality due to a lack of information regarding baseline comparability of the two arms, as well as attrition and contamination rates (contamination was estimated at 3%, but it is unclear how this estimate was obtained). As noted, the Göteborg center became associated with the larger ERSPC trial shortly after its inception, and outcomes for men born

between 1930 and 1939 (60% of the center's participants) were previously reported as part of the overarching ERSPC publication. No other center from the ERSPC trial separately reported mortality results, but an analysis of the effect of study center exclusion on the overall ERSPC findings demonstrated that exclusion of the Swedish center data alone resulted in loss of the statistically significant effect of screening on prostate cancer mortality (RR, 0.84 [95% CI, 0.70–1.01]), suggesting better results than the other centers.[7]

Djulbegovic Meta-Analysis

In 2010, a systematic review and meta-analysis covering the period from January 2005 to July 2010 was published.[15] The authors included the following studies in the analysis (total population, 387,286): 1) Quebec (Labrie at al); 2) Nörrkoping; 3) ERSPC, including data from the French and Swedish (Göteborg) centers; and 4) PLCO. To avoid double-counting, participant outcomes that were included in both the Göteborg and overall ERSPC publications were only utilized from the Göteborg paper.

All except for the Quebec study contributed information on diagnosis of prostate cancer; the meta-analysis showed a statistically significant increase in prostate cancer incidence in the screened versus control group (RR, 1.46 [95% CI, 1.21–1.77]). There was a high degree of heterogeneity in the trials for this outcome (I^2=97%), and the overall quality of evidence was considered low. Prostate cancer mortality was assessed using data from all studies with the exception of the ERSPC French center, as this publication only provided information on prostate cancer incidence. Screening was not associated with a statistically significant reduction in prostate cancer mortality (RR, 0.88 [95% CI, 0.71–1.09]). There was heterogeneity (I^2=55%), and the quality of evidence for this outcome was rated as moderate. All-cause mortality was assessed using information from PLCO, Nörrkoping, ERSPC, and the Göteborg substudy. No statistically significant difference in overall mortality was observed (RR, 0.99 [95% CI, 0.97–1.01]). The quality of evidence for this outcome was rated as moderate.

Cochrane Meta-Analysis

An update of the previously described meta-analysis was published in 2011.[14] It included five trials (total population, 341,351): 1) Nörrkoping, 2) ERSPC (including the results of the Göteborg center), 3) PLCO, 4) Quebec (Labrie et al), and 5) Stockholm, as well as reports on prostate cancer diagnosis, prostate cancer-specific mortality, and overall mortality. The Nörrkoping, Quebec, and Stockholm studies were rated as being at high risk of bias, whereas PLCO and ERSPC were both rated at low risk of bias.

Meta-analysis indicated that screening was associated with a statistically significant increase in the number of men diagnosed with prostate cancer compared with controls (RR, 1.35 [95% CI, 1.06–1.72]). However, no statistically significant difference in prostate cancer-specific mortality was observed between screened and control groups when all trials (RR, 0.95 [95% CI, 0.85–1.07]), or only trials at low risk for bias (i.e., PLCO and ERSPC) (RR, 0.89 [95% CI, 0.77–1.04]), were included. In subgroup analyses, age at screening did not change the outcome. Meta-analysis of the two studies providing information on overall mortality—ERSPC and Stockholm—showed no differences in death from any cause between screened and control

groups (RR, 1.00 [95% CI, 0.98–1.02]).

Key Question 2. What Are the Harms of PSA-Based Screening for Prostate Cancer?

Information about the harms of PSA-based screening for prostate cancer has been reported by two of the randomized trials that directly assess the impact of PSA-based screening on prostate cancer mortality.

The Finnish center of the ERSPC trial reported that after three rounds of PSA testing (using a cut-off point of 4.0 ng/mL and testing every 4 years), 12.5% of participants received at least one false-positive result. A false positive was defined as a positive result and consequent workup with no histopathologic diagnosis of cancer within 1 year of the screening test.[24] In the entire ERPSC trial, 75.9% of men that underwent a biopsy because of an elevated PSA value had a false-positive result.[7] The PLCO trial also published findings related to false-positive tests. After four PSA tests, men had a 12.9% cumulative risk of receiving at least one false-positive result (defined as a PSA level of ≥4.0 ng/mL and no prostate cancer diagnosis after 3 years), and a 5.5% risk of having at least one biopsy as a direct consequence of a false-positive screening test.[25]

Physical harms of screening documented in the PLCO trial included rare bleeding or pain from digital rectal examination (0.3 events per 10,000 men screened), bruising or fainting due to venipuncture (26.2 events per 10,000 men screened), and complications of diagnostic procedures (e.g., biopsy), such as infection, bleeding, and urinary difficulty (68 events per 10,000 evaluations).[6] The overarching ERSPC publication did not report on prostate biopsy-related harms, except to note that no deaths were associated with the procedure.[7] However, the Rotterdam study center published a site-specific assessment of biopsy-related harms.[26] Of 5,802 biopsies performed from 1994 to 2001, 200 men (3.5%) developed a fever, 20 men (0.4%) experienced urinary retention, and 27 men (0.5%) required hospitalization for signs of prostatitis or urosepsis. Reports of hematuria (22.6%) and hematospermia (50.4%) more than 3 days after the biopsy were common.

None of the randomized controlled trials of PSA-based screening and prostate cancer mortality provided information on potential psychological harms of prostate cancer screening, such as anxiety, or impact on health-related quality of life. The 2008 evidence review performed for the USPSTF found evidence that false-positive PSA test results are associated with adverse psychological effects, but could not determine the exact magnitude of psychological harms of prostate cancer screening.[10]

Chapter 4. Discussion

Most randomized controlled trials have not reported an effect of PSA-based screening on prostate cancer mortality. Of the two largest and highest-quality trials, the ERSPC trial found a statistically significant decrease in prostate cancer mortality for a prespecified subgroup of men (although it did not find a difference for all participants), while the PLCO trial demonstrated no difference in prostate cancer mortality between the screen-invited and control groups. Several factors may have contributed to these disparate findings, although there is no single explanation that can definitively resolve the disagreement at this point in time.

Incomplete Followup and the Role of Chance

Given the long lead times (10 to 15 years) associated with PSA-based prostate cancer screening, the findings of the PLCO and ERSPC trials may change with additional followup. The observed mortality benefit in the ERSPC trial began to emerge around the same time that the median length of study followup was reached. As several centers have not yet provided data for the time period at which the effect starts to occur, it is possible that the observed mortality benefit could increase or disappear with additional followup. Although the point estimates for the effect on prostate cancer mortality are qualitatively different for the two trials, the confidence intervals overlap (0.75–1.70 for PLCO; 0.73–1.00 for ERSPC).[6,7] As such, both could potentially be consistent with either a small mortality benefit or no effect. The confidence intervals from the Djulbegovic and Cochrane meta-analyses are consistent with this conclusion (0.71–1.09 and 0.85–1.07, respectively).[14,15]

Differences in the Proportion of Men With Prior PSA Testing

Neither trial excluded men who had a history of PSA testing (starting in 1995, PLCO excluded men with more than one PSA test in the previous 3 years). A relatively high rate of prescreening among participants, as documented in the PLCO trial, would have reduced the number of prevalent tumors that could be detected within the confines of the trial, thus lowering its power to detect a modest mortality benefit. As with contamination, however, this does not provide an explanation for the trend toward increased risk of prostate cancer mortality that was observed in men invited to screening in the PLCO trial compared with men assigned to usual care.

Effects of Screening in Controls and Noncompliance in the Intervention Arm

Opportunistic screening in control groups may result in underestimates of screening efficacy. In the ERSPC trial, contamination rates were extrapolated to be about 20% across all centers. Eighty-two percent of participants in the screening arm received at least one screening test. ERSPC study investigators published a separate, post-hoc statistical analysis to adjust for noncompliance and contamination, and concluded that the true effect of PSA-based screening on prostate cancer mortality was a 30% relative reduction in deaths.[23] In the PLCO trial, approximately half of the men in the control arm received a PSA test at least once during the

course of the study, and 85% of participants in the screening arm were compliant with at least one PSA test.[6] However, adjusting for compliance and contamination in this trial further *increases* the prostate cancer mortality rate ratio in screened men (from 1.13 to 1.47 or 1.72, depending on the level of contamination), making it less likely that a substantial mortality benefit was missed due to these factors. (See **Appendix 5** for details about the model utilized.)

Differences in PSA Cut-Off Points, Screening Intervals, and Treatment Choices

A lower PSA cut-off point will lead to the detection of more cases of prostate cancer.[27,28] As such, generally lower PSA cut-off points utilized in the ERSPC trial (≥2.5 to 4.0 ng/mL)—compared with the PLCO cut-off point of ≥4.0 ng/mL—may have led to the detection of more cases of prostate cancer potentially amenable to curative interventions. On the other hand, more frequent screening also tends to increase the detection of prostate cancer cases, and while most ERSPC study centers screened men every 4 years, the PLCO trial performed annual screenings.

There were also different treatment preferences in the ERSPC and PLCO trials. The proportion of men in the ERSPC trial that initially chose active surveillance or expectant management instead of curative treatment was higher than in the PLCO trial (18.6% vs. 10%). More conservative management in the ERSPC trial may have reduced treatment-associated morbidity and mortality, which could be important within the context of overdiagnosis. Conversely, the shorter screening interval used in the PLCO trial, coupled with a high frequency of immediate intervention, may provide some explanation for the trend toward increased harm in the screen-invited population.

Limitations

Evidence from the two highest-quality discrete trials is inconsistent regarding the efficacy of PSA-based screening. Additionally, information for both trials is currently limited to interim results. We restricted the search on potential harms of PSA-based screening to information available from randomized efficacy trials; new information from other study designs may have become available since the previous evidence review.

Future Research

Longer-term followup of both the PLCO and ERSPC trials is important to assess the potential effects of PSA-based screening on prostate cancer mortality beyond 10 years. Given the risk of overdiagnosis and subsequent overtreatment observed within trials of prostate cancer screening, new methods that would allow for the distinction between indolent disease and disease that is likely to clinically progress are critically needed. Research that clarifies the long-term benefits and harms of immediate treatment versus initial conservative management in men with screen-detected prostate cancer would be of great importance. Results from the ongoing U.S. Prostate Cancer Intervention Versus Observation Trial[29] and the U.K. Prostate Testing for Cancer and Treatment Trial[30] should shed some light on the groups of men who might benefit most from treatment of PSA-detected prostate cancer.

Conclusions

Five randomized controlled trials (two fair- and three poor-quality) and two meta-analyses have evaluated the impact of PSA-based screening on prostate cancer mortality. After about 10 years, PSA-based screening is associated with the detection of additional cases of prostate cancer, but small to no reduction in prostate cancer-specific mortality.

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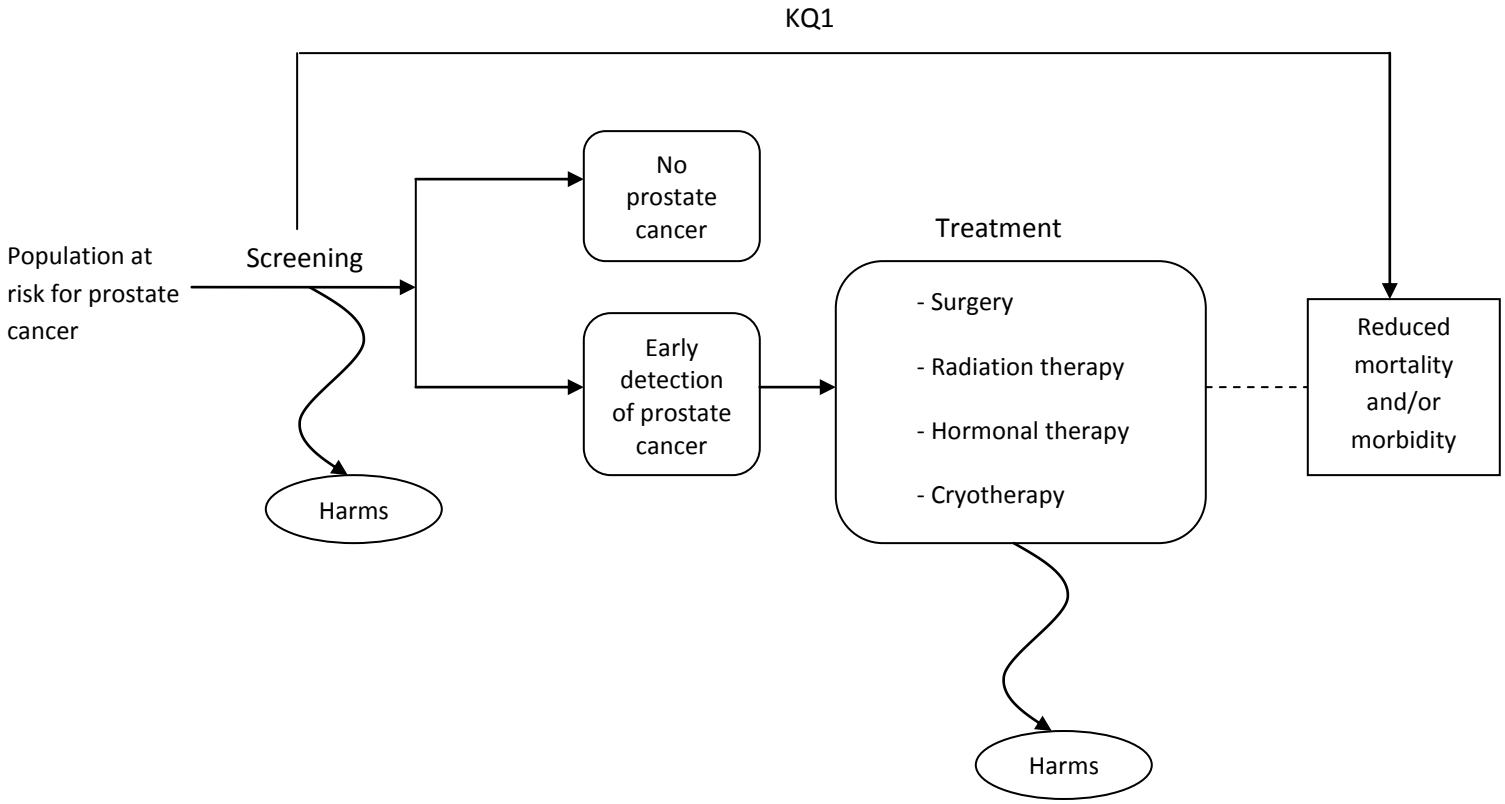
Figure 1. Analytic Framework and Key Questions

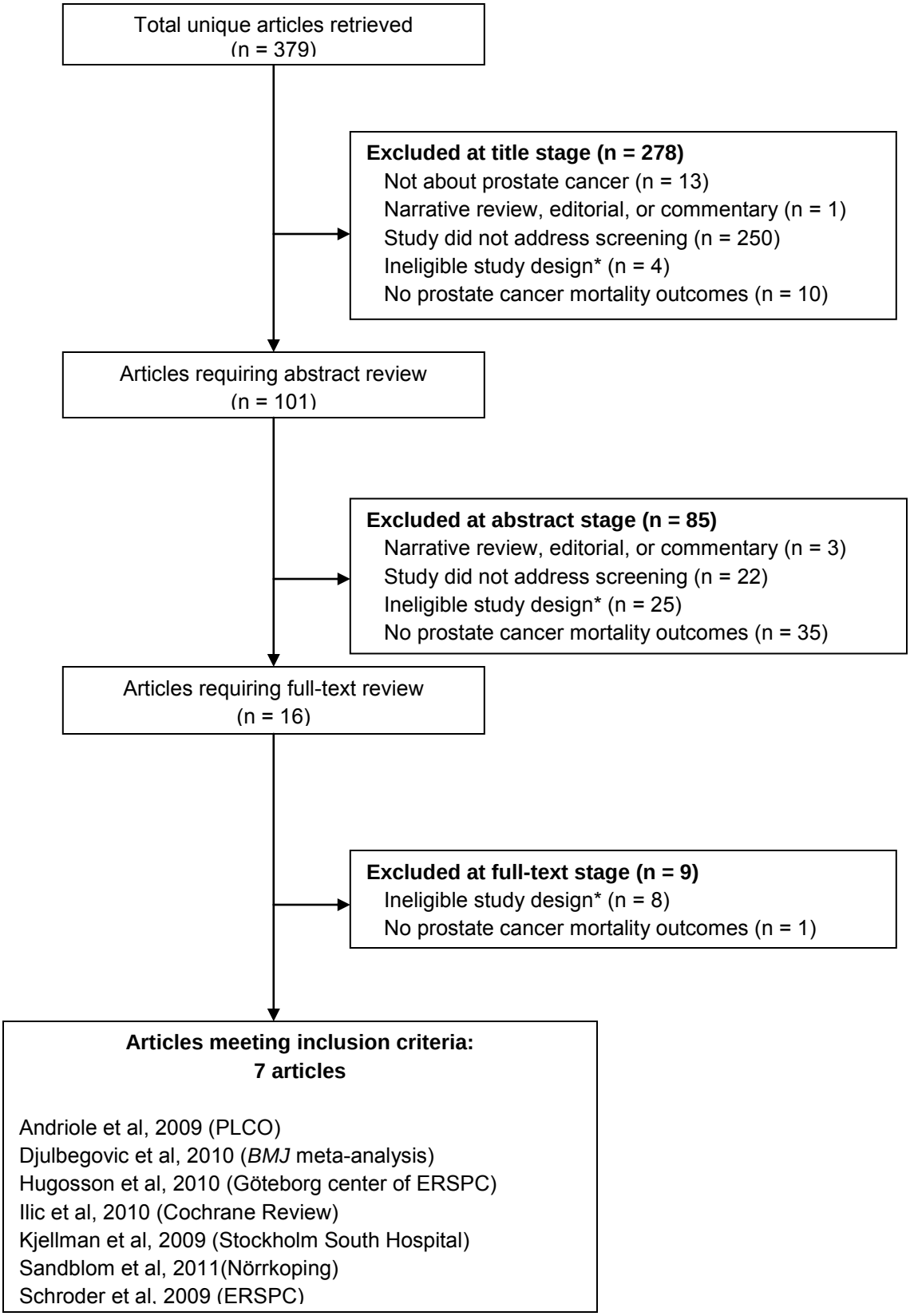


Key Questions

1) What is the direct evidence that screening for prostate cancer with prostate-specific antigen (PSA), as a single-threshold test or as a function of multiple tests over time, decreases morbidity and/or mortality?

2) What are the harms of PSA-based screening for prostate cancer?

Figure 2. Literature Flow Diagram



* Study was not an RCT, systematic review, or meta-analysis, or was a nonrandomized analysis of an RCT.

Table 1. Randomized, Controlled Trials of Prostate Cancer Screening With Mortality Outcomes

Trial	Study Population	Study Population Description	Intervention	Median/ Maximum Length of Followup (Years)	Results	Limitations	Quality Rating	Comments
Quebec Labrie et al 2004 (17)	Men registered on the Quebec City area electoral rolls in 1988	46,486 men aged 45-80 years 31,133 men invited for screening; 23.6% received screening 15,353 controls not invited; 7.3% received screening	DRE + PSA at first visit PSA alone at subsequent screens PSA cut-off point >3.0 ng/mL; if PSA previously >3.0 ng/mL, a PSA increase of 20% over previous year value or over predicted PSA (prPSA) Positive screening test led to TRUS-guided biopsy	7.9/11	No difference in prostate-cancer specific mortality when data are analyzed via intention-to-screen: RR, 1.01 (95% CI, 0.82-1.40)	No information to assess adequacy of randomization Unclear if outcome assessment was blinded No baseline sociodemographic comparison of the two groups Inadequate reporting of attrition Authors did not primarily use intention-to-screen analysis	Poor	Trial included in the 2008 evidence review and previously considered by the USPSTF
Nörrkoping Sandblom et al 2004 (18) 2011 (13)	Male residents of Nörrkoping, Sweden identified in the Swedish National Population Register in 1987	9,026 men aged 50-69 years 1,494 men (every 6th man) invited for screening; 70%-78% received screening, depending on year 7,532 controls received usual care; unknown how many received screening	DRE only in 1987 and 1990 DRE + PSA in 1993 and 1996 PSA cut-off point >4.0 ng/mL Positive screening test led to biopsy; confirmed prostate cancer treated according to regional standardized management program	6.3/20	No difference in prostate-cancer specific mortality (RR, 1.16 [95% CI, 0.78-1.73]) or overall survival (log rank test, p=0.14) between invited and non-invited groups	Inadequate randomization and allocation concealment procedures (predictable group assignment) No baseline sociodemographic comparison of the two groups Contamination rate in control group not assessed Inadequate reporting of attrition	Poor	Trial included in the 2008 evidence review and previously considered by the USPSTF; extended followup now available Trial (and sample size/power calculation) originally designed to assess acceptance and feasibility of prostate cancer screening program, not prostate cancer mortality

Table 1. Randomized, Controlled Trials of Prostate Cancer Screening With Mortality Outcomes

Trial	Study Population	Study Population Description	Intervention	Median/ Maximum Length of Followup (Years)	Results	Limitations	Quality Rating	Comments
Stockholm Kjellman et al 2009 (12)	Men living in the catchment area of Stockholm South Hospital in Sweden in 1988	26,602/27,204* men aged 55-70 years 2,400* men invited for screening, 74% received screening 24,202/24,804* controls from source population received usual care; contamination not reported	Single screening with DRE, TRUS, and PSA Abnormal DRE or TRUS led to biopsy PSA cut-off point >7.0 ng/mL led to repeat TRUS PSA cut-off point >10.0 ng/mL led to biopsy Treatment was "the standard care at the clinic at that time"	12.9/15.7	No difference in prostate cancer mortality: IRR, 1.10 (95% CI, 0.83-1.46) No difference in death from other causes: IRR, 0.98 (95% CI, 0.92-1.05)	Methods of randomization and allocation concealment unclear Unclear if outcome assessment was blinded No baseline sociodemographic comparison of the two groups Contamination rates in control group not assessed Inadequate reporting of attrition Limited applicability to current U.S. practice (high PSA threshold)	Poor	Report has internal discrepancies about the total number of participants because the file containing the registration numbers of the original cohort could not be retrieved
PLCO Andriole et al 2009 (6)	Men enrolled at 10 study centers in the United States from 1993-2001	76,693 men aged 55-74 years 38,343 men assigned to screening; overall compliance with screening was 85% for PSA and 86% for DRE 38,350 men assigned to usual care; 52% had at least one PSA during trial	Annual PSA for 6 years Annual DRE for 4 years PSA cut-off point >4.0 ng/mL Positive PSA or DRE referred to patient's primary care physician for management	11.5/14.8	No difference in prostate cancer-specific mortality at 7 or 10 years: rate ratios, 1.13 (95% CI, 0.75-1.70) and 1.11 (95% CI, 0.83-1.50), respectively No difference in overall mortality (excluding prostate, lung, or colorectal cancer) at 7 or 10 years: rate ratios, 0.98 (95% CI, 0.92-1.03) and 0.97 (95% CI, 0.93-1.01), respectively	High rate of contamination in control arm (up to 52% by 6 years) Approximately 44% of men in each arm had undergone one or more PSA tests prior to trial entry	Fair	

Table 1. Randomized, Controlled Trials of Prostate Cancer Screening With Mortality Outcomes

Trial	Study Population	Study Population Description	Intervention	Median/ Maximum Length of Followup (Years)	Results	Limitations	Quality Rating	Comments
ERSPC Schroder et al 2009 (7)	Men in 7 European countries enrolled from 1991-2003	182,160 men aged 50-74 years; 162,387 men in prespecified "core" subgroup of 55-69 years 82,816 men assigned to screening; 82% had at least one PSA test during trial 99,184 men assigned to the control group; based on single site, screening in controls estimated at ~20%	Variable by center; see Appendix 2 for details Most centers performed PSA every 4 years; some also utilized DRE or TRUS PSA cut-off points ranged from 2.5 to 10.0 ng/mL; 3.0 ng/mL most often utilized, some ancillary testing with lower PSA values Positive screen led to biopsy; treatments according to local policies and guidelines	9/14.5	No difference in prostate cancer-specific mortality in all enrolled men: RR, 0.85 (95% CI, 0.73-1.00) Reduced prostate cancer-specific mortality in "core" subgroup: ARR, 0.071%; RR, 0.80 (95% CI, 0.65-0.98); NNS=1,410;NNT=48	Inconsistencies in screening intervals and PSA cut-off points among study centers Method of allocation concealment not described Differences in exclusion of men by age between centers Exclusion of data from 2 study centers (Portugal and France, which would bring the number of participating countries to 9) Inadequate reporting of attrition	Fair	
Substudy of ERSPC: Göteborg Hugosson et al 2010 (16)	Men born between 1930 and 1944 identified from the population register of Göteborg, Sweden in December 1994	19,904 men aged 50-64 years 9,952 invited to screening; 76% had at least one PSA 9,952 controls not invited to screening; contamination rate estimated at 3%	PSA every 2 years for 7 rounds PSA cut-off point ranged from 2.5 to 3.0 ng/mL, depending on year Positive screen led to DRE, TRUS, and biopsy Treatment was at the discretion of the participant's personal physician	14/14	Reduced prostate cancer-specific mortality: ARR, 0.40% (95% CI, 0.17 -0.64); RR, 0.56 (95% CI, 0.39-0.82); NNS=293 (95% CI, 177-799); NNT=12	60% of participants (men born between 1930 and 1939) previously included in overall ERSPC results No baseline demographic comparison of the two groups Inadequate reporting of attrition Contamination rate in controls not formally assessed; unclear how 3% estimate was obtained	Fair	This publication represents single center results reported separately from the overarching ERSPC trial

* Report has internal discrepancies about this number, because the file containing the registration numbers of the original cohort could not be retrieved.

Abbreviations: DRE=digital rectal examination; PSA=prostate-specific antigen; TRUS=transrectal ultrasonography; RR=relative risk; CI=confidence interval ; ARR=absolute risk reduction; NNS=number needed to screen; NNT=number needed to treat; IRR=incidence rate ratio.

Appendix 1. Literature Search Strategy

Database: PubMed

1. Prostatic Neoplasms[Mesh]
2. Screening OR prostate-specific antigen[Mesh]
3. Early diagnosis[Mesh]
4. PSA velocity[All Fields]
5. Prostate specific antigen velocity[Title/Abstract]
6. PSA doubling time[Title/Abstract]
7. Prostate specific antigen doubling[Title/Abstract]
8. 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. 1 AND 8
10. Limit 9 to English[lang] AND Randomized Controlled Trial[ptyp] AND Publication Date from 2007/01/01 to 2011/07/01

Appendix 2. USPSTF Quality Rating Criteria

Randomized Controlled Trials and Cohort Studies

- Initial assembly of comparable groups:
  -for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of the interventions
- All important outcomes considered

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: If any of all of the following problems occur: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: If any of the following major limitations exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Systematic Reviews

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews.

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Appendix 3. Quality Ratings of Randomized, Controlled Trials of Screening

Trial Author Year	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline	Maintain Comparable Groups	Eligibility Criteria Specified	Outcome Assessors Masked	Care Provider Masked	Patient Masked	Reporting of Attrition, Crossovers, Adherence, Compliance	Differential/ High Loss to Followup	ITT Analysis	Post-randomization Exclusions	Outcomes Prespecified	Quality Rating
Quebec Labrie et al 2004 (17)	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	Incomplete	Differential: Unclear High overall: Unclear	No	Unclear	Yes	Poor
Nörrkoping Sandblom et al 2004 (18), 2011 (13)	No	No	Unclear	Unclear	Yes	Unclear	No	No	Incomplete	Differential: No High overall: No	Yes	Unclear	Yes	Poor
Stockholm Kjellman et al 2009 (12)	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	No	Differential: Unclear High overall: Unclear	Yes	Unclear	Yes	Poor
PLCO Andriole et al 2009 (6)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Differential: No High overall: No	Yes	No	Yes	Fair
ERSPC Schroder et al 2009 (7)	Yes	Unclear	Yes	Unclear	Yes	Yes	No	No	Incomplete	Differential: Unclear High overall: Unclear	Yes	Unclear	Yes	Fair
Substudy of ERSPC: Göteborg Hugosson et al 2011 (16)	Yes	Yes	Unclear	Unclear	Yes	Yes	No	No	Incomplete	Differential: Unclear High overall: Unclear	Yes	Yes	Yes	Fair

Appendix 4. ERSPC Protocol Differences By Study Center*

Variable	Study Center						
	Belgium	**The Netherlands**	**Sweden**	**Finland**	**Spain**	**Italy**	**Switzerland**
Randomization procedures	Randomization after consent	Randomization after consent	Randomization before consent	Randomization before consent	Randomization after consent	Randomization before consent	Randomization after consent
Period of randomization	6/91 – 12/03	11/93 – 3/00	12/94	1/96 – 1/99	2/96 – 6/99	10/96 – 10/00	9/98 –8/03
Age eligibility (years, at study entry)	55–74	55–74	50–69	Recruited at 55, 59, 63, 67, screened until 71	55–74	55–74	55–69 with screening until 75
Screening interval (years)	4–7	4	2	4	4	4	4
PSA cut-off point (ng/mL)	1991–1994: 10.0 1995–1997: 4.0	1993–1997: 4.0 1997+: 3.0	1995–1998: 3.0 1999+: 2.5	4.0 prompted biopsy 3.0–3.9 prompted DRE and, after 1999, calculation of free PSA: total PSA ratio, with biopsy if either positive	3.0	4.0 prompted biopsy 2.5–3.9 prompted DRE and TRUS	3.0
Screening procedure	1991–1997: DRE + TRUS + PSA (cut-off point, 4.0 ng/mL) 1997+: PSA only	1991–1997: DRE + TRUS + PSA (cut-off point, 4.0 ng/mL) 1997+: PSA only	PSA alone	PSA alone, unless result was 3.0–3.9 ng/mL (see above)	PSA alone	PSA alone, unless result was 2.5–3.9 ng/mL (see above)	PSA alone

* Excludes two centers, Portugal and France, as results from these centers were not included in the 2009 ERSPC publication.

Abbreviations: PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasonography.

Model Assumptions

1. Mortality due to cancer after 7 years is the primary endpoint.

2. All of the information that is necessary to model the correct ratio of the screened group's prostate cancer mortality rate to the control group's prostate cancer mortality rate is in the PLCO trial. Key parameters reported in this trial:
   a. Prostate cancer mortality rate in the screened arm: 2.0 prostate cancer deaths per 10,000 person-years
   b. Prostate cancer mortality rate in the control arm: 1.7 prostate cancer deaths per 10,000 person-years
   c. Prostate cancer mortality rate ratio: 1.13 (95% CI, 0.75–1.70)
   d. Compliance rate in the screened arm: 85%
   e. Contamination rate in the controlled arm: varied by trial year; range, 40%–52%

3. There is a true underlying prostate cancer mortality rate per 10,000 person-years in a completely screened group, denoted as "x."

4. There is a true underlying prostate cancer mortality rate per 10,000 person-years in a completely unscreened group, denoted as "y."

5. Adjusting for compliance in the screened arm: the reported compliance implies that the rate of 2.0 prostate cancer deaths per 10,000 person-years is $0.85x + 0.15y$.

6. Adjusting for contamination in the control arm:
   a. To calculate the effect of the lowest rate of contamination: the 40% contamination rate in the control group implies that the observed rate of 1.7 deaths per 10,000 person-years is $0.4x + 0.6y$.
   b. To calculate the effect of the highest rate of contamination: the 52% contamination rate in the control group implies that the observed rate of 1.7 deaths per 10,000 person-years is $0.52x + 0.48y$.

7. Estimating the lower bound of the confidence interval after adjustment: the lower confidence interval bound of 0.75 for the observed prostate cancer mortality rate ratio of 1.13 gives a lower width of 0.38 (1.13–0.75 = 0.38). Due to the large sample size of this trial, it is assumed that the maximum increase in the confidence interval lower width would be no greater than 20%. Therefore, under this assumption, the lower confidence interval bound will not be more than 0.46 (0.38 x 0.2 = 0.076; 0.38 + 0.076 = 0.46) below the modeled ratio.

Calculation of Adjusted Prostate Cancer Mortality Estimate and Lower Confidence Interval Bound

- Given the lowest rate of contamination (40%):
  - The system of linear equations to solve is: $0.85x + 0.15y = 2.0$ and $0.40x + 0.60y = 1.7$
  - Solving for these equations gives $x = 2.10$ and $y = 1.43$

  - **The adjusted prostate cancer mortality rate ratio is x/y, or 2.10/1.43 = 1.47**
  - The estimated lower confidence bound (see assumption #7) is 1.47 − 0.46 = 1.01

- Given the highest rate of contamination (52%):
  - The system of linear equations to solve is: 0.85x + 0.15y = 2.0 and 0.52x + 0.48y = 1.7.
  - Solving for these equations gives x = 2.13 and y = 1.24
  - **The adjusted prostate cancer mortality rate ratio is x/y, or 2.13/1.24 = 1.72**
  - The estimated lower confidence bound (see assumption #7) is 1.72 − 0.46 = 1.26

Appendix 6. Excluded Studies

Aggarwal R, Weinberg V, Small EJ, et al. The mechanism of action of estrogen in castration-resistant prostate cancer: clues from hormone levels. *Clin Genitourin Cancer*. 2009;7(3):E71-6.

Ahmad IU, Forman JD, Sarkar FH, et al. Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer. *Nutr Cancer*. 2010;62(7):996-1000.

Akaza H, Kanetake H, Tsukamoto T, et al. Efficacy and safety of dutasteride on prostate cancer risk reduction in Asian men: the results from the REDUCE study. *Jpn J Clin Oncol*. 2011;41(3):417-23.

Akaza H, Hinotsu S, Usami M, et al. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. *Cancer*. 2009;115(15):3437-45.

Aktoz T, Kaplan M, Turan U, et al. "Multimodal" approach to management of prostate biopsy pain and effects on sexual function: efficacy of levobupivacaine adjuvant to diclofenac sodium—a prospective randomized trial. *Andrologia*. 2009;42(1):35-40.

Alexander A, Crook J, Jones S, et al. Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? An analysis of the 3- versus 8-month randomized trial. *Int J Radiat Oncol Biol Phys*. 2010;76(1):23-30.

Algotar AM, Thompson PA, Ranger-Moore J, et al. Effect of aspirin, other NSAIDs, and statins on PSA and PSA velocity. *Prostate*. 2010;70(8):883-8.

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Andriole GL, Bostwick D, Brawley OW, et al. The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study. *J Urol*. 2011;185:126-31.

Appendix 6. Excluded Studies

Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192-202.

Aragon-Ching JB, Gillespie J, Price DK, et al. Lack of prognostic significance of prostate biopsies in metastatic androgen independent prostate cancer. *BJU Int*. 2007;100(6):1245-8.

Arai Y, Akaza H, Deguchi T, et al. Evaluation of quality of life in patients with previously untreated advanced prostate cancer receiving maximum androgen blockade therapy or LHRHa monotherapy: a multicenter, randomized, double-blind, comparative study. *J Cancer Res Clin Oncol*. 2008;134(12):1385-96.

Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010;78(1):11-8.

Arcangeli G, Strigari L, Arcangeli S, et al. Retrospective comparison of external beam radiotherapy and radical prostatectomy in high-risk, clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(4):975-82.

Armstrong AJ, Creel P, Turnbull J, et al. A phase I-II study of docetaxel and atrasentan in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res*. 2008;14(19):6270-6.

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Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res*. 2007;13(21):6396-403.

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