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Prostate-Specific Antigen (PSA)–Based Population Screening for Prostate Cancer: An Evidence-Based Analysis

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ABSTRACT

Background
Prostate cancer (PC) is the most commonly diagnosed non-cutaneous cancer in men and their second or third leading cause of cancer death. Prostate-specific antigen (PSA) testing for PC has been in common practice for more than 20 years.

Objectives
A systematic review of the scientific literature was conducted to determine the effectiveness of PSA-based population screening programs for PC to inform policy decisions in a publicly funded health care system.

Data Sources
A systematic review of bibliographic databases was performed for systematic reviews or randomized controlled trials (RCT) of PSA-based population screening programs for PC.

Review Methods
A broad search strategy was employed to identify studies reporting on key outcomes of PC mortality and all-cause mortality.

Results
The search identified 5 systematic reviews and 6 RCTs. None of the systematic reviews found a statistically significant reduction in relative risk (RR) of PC mortality or overall mortality with PSA-based screening. PC mortality reductions were found to vary by country, by screening program, and by age of men at study entry. The European Randomized Study of Screening for Prostate Cancer found a statistically significant reduction in RR in PC mortality at 11-year follow-up (0.79; 95% CI, 0.67–0.92), although the absolute risk reduction was small (1.0/10,000 person-years). However, the primary treatment for PCs differed significantly between countries and between trial arms. The American Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) found a statistically non-significant increase in RR for PC mortality with 13-year follow-up (1.09; 95% CI, 0.87–1.36). The degree of opportunistic screening in the control arm of the PLCO trial, however, was high. None of the RCTs found a reduction in all-cause mortality and all found a statistically significant increase in the detection of mainly low-risk, organ-confined PCs in the screening arm.

Conclusions
There was no evidence of a PC mortality reduction in the American PLCO trial, which investigated a screening program in a setting where opportunistic screening was already common practice. Given that opportunistic PSA screening practices in Canada are similar, it is unlikely that the introduction of a formal PSA screening program would reduce PC mortality.

PLAIN LANGUAGE SUMMARY

The prostate-specific antigen (PSA) blood test is a widely used test for prostate cancer, the most common non-skin cancer among men in Canada. In cases where prostate cancer progresses, it can decrease a man's quality of life or cause death. However, most of these cancers grow slowly and have a good prognosis, even without treatment. To inform public policy on whether to screen the general population of men for prostate cancer, Health Quality Ontario conducted a systematic review of published research on the effectiveness of population-based screening programs using the PSA test.

We reviewed 11 studies (5 systematic reviews and 6 randomized controlled trials). None of the systematic reviews found that PSA screening programs significantly reduced deaths from prostate cancer or led to reduced mortality overall. The evidence from large randomized controlled trials in Europe and North America was mixed: PSA screening was associated with a reduction in prostate cancer mortality in some European countries but not in the United States. The trials are not directly comparable because of major differences in the way men were screened, diagnosed, and treated. All of the trials, however, detected significantly greater numbers of low-risk prostate cancers in men who were screened, compared to the control groups, but their risk of dying from prostate cancer over 10 years was low and they were much more likely to die from other causes. Given that PSA testing for early detection of prostate cancer is already fairly widespread in Canada, as it is in the United States, it is unlikely that introducing a formal screening program for the general population of average-risk men would reduce mortality from prostate cancer.

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LIST OF ABBREVIATIONS

CI	Confidence interval(s)
DRE	Digital rectal exam
ERSPC	European Randomized Study of Screening for Prostate Cancer
FN	False-negative
FP	False-positive
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GS	Gleason score
PC	Prostate cancer
PIN	Prostate intraepithelial neoplasia
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PSA	Prostate-specific antigen
P-YR	Person-year(s)
RCT	Randomized controlled trial
RR	Relative risk
TRUS	Transrectal ultrasound
USPSTF	U.S. Preventive Services Task Force

BACKGROUND

Objective of Analysis

This analysis was designed to evaluate the efficacy of prostate-specific antigen (PSA)-based population screening programs in asymptomatic males of average risk to reduce prostate cancer mortality or overall mortality, increase detection of prostate cancer, or decrease rates of aggressive or metastatic cancers.

Clinical Need and Target Population

Prevalence and Incidence

Worldwide, prostate cancer (PC) is the most commonly diagnosed non-cutaneous (non-skin) cancer in men (1) and their second or third most common cause of cancer-related deaths. (2) Reported rates of PC vary widely across countries, reflecting differences in detection or diagnostic practices, treatments, and lifestyle and genetic factors. (3) Between 2000 and 2004, age-standardized incidence rates of PC per 100,000 population, ranged from high rates in North America (United States, 118.2; Canada, 96.6) to lower rates in western Europe (France, 88.8; Switzerland, 85.8; Netherlands, 61.7), northern Europe (Sweden, 97.0; Denmark 47.7) and southern Europe (Spain 45.6). The lowest rates for PC incidence were reported for countries in Asia (Japan, 15.1; China, 12.0; Korea, 9.5; Thailand 4.4). (3)

The prevalence of cancer is a function of incidence and survival. For prostate cancer, increasing detection of cancers and the overall high survival rates, along with an aging population, have led to increasing prevalence. In Canada, the incidence of PC has been gradually increasing. The age-standardized incidence rate was 53.8/100,000 in 1970 and 124.7 in 2007. (4) Over the same period, incidence of PC grew much more than it did for lung cancers (increase from 59.3 to 67.8/100,000) or colorectal cancers (47.8 to 60.4/100,000) in men. In Ontario, the age-standardized incidence of PC in 2012 was 121/100,000; in 2007, the 9,300 incident cases diagnosed were 28% of all the incident male cancers. (5)

The relative survival rates in Canada for PCs diagnosed between 2004 and 2006 (5-year, 96%; 10-year, 95%) are the highest survival rates for any cancers. (6) Similarly, the age-standardized mortality rate for PC in Ontario in 2009 was relatively low, at 19/100,000 (compared to 185/100,000 for all cancers), and the PC deaths in Ontario represented 10.2% (1,400/13,700) of all the male cancer deaths. (5)

As a result of these trends, period prevalence rates for PC in Canada have increased dramatically, with a 2-year (2007–2008) period prevalence of 280.4/100,000, a 5-year (2004–2008) period prevalence of 610.0/100,000, and a 10-year (1999–2008) period prevalence of 1,016.2/100,000. The prevalence rates for the same periods were also dramatically higher for PC than they were for the next most common cancers in men: lung cancer (53.4, 81.1, and 106.7/100,000) and colorectal cancer (104.5, 211.2, and 325.6). (6) The 10-year prevalence rate for prostate cancer represents 42% (176,361/422,914) of the total cancer prevalence burden in Canada.

Disease Natural History

Prostate cancer is a heterogeneous disease with a variable natural history ranging from low-risk tumours unlikely to threaten the quality or length of men's lives to highly aggressive forms. (7) The etiology of PC, however, is largely unknown, and established risk factors—older age,

ethnicity, and family history— explain only a fraction of variation in disease occurrence. (8) Androgens are known to be essential to PC growth, although it is not known if high androgen levels initiate the cancer. (4)

The natural history of early localized PC (cancer confined to the prostate) has been examined in several longitudinal cohort studies, 2 in the United States (9;10) and 1 (11) in Sweden. The first American study, by Albertsen et al, (9) was designed to estimate the risk, for younger men, of dying from PC or competing causes, given the histology of their cancer. The cohort included 767 patients with localized PC, although accurate staging information was unavailable for many patients (bone scans for only 30%). After 15 years of follow-up, few men who had low-grade tumours, with histology Gleason scores (GS) of 2 to 4 at any age at diagnosis, died from PC, although men at increasing ages died from other causes. However, men who had high-grade tumours (GS 8–10), although these occurred infrequently, faced a high risk of PC mortality at any age of diagnosis: 87% for ages 55 to 59 years, 81% for ages 60 to 64 years, 72% for ages 65 to 69 years, and 60% for ages 70 to 74 years. With 20-year follow-up, the PC mortality rate (deaths/1,000 person-years [P-YRs]) remained low for low-grade tumours (6; 95% confidence interval [CI], 2–11) and high for high-grade tumours (121; 95% CI; 90–156). (12)

The second American cohort study, by Lu-Yao et al, (10) included 14,516 men older than 65 years (median age, 78 years) diagnosed between 1992 and 2002 with localized PC (T1 or T2managed conservatively. During the 10-year follow-up, of the 222 patients whose cancer was diagnosed as low risk (GS 2–4), 15 died from PC (8.3%; 95% CI, 4.2–12.8) and 133 died of other causes. The 10-year PC mortality rate for men with intermediate-risk tumours (GS 5–7; n = 10,988) and with high-risk tumours (GS 8–10; n = 3,306) was 9.1% (95% CI, 8.3–10.1) and 25.6% (95% CI, 23.7–28.3), respectively.

The Swedish cohort study by Johansson et al has reported the longest PC natural history experience, with follow-up for 642 PC patients (mean age, 72 years), 300 with localized disease (T1 or T2) at 15 years (11), 21 years, (13) and more than 30 years. (14) During the 21-year follow-up of men with local disease treated conservatively, 40% (89/223) experienced disease progression through the capsule, and, of these, 39 men (17% of cohort) developed generalized disease. The majority of the cohort (91%; 203/223) had died during follow-up, with PC considered the cause of death in 35 men (16% of the cohort). The rate of metastatic disease progression, averaged over 15 years, was 18/1,000 P-YRs and the PC mortality rate was 15/1,000 P-YRs.

Also in the Swedish study, the causes of death from PC and other conditions were related in opposite ways to increasing age and tumour grade. With increasing age (< 61, 61–70, 71–80, and ≥ 81 years), PC mortality risk decreased (23%, 22%, 12%, 4%, respectively) and mortality from other causes increased (23%, 69%, 82%, 96%, respectively). With increasing tumour grade (grade 1 [GS 2–4], grade 2 [GS 5–7], grade 3 [GS 8–10]), PC mortality increased (9%, 24%, 56%, respectively) and mortality from other causes decreased (80%, 70%, 44%, respectively). The relative risk (RR) of PC mortality for those with GS 5–7 tumours, compared to GS 2–4 tumours, was 3.4 (95% CI, 1.6–7.3) and the RR for PC mortality for those with GS 8–10 tumours was 46.6 (95% CI, 12.3–177.4).

Autopsy studies in men who have died from causes other than prostate cancer have yielded useful perspectives on the biology of prostate cancer. The incidence of latent prostate cancer—undiagnosed PC in men who have died from other causes—has been reported in autopsy studies since the 1950s. (15) The studies varied in terms of their subject selection, tissue preparation, and degree of examination and were usually performed for a particular region.

They uniformly showed, however, that the prevalence of latent PC at biopsy was much higher than expected from the known PC incidence and mortality rates.

A multinational collaborative study from 7 different geographical regions, conducted by the International Agency for Research on Cancer, was one of the most detailed autopsy investigations on latent PC. (16) In general, the frequency of latent PC was approximately 20% for all males over age 44 years and was not evenly distributed across age or geographic regions. There was a steady increase of latent carcinoma in the prostate with advancing age, increasing roughly 4-fold over 4 decades, from approximately 10% at age 50 to 40% at age 80. Geographic variation was also noted, with the lowest frequency of latent PC in Singapore and the highest in Sweden, similar to the ranking of PC incidence and mortality of the countries included in the study.

In another autopsy series, the occurrence of prostate intraepithelial neoplasia (PIN) along with PC was evaluated in a series representative of a white Mediterranean population. (17) PIN, particularly high-grade neoplasia, is of interest as it is generally considered a precursor to PC because of their epidemiological and morphological similarities. High-grade PIN, like carcinoma, was frequently diagnosed in the autopsy prostate specimens; 29% (42/146) occurred equally as unifocal or multifocal disease. High-grade PIN occurred in an isolated form in 21 prostates and in association with PC in 21 prostates and was more commonly diagnosed than PC in all age groups. The occurrence of high-grade PIN, similar to PC, increased steadily with age, from 7% in 20- to 29-year-olds to 48% in 70- to 80-year-olds.

Technology/Technique

Prostate-specific antigen (PSA) is a widely used tumour marker. Although normal prostate cells can express PSA, PC tissue releases approximately 10 times more PSA into serum than normal or benign prostatic hyperplasia tissue. (18) The release of PSA is thought to be related to the disruption of normal prostatic membranes occurring in PC. There is biological variation of PSA in the general population and no PSA value excludes the possibility of PC detection at biopsy. (19) A total serum PSA level of 4.0 ng/ml is often considered the upper limit of normal and frequently used as the threshold for referral for further investigation and biopsy.

An estimate of the PC prevalence in men with PSA values less than 4.0 ng/ml was generated in the Prostate Cancer Prevention Trial. (19) Men who were in the control group—and who never had a PSA value of 4.0 ng/ml or greater, or had an abnormal digital rectal examination (DRE), or underwent prostate biopsy or transurethral resection of the prostate during follow-up—were biopsied at the end of the 7-year follow-up. Fifteen percent of the men (449/2,950), all with total serum PSA less than 4.0 ng/ml, were found to have PC at biopsy. In this cohort, the risk of PC was also found to increase with increasing PSA level, from 6.6% for PSA values of 0.5 ng/ml or less to 26.9% for PSA levels between 3.1 and 4.0 ng/ml.

Screening Programs

Population-based screening programs aim to reduce disease-specific mortality and/or morbidity by identifying disease at an earlier stage where it is more likely to be curable. (20) In addition to these outcomes is a requirement that the benefits of the program outweigh the costs and adverse effects of early detection. The criteria for an effective screening program are well established and have been formally documented in the World Health Organization's screening guidelines. (20)

According to these criteria, the success or effectiveness of screening depends on the inter-relationships of the disease experience of the target population, characteristics of the screening program, and the effectiveness of the diagnosis and treatment. (21) The disease should occur commonly or have a significant morbidity or mortality impact on the population. It should have a long preclinical phase, as diseases that progress rapidly would be less likely to be detected at screening and more likely to occur within screening intervals. This need for a long preclinical phase is the reason that the latent periods or lead- and length-time biases be taken into account when evaluating screening programs. Screen-detected cases must account for a substantial proportion of disability or death from disease. With prostate cancer, it is not entirely clear to what extent the early forms of the disease progress to or are associated with high-risk or potentially lethal disease.

In addition to diagnostic efficacy, screening programs require that early treatment be effective to reduce mortality. The management of PC has been changing over time, and optimal therapeutic approaches for the various stages of the disease are far from certain. (22) At least 3 major randomized controlled trials (RCT) are being conducted worldwide, in which screen-detected PCs are being randomized to different treatment options, including active surveillance. These trials are the Prostate Testing for Cancer and Treatment (ProtecT) study in the United Kingdom, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) in the United States, and the Active Surveillance Therapy Against Radical Treatment (START) for Favourable Risk Prostate Cancer trial in Canada, United States, and United Kingdom. (22-24)

Regulatory Status

The PSA test was approved for PC diagnosis and surveillance in Canada in 2008. No province in Canada has a population-based PSA screening program for PC. In Ontario, PSA testing through a hospital or community laboratory service is covered by the provincial health care plan under several conditions: when a man has been diagnosed with PC and is either receiving treatment or is being followed after treatment for the disease, or when a physician suspects PC because of a man's history and/or the results of his physical examination (including digital rectal examination).

In men without symptoms, the provincial health plan does not pay for PSA testing. A man can have the PSA blood test if he is willing to pay for it himself. However, professional societies recommend that this decision be made only after discussion with his physician. The PSA test costs approximately $30.

No home-based PSA test kits are licensed in Canada. France recently banned home-based kits that had been previously licensed in that country. (25) The regulatory change for the kits was motivated by concerns about the lack of informed discussion or guidance from a physician on the interpretation of test results and possible choices arising from them.

PSA Testing

The degree of PSA testing in men who have not been diagnosed with PC was evaluated from the 2000–2001 Canadian Community Health Survey, a cross-sectional self-report survey. (26) The lifetime prevalence of PSA testing (the proportion ever having had a test) among men older than age 50 years was 47.5% (95% CI, 46.4–48.5) and the majority of them (72%) had received the test recently, within the year prior to the survey. The lifetime (53.1%; 95% CI, 51.1–55.1) and recent (34%; 95% CI, 37.6–41.2) PSA screening prevalence was highest among 60- to 69-year-olds. The self-reported screening history for men in Ontario also increased with age

(18.1% for men age 40–49 years; 46.3% for men age 50–59; 57.4% for men age 60–69; and 51.4% for men age 70 or older).

PSA screening practices in the United States are similar, if not higher, with 50% of men age 65 to 74 years ever having had a PSA test. (27) There has been some suggestion that PSA screening in the United States may have been modified by the U.S. Preventive Services Task Force (USPSTF) 2008 report, which recommended against screening for PC in men age 75 years and older. (28) A review of PSA testing in the United States, using 2006 to 2010 administrative databases, reported unchanged PSA testing rates for men age 75 and older between 2006 and 2007 but found a 7.9% decline between 2009 and 2010, after the 2008 recommendation. (29) Although the use of the PSA test for suspected cancer or for screening could not be differentiated in the study, more than 40% of men age 75 or older continued to receive PSA tests. For men age 65 to 74, however, the proportion receiving PSA testing remained approximately 50% throughout the study period.

Men's perceptions of PSA screening for PC in Ontario were evaluated in a 2012 survey of 74 patients (mean age, 59 years) without a history of PC, attending 2 primary care clinics. (30) The majority (60%) reported ever discussing the PSA test with their family doctor, and 49% reported having had a PSA test in the past 2 years; 66% of those age 51 to 70 years reported having a PSA test. The vast majority of men (95%) did not feel that the PSA test was risky. They also reported that the PSA test was very important to their health (79%) and that the test was good or very good (68%) at preventing death from prostate cancer.

Physicians' attitudes and PSA screening practices were examined in a 2012 survey of Ontario family physicians. (31) Of the responding physicians (13%; 969), 81% reported screening with both PSA and DRE and 7% reported screening only with PSA. Although the majority of physicians (73%) offered screening to men at age 50 years, 17% reported offering screening to men at age 40. The age at which screening was no longer offered was variable; 30% did not offer screening to men older than 70 years and 38% did not offer screening to those over age 80. A small proportion (4%) offered screening to age 90, and 8% offered lifelong screening. Physicians estimated that the majority of their patients (≥ 75%) accepted their screening recommendation. Physicians also agreed or strongly agreed that PSA screening should be routinely offered at age 50 (62%), that the benefits outweigh the risks (54%), and that screening provides a survival benefit (43%). Thirty-seven percent agreed or strongly agreed that screening with DRE also provides a survival benefit.

The widespread use of PSA screening for asymptomatic men has given rise to concerns for several reasons. (32-34) Prostate cancers commonly occur and have a variable natural history ranging from mainly low-risk tumors to highly aggressive forms. (8) In this context, widespread testing can lead to overdiagnosis (the detection of latent or low-risk tumors that might never have been detected or developed to a clinically significant stage). Estimates of overdiagnosis with PSA screening range from 23% to 42%. (35) Treatment of overdiagnosed cases is considered both unnecessary because it does not improve disease outcome and harmful because the radiation or surgical treatments that follow are associated with substantial costs, increased morbidity, and decreased quality of life for men and their families. (32;36;37)

EVIDENCE-BASED ANALYSIS

Research Questions

What is the efficacy of PSA-based population screening programs in asymptomatic males of average risk to reduce prostate-specific cancer mortality or overall mortality, to increase detection of prostate cancer, or to decrease rates of aggressive or metastatic cancers?

Research Methods

Literature Search

Search Strategy

A literature search was performed on September 24, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews, for studies published from January 1, 2008, to September 24, 2013. The search was an update to a previous evidence search conducted by Health Quality Ontario in 2008 involving publications between 2000 and 2007. The details of the current search strategy are provided in Appendix 1. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- Studies published between 2008 and 2013
- Study design, methods, population, and subject characteristics clearly defined
- Effectiveness outcome measures of PSA-based population screening programs (prostate cancer detection, metastatic disease, disease-specific or all-cause mortality)

Exclusion Criteria

- Non-systematic reviews, observational studies, letters, editorials, comments, and case reports or case series
- Duplicate publications
- Non-English language studies
- Animal and in vitro studies
- Studies not examining an outcome of interest
- Subjects not within the population of interest
  - symptomatic patients
  - men with previous prostate cancer diagnosis
  - special populations including patients attending a urology clinic
  - non-screened populations

Outcomes of Interest

- Prostate cancer mortality

- All-cause mortality
- Prostate cancer detection rates

Statistical Analysis

The RCTs of PSA-based population screening programs for PC were conducted in diverse geographic settings with varied screening program objectives, design, and evaluation methods, which precluded any valid pooling of outcomes. Therefore, the major results were summarized and compared between and within the trials.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (38) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual confounding factors. (38) For more detailed information, please refer to the latest series of GRADE articles. (38)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

The database search yielded 2,496 citations published between January 1, 2008, and September 24, 2013 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of reasons that citations were excluded from the analysis.

Eleven reports—5 systematic reviews and 6 RCTs—were included in the review. The reference lists of the included studies and of health technology assessment websites were hand-searched to identify other relevant studies. An additional 12 citations were identified but they represented earlier or additional reports on the original 6 RCTs.

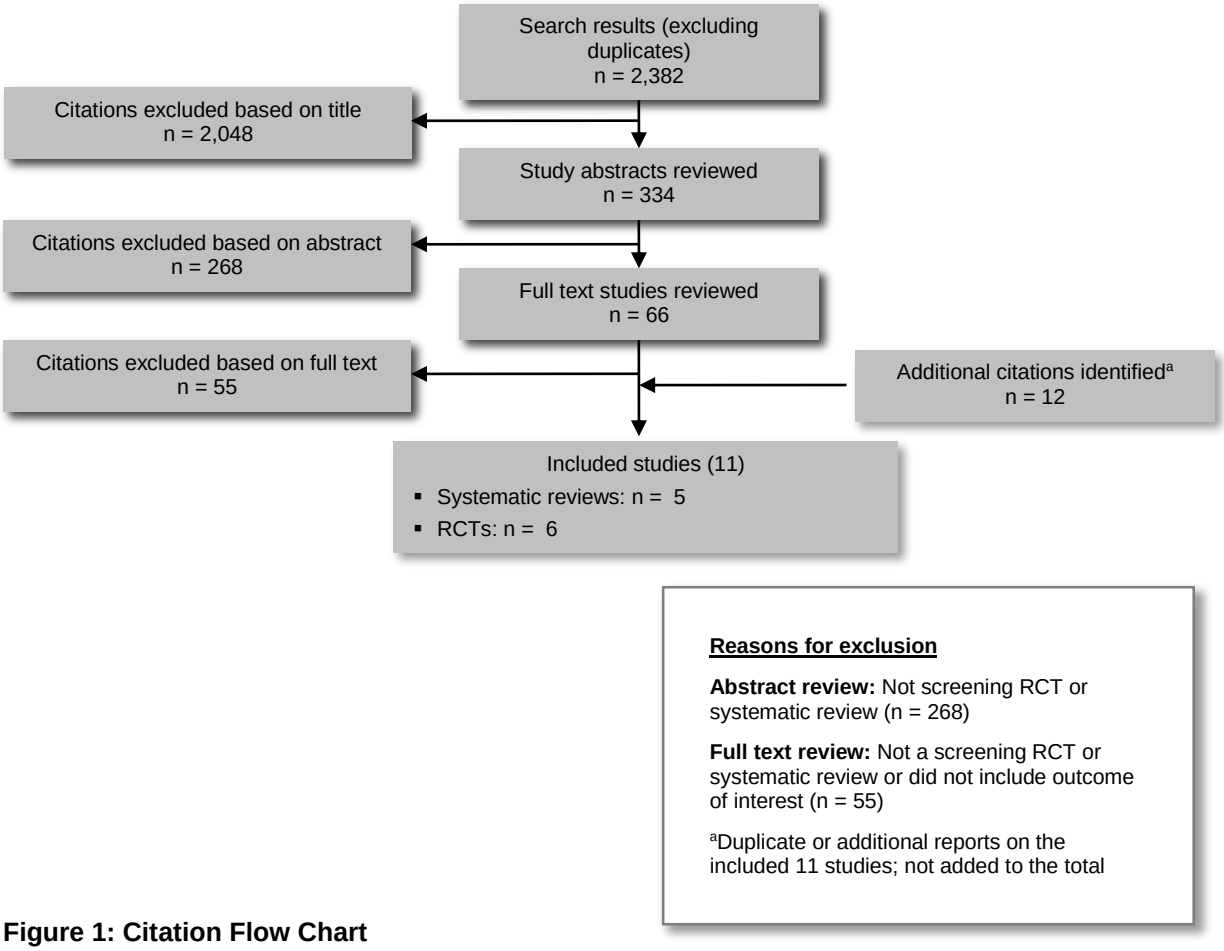

Figure 1: Citation Flow Chart

Abbreviation: RCT, randomized controlled trial.

For each included study, the study design was identified and is summarized in Table 1, a modified version of a hierarchy of study design by Goodman. (39)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCTs	
Systematic review of RCTs	5
Large RCT	6
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**11**

Abbreviation: RCT, randomized controlled trial.

The results are detailed in the following 3 sections: A) Design of Primary RCTs of PSA-Based Population Screening for Prostate Cancer; B) Systematic Reviews of Primary RCTs of PSA Screening for Prostate Cancer; and C) Outcomes in Primary RCTs of PSA Screening for Prostate Cancer.

A) Design of Primary RCTs of PSA-Based Population Screening for Prostate Cancer

Six RCTs on PSA-based screening programs for PC were identified: 2 from North America (40;41) and 4 from Europe. (42-45) These trials are summarized in Table 2 and described below. The North American trials included a Canadian trial from Quebec involving 46,486 randomized men (46) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a large American multistate study of 76,685 randomized men. (40) The European trial, referred to as the European Randomized Study of Screening for Prostate Cancer (ERSPC), included an 8-country multinational PSA screening program of 182,000 randomized men. (45) Three other trials involved PSA screening programs in cities in Sweden: Goteborg, (42) Stockholm, (43) and Norrkoping. (44)

North American RCTs

Quebec RCT

The Quebec trial by Labrie et al, (46) initiated more than 26 years ago, was the first RCT evaluating a PSA-based population screening program for PC and reported primary mortality outcomes with 8 years (46) and 11 years (41) of follow-up. The study involved a random 2 to 1

selection in favour of screening of 46,486 men age 45 to 80 years identified from a population registry. Of the 31,133 men invited for screening, 7,348 (23.6%) accepted and 15,353 were allocated to the control arm.

The screening at the first exam involved PSA and digital rectal exam (DRE). Transrectal ultrasound (TRUS)-guided biopsy was performed at the radiologist's judgment when total serum PSA was greater than 3.0 ng/ml or if serum PSA had increased by 20% or more over the previous year. The frequency and number of screening rounds were defined by the PSA level: 2-year frequency for PSA values 0 to 2.0 ng/ml; 1-year frequency for PSA values of 2.1 to 3.0 ng/ml. The authors reported only on PC mortality. The degree of opportunistic screening in the control group was not reported. Although treatment for the diagnosed cases was reported (42% prostatectomy and 30% radiotherapy), the distribution between study arms was not given. In addition, the 65% (239/367) rate of combined androgen blockade for trial subjects was also not reported by trial arm.

American Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial
The PLCO trial was a 10-state RCT in the United States that recruited 76,693 men, initially age 60 to 74 years; due to low recruitment, eligibility was later lowered to 55 years of age. Long-term primary mortality outcome measures were reported at 7-year, (40) 10-year, (47) and 13-year (48) follow-up. Because of a lack of a population-based registry, the screening centres employed various mechanisms to recruit healthy volunteers, including motor vehicle registries, commercial mailing lists, mass media, and outreach strategies. (49) The trial had a multiphase design for screening for 3 cancers in men (prostate, lung, and colorectal), with a stop-screen approach where screening was stopped at a fixed point of 6 annual screens. (50) A protocol change in April 1999 excluded participants who had 1 or more PSA tests in the prior 3 years.

PSA screening tests were performed at the initial visit and then annually for 6 years. In addition, DRE and chest x-rays were performed at entry and then annually for 4 years. Sigmoidoscopy was also performed at entry and then at the 5-year point. All participants were followed for at least 13 years from randomization. Patients with total serum PSA values of greater than 4 ng/ml or a suspicious DRE were referred to their personal physicians for diagnostic work-up and treatment. The trial did not prescribe protocols for diagnosis or treatment. The trial did have an annual, active follow-up process using a mailed questionnaire. The completeness of mortality assessments was evaluated both by periodic linkage to national death registries and reviews by an independent cause of death review committee.

European RCTs

Norrkoping, Sweden, RCT
The first European RCT of a PSA-based screening program for PC was conducted in 1987 in Norrkoping, Sweden. (44) Men age 50 to 69 years and residing in Norrkoping were eligible and were identified through the national population registry. The total study population was 9,026 men, with every sixth man randomized to the screening arm and the 7,532 remaining men assigned to the control arm. As the study was initiated in 1987, before PSA screening was established, the first 2 screening rounds involved only DRE and the next 2 involved DRE and total serum PSA at 3-year intervals. The primary mortality outcomes were reported at 15 years (44) and 20 years (51) of follow-up.

Stockholm, Sweden, RCT
A second RCT of a PSA-based screening program for PC was initiated in Stockholm in 1988. (43) A population-based sample of men age 55 to 70 years and living in Stockholm was

identified from the population census, and 2,400 men were randomly selected and asked to participate in the screening program. The remaining 24,202 men served as the control population. Participants underwent PSA, DRE, and TRUS investigations, and those with abnormal DRE or TRUS underwent TRUS-guided quadrant biopsy. A repeat biopsy was performed when total serum PSA was greater than 7 ng/ml; for PSA greater than 10 ng/ml, randomized quadrant biopsies were taken. For men not diagnosed with PC, no further surveillance was performed. Mortality outcomes were prospectively followed through the National Cause of Death Registry and the Swedish Cancer Registry and were reported at 12 years of follow-up.

Goteborg, Sweden, RCT

The third Swedish RCT of PSA-based screening programs for PC was initiated in Goteborg in 1995. (42) Using the national population registry, 20,000 of the 32,298 men age 50 to 64 years (born between 1930 and 1944) and living in Goteborg were randomly selected, proportionally stratified by birth cohort, and allocated to either the screening arm or a control group. Three birth cohorts (1930–1934, 1935–1939, and 1940–1944) were identified. Subsequently, the 2 cohorts of men born between 1930 and 1939 were included, without changing their protocol, in the multinational ERSPC study.

The screening program included total serum PSA tests every 2 years, until age 70. Men having a threshold PSA value of 3 ng/ml or greater were referred for further work-up using DRE, TRUS, and laterally directed biopsies. Mortality outcomes were prospectively followed through linkages with the National Cause of Death Registry and the regional cancer registries in Sweden. An independent cause of death review committee also performed blind reviews. The long-term primary PC mortality outcome measures were reported at 12-year (52) and 14-year (53) follow-up.

European Randomized Study of Screening for Prostate Cancer (ERSPC)

The largest RCT conducted in Europe, the European Randomized Study of Screening for Prostate Cancer (ERSPC), began with pilot trials in the Netherlands and Belgium. (54) Subsequently, other countries—Sweden (part of the Goteborg cohort), Finland, France, Italy, Portugal, Switzerland, and Spain—joined the trial in phases. France was the last to join and therefore results in that country generally involved short-term outcomes. Portugal withdrew because it was unable to complete recruitment, resulting in an 8-country trial.

The long-term primary mortality outcomes for the ERSPC trial were reported as pooled results for all countries except France at 9-year (45) and 11-year (55) follow-up. In addition, 4 countries independently reported their long-term mortality outcomes—Sweden with 10-year, (56) 12-year, (52) and 14-year (53) follow-up; Finland with 12-year follow-up; (57) Netherlands with 4.6-year, (58) 11-year, (59) and 12.8-year (60) follow-up; and Spain with 15-year follow-up. (61)

Table 2: RCT Studies Evaluating PSA Screening Programs for Prostate Cancer

Author, Year	Country, Region	Source Population	Randomization Start or Period	Randomized Total	Median Follow-Up
North America RCTs					
Labrie et al, 1999 (46) Labrie et al, 2004 (41)	Canada, Quebec (1 site)	Men age 45–80 years of 9 constituencies in Quebec City, identified from 1985 electoral rolls	1988	46,486 (2:1 ratio)	8 years 11 years
Andriole et al, 2012 (48)	United States, (PLCO)[a] all centres (10 states)	Men age 55–74 years living in cities in 10 states, no population registry available	1993–2001	38,343 volunteers randomized to screening and 38,350 to the control arm	7 years 10 years 13 years
European RCTs					
Sandblom et al, 2004 (44) Sandblom et al, 2011 (51)	Sweden, Norrkoping	Men age 50–69 years residing in city of Norrkoping, identified from national population register	1987	From 9,026 eligible, 1,494 screened (every sixth man from birth date) and remaining 7,532 as controls	15 years 20 years
Kjellman et al, 2009 (43)	Sweden, Stockholm	Men age 55–70 years living in catchment area of Stockholm South Hospital, identified from census records	1988	From 26,602 eligible, 2,400 randomly selected and invited and 24,202 as controls	12.9 years
Aus et al, 2007 (56) Bergdahl et al, 2009 (52) Hugosson et al, 2010 (53)	Sweden, Goteborg	Men age 50–66 years (born between 1930 and 1944) living in Goteborg, identified from a population registry	1995–1996	From target population of 32,298 men, 10,000 randomized to screening and 10,000 to the control arm	10 years 12 years 14 years
Schroder et al, 2009 (45) Schroder et al, 2012 (55)	ERSPC (Pooled from 7 countries)[b]	Men age 50–74 years; includes men of all ages from the different centres in 7 countries and the core age group (55–69 years)		72,890 were randomized to screening and 89,353 to the control arm	9 years 11 years
De Koning et al, 2002 (62)	ERSPC Belgium	Men age 55–74 years living in Antwerp, identified from population registries	1992–1999	8,750 were randomized to the screening arm and 8,750 to the control arm	Not reported individually
de Vries et al, 2007 (58) Zhu et al, 2011 (59) Roobol et al, 2013 (60)	ERSPC Netherlands, Rotterdam	Men age 55–75 years living in Rotterdam and 12 neighbouring municipalities, identified from population registries	1993–2000	From 42,376 men, 21,210 were randomized to screening and 21,166 to the control arm.	4.6 years 11 years 12.8 years
Kilpelainen et al, 2010 (63) Kilpelainen et al, 2013 (57)	ERSPC Finland	Men born 1929–1944 (and age cohorts 55, 59, 63, or 67 years) identified from the Finnish Population Registry	1996–1999	From 80,144 men, 31,866 were randomized to screening and 48,278 to the control arm	9 years 12 years
Ciatto et al, 2003 (64)	ERSPC Italy	Identified from the residence population database of Florence	1996	7,271 randomized to screening and 7,271 allocated to the control arm	Not reported individually
Lujan et al, 2012 (61)	ERSPC Spain	Men age 45–70 years with > 10 years life expectancy, identified from population registries	1996–1999	From 27,481 men, 2,416 were allocated to screening and 1,862 to the control arm	15 years
Hugosson et al, 2007 (56) Hugosson et al, 2009 (52) Hugosson et al, 2010 (53)	ERSPC Sweden, Goteborg	Men age 50–65 years living in the community Goteborg, identified from Swedish population registry	1991–2003	From 32,298 men, 10,000 were randomized to screening and 10,000 to the control arm	10 years 12 years 14 years

Author, Year	Country, Region	Source Population	Randomization Start or Period	Randomized Total	Median Follow-Up
Kwiatkowski et al, 2003 (65)	ERSPC Switzerland	Men age 55–70 years living in Canton Aargau, identified from unspecified registries	1998–2003	From 18,361 men, 3,562 were randomized to screening and 3,562 to the control arm	Not reported individually
Jegu, 2009 (66)	ERSPC France	Men age 55–69 years living in cities Tarn or Herault, identified from public health insurance systems	2003–2005	From 84,781 men, 42,509 were randomized to screening and 42,191 to the control arm	4 years

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.
[a]PLCO includes sites in 10 states: Denver, CO; Washington, DC; Honolulu, HI; Detroit, MI; Minneapolis, MN; St. Louis, MO; Brooklyn, NY; Pittsburgh, PA; Salt Lake City, UT; Marshfield, WI.
[b]Portugal discontinued in October 2000 and was unable to provide data; France started late in 2001.

Key Variations Among the RCTs

Screening programs in these trials, particularly among the countries participating in the ERSPC trial, differed in several important aspects, including recruitment method, targeted age range of participants, screening interval, and biopsy threshold. (62) These differences are outlined in Table 3 and summarized below.

Most of the countries in which the trials were conducted had population-based registries from which to recruit trial participants. Population-based sampling frames were not used in the American PLCO trial or in 2 countries, Belgium and Spain, involved in the ERSPC trial. Trials also varied as to whether consent was obtained before or after randomization. For trials employing consent after randomization, invitations were sent and consent was obtained only from those in the screen arm. This design element was regulated by varying privacy laws. Belgium, Spain, and the Netherlands required consent from all participants in the study, including those in control arms where no screening was performed. The randomization ratio between study arms was 1:1 in all countries except Canada (Quebec) and Finland where a 2:1 ratio of control to screening arms was employed.

Although the target population ages for the PC screening trials were variable, the entry age in most of the trials was 50 or 55 years. In the Quebec trial, eligibility began at 45 years of age and included men up to age 80. In the ERSPC trial, although the age of eligibility was defined by protocol to be 55 to 69 years (referred to a priori as the defined core age group for the study), individual countries included different age groups ranging from 50 years (Sweden, Portugal, Spain) to more than 70 years (Netherlands, Belgium, Portugal). Age criteria were also noted to vary throughout the ERSPC trial depending on the success of recruitment in various countries.

The frequency of screening exams in most countries ranged from every 2 years to every 4 years, and the stopping rules at age 70 years were variably applied. The American PLCO and Quebec trials involved annual PSA-based screening programs. Although total serum PSA was the main element of the screening programs, ancillary PSA isoforms such as the ratio of free to total PSA (usually < 20%) were also employed. The main method of PSA measurement in the early stages of most trials involved the use of semi-automated detection methods. After the year 2000, centres switched to automated detection of PSA. Trial centres measuring both total and free to total ratios of serum PSA used different assay methods than those measuring only total PSA. Threshold values for abnormal total PSA results varied from 3.0 ng/ml to 4.0 ng/ml. Centres also reported lowering PSA cut-off values from 4 to 3.0 or 3.0 to 2.5 ng/ml throughout the screening program. In the Rotterdam section of the ERSPC trial, several substudies were performed during the trial to evaluate different threshold ranges for PSA screening (PSA value 1.0–3.0 ng/ml or 2.0 –3.0 ng/ml). The use of DRE was employed variably, sometimes in

combination with PSA as the screening method and sometimes as a further diagnostic evaluation alongside TRUS and biopsy. In the PLCO trial, participants received both PSA and DRE in the screening exam.

In most trials, the decision to refer for a biopsy was driven by criteria specified in the trial protocol. In the PLCO trial, however, patients with abnormal PSA or DRE results were referred to their primary physician for discussions on how to proceed and whether to have a biopsy. The criteria for biopsy referral in the European trials were based solely on abnormal PSA values or, at some centres, on either an abnormal PSA value or DRE examination. The biopsy procedure itself also varied across centres and over time. Some sites initially sampled using only needle biopsy; others sampled blindly in a specified quadrant and at some sites TRUS-guided biopsies were performed. Although the biopsies were read independently by pathologists, the European trial did not have a centralized pathology centre. Individual centres in participating countries had reference pathologists.

In all trials and at all sites, subsequent primary and ancillary treatments for screened PCs were not defined by protocol but were left to the discretion of the treating general practitioner or urologist in line with local practices or clinical guidelines. The identification of PC cases was made through the various national and regional cancer registers. Mortality outcomes, including all-cause and disease-specific mortality, were identified through national death registries and were adjudicated by an independent cause of death review committee. The death review process protocol in the PLCO trial was particularly rigorous. (67)

Table 3: Key Characteristics of RCTs of PSA Screening Programs for Prostate Cancer

Study, Country	Randomization Process	Entry Age Range, Mean, Years	Screening Intervals and Rounds	Sample Size Screen/Control, n	Screen Tests and Biopsy Threshold
North America					
PLCO, United States	Volunteers; after consent	55–74	Annual	38,343 / 38,350	Total PSA (6 years) and DRE (4 years) Total PSA > 4 ng/ml or abnormal DRE
Canada, Quebec	Population; before consent	45–80	Annual	30,956 / 15,237	Total PSA, DRE, TRUS Visit 1: PSA + DRE and TRUS (if PSA > 3.0 ng/ml or abnormal DRE; first 1,002 had all 3 tests) Visits > 1: TRUS if PSA > 3.0 ng/ml
Europe					
ERSPC, Belgium	Volunteers; after consent	55–74	7-year interval (between first and second round) and then 4-year interval for 3 screening rounds	8,750 / 8,750	Total PSA
ERSPC, Netherlands, Rotterdam	Population; after consent	55–69 (core) and 70–74	4-year interval	21,210 / 19,970	Total PSA, DRE and TRUS 3 different screens First screen PSA ≥ 4.0 ng/ml or abnormal DRE or abnormal TRUS; Subsequent screens PSA ≥ 3.0 ng/ml
ERSPC, Finland	Population; before consent	Age cohorts 55, 59, 63, or 67 years	4-year interval for 3 screening rounds	31,866 / 48,278	Total PSA ≥ 4 ng/ml or total PSA 3.0–3.9 ng/ml and abnormal DRE (1996–1998) and since 1999 free/total PSA of < 16%
ERSPC, Italy	Population; before consent	55–70	4-year interval	7,286 / 7,271	Total PSA 2.5 to 3.9 ng/ml followed by DRE and TRUS
ERSPC, Spain	Volunteers; after consent	50–70	4-year interval for screening rounds	2,416 / 1,862	Total PSA Total PSA > 4 ng/ml initially, total PSA > 2.99 ng/ml, then total PSA 1–2.99 mg/ml and free/total PSA ≤ 20%
ERSPC, Sweden, Goteborg	Population; before consent	50–65	2-year intervals for 7 screening rounds	9,972 / 9,973	Total PSA, DRE, TRUS Initially Total PSA > 3.0 ng/ml (1995–1998) lowered to 2.5 ng/ml 92005)
ERSPC, Switzerland	Population; after consent	55–70	4-year interval	5,150 / 5,150	Total PSA Free-to-Total PSA Total PSA > 3.0 ng/ml or Total PSA = 1-3 ng/ml and free-to-total PSA < 20%
ERSPC, France	Population; before consent	55–69	2-year interval	42,590 / 42,191	Total PSA ≥ 3 ng/ml
Sweden, Norrkoping	Population; before consent	50–69	3-year interval	1,494 / 7,532	First screen, DRE by urologist and GP (second and subsequent screens by GP only); third and fourth screen DRE and PSA (1993) Abnormal DRE and PSA > 4ng/ml
Sweden, Stockholm	Population; before consent	55–70	Screened once	2,400 / 24,202	Total PSA, DRE, and TRUS PSA > 7 ng/ml, repeat TRUS Total PSA > 10 ng/ml
Sweden, Goteborg	Population; before consent	50–65	2-year interval	10,000 / 10,000	Total PSA Total PSA ≥ 3.0 ng/ml

Abbreviations: CODC, Cause of Death Committee; DRE, digital rectal exam; ERSPC, European Randomized Study of Screening for Prostate Cancer; GP, general practitioner; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA; prostate-specific antigen; TRUS, transrectal ultrasound.

The performance characteristics of the screening trials are summarized below and outlined in Table 4.

Participation, Compliance, and Contamination

In most trials, consent to participate in screening trials was only sought from the men randomized to the screening arm, and the participation rate varied greatly across countries, from 24% to 78% (see Table 4). Compliance with screening protocols, however, was generally high (≥ 76% for prevalence screens in the ERSPC trial). (45) Biopsy rates among participants with abnormal screening results also varied greatly across countries. (45) Although the overall biopsy rates were generally high in the ERSPC trial (86%), they were lowest in Italy (65%) and France (68%). In the PLCO trial, the biopsy rate (40%), defined as biopsy within a year of the abnormal screening test, was lower than in the ERSPC trial countries. In the American trial, decisions on diagnostic follow-up after abnormal screens were made by the patient in conjunction with their physicians, and most men were advised against or chose not to undergo a biopsy with the first abnormal screen. (68) The rate of biopsy conducted within 3 years for men with an initial abnormal PSA screen and further follow-up improved to 64%. (69)

Contamination (the degree to which men in the control or usual-care arm had already had a PSA test at trial entry) and crossover (the extent to which control participants acquired the screening intervention during the trial) are important features of screening trials. Both of these effects can dilute or decrease the effectiveness of a screening trial. In the PLCO study, the degree of contamination and crossover was evaluated through ongoing surveys and reported extensively. (70) Contamination in the PLCO trial, defined as a PSA or a DRE in the control arm as part of a routine health checkup as opposed to for a specific health problem or follow-up of a previous health problem, was assessed through annual surveys of a sample of participants. Overall, 40% of men in the control arm reported routine PSA testing within the previous year; this rate increased from 33% in the first year of the trial to 46% in year 5. In comparison, 78% of the screened arm in year 5 received a routine PSA test in the prior year, with a mean number of 2.7 and 5.0 PSA tests performed for control and screen participants, respectively. Rates of effective contamination, which has been further defined as the proportion of the control group who receive an abnormal PSA test and who actually proceed to a biopsy, were generally not reported.

Contamination rates were generally not reported for the ERSPC countries. Estimates of PSA contamination for both the control arm and the screening arm (PSA tests outside the trial) were reported for the Rotterdam section of the ERSPC trial, using regional laboratory databases. (71) In the Netherlands, randomization was performed after consent, so men in the control arm were aware of a PSA screening program, and the rate of contamination over the 4-year interval in this group (73/1,000 P-YRs) was much higher than those based on the general regional (33/1,000 P-YRs) or national (38/1,000 P-YRs) populations. The rate of PSA testing in the control group over the 4-year interval was 20.2%, and the contamination rate in the screen group was 14.1%. However, the indication for the PSA test (screen, test, or follow-up) in either group was not known.

In another report, estimates of PSA contamination in the control arms of the French and Italian sites of the ERSPC trial were reported. (72) The self-reported use of PSA screening in the prior year by the control group in the French study in 2001 (66% responded) was 28%, and 35% reported ever having had a PSA test. A survey of a random sample of control participants in the Florence, Italy, ERSPC site reported increasing rates of PSA use (prior year) over 2 time points, from 28% in 1997 (200 men) to 37% in 2001 (300 men). The extent of PSA testing in the general population outside of the ongoing ERSPC screening trial at the Getafe, Spain, participating site, was reported using information from a laboratory database. Overall, the rate of PSA testing was 21.6/1,000 P-YRs but was age dependent (86.8/1,000 P-YRs for men age 55 to 69 years and 152.6/1,000 P-YRs for those 70 years and older).

Table 4: Performance Characteristics of PSA Screening Programs for Prostate Cancer

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

	Europe											North America	
	ERSPC, Belgium (45)	ERSPC, Netherlands (45)	ERSPC, Finland (45)	ERSPC, Italy (45)	ERSPC, Spain (45)	ERSPC, Sweden, Goteborg (45)	ERSPC, Switzerland (45)	ERSPC, France (73)	Norrkoping, Sweden (44)	Stockholm, Sweden (43)	Sweden, Goteborg (52)	USA, PLCO (40)	Canada, Quebec (46)
Study participation, %	NR	49	68	70	23	60	39	44	78	74	76	NR	24
Screening compliance, %	88.1	95	65	68	100	62	95	38	74	NR	59.7	85	NR
Biopsy rates, %	74.0	90	90	65	74	87	77	68	98	NR	93	40[a]	NR

[a]Biopsy participation was not by protocol.

Screening Test Performance

The efficiency of the PSA screening test can be evaluated through error rates, both false-positive (FP) and false-negative (FN), estimated at diagnosis through biopsy. Both the ERSPC and the PLCO trials provide information on measures of screening performance.

In the ERSPC trial, FPs (defined as no histological confirmation of PC within a year) were reported in the ERSPC study for 61,604 men from 5 participating countries (Italy, Belgium, Finland, Sweden, and the Netherlands). (74) The FP rates were estimated from 3 screening rounds in all countries except Sweden, which was on 6 rounds. The proportion of FPs in the first, second, and third screening round was 10.2% (95% CI, 10.0–10.5; specificity, 89.8%), 11.0% (95% CI, 10.7–11.3; specificity, 89.0%), and 11.1% (95% CI, 10.7–11.5; specificity, 88.9%), respectively. Overall the FP rate was 17.8% for the 10,972 men who had 1 or more FPs. Of these men, 7,752 had 1 FP, 2,098 had 2 FPs, and 538 men had 3 FPs.

The FP rate varied across countries ranging from 10.5% in Italy to 26.1% in the Netherlands (see Table 5). The FP rate also varied with age, increasing from 3.5% for men under 55 years of age to 20.6% for those over 70 years of age (see Table 6). To aid in interpretation, the use of medications (finasteride and/or alpha blockers) for benign prostatic hypertrophy was evaluated for 98% (23,319/23,771) of the men participating in the Finnish arm of the trial. (75) The rates of medication use at first, second, and third screen were 3.8%, 10.1%, and 14.5%, respectively. Men using these medications had an increased risk of an FP compared to those not taking the medications (14.0% vs. 6.1% at first screen) and the risk increased with each screening round. The relative risk of an FP (taking versus not taking medications) at the first, second, and third screening rounds was 1.9 (95% CI, 1.5–2.2), 1.6 (95% CI, 1.4–1.8), and 1.3 (95% CI, 1.0–1.8).

Estimation of the performance of screening methods in the American PLCO trial was problematic for several reasons. As previously noted, decisions on diagnostic follow-up after abnormal screens (PSA > 4 ng/ml or an abnormal DRE) were made by the patient in conjunction with his private physicians, and most men were advised against or chose not to undergo a biopsy with the first abnormal screen. (68) Biopsy rates with the first abnormal PSA (2,718 men), abnormal DRE (2,083 men), or both abnormal PSA and DRE were 40.2%, 18.9%, and 31%, respectively. Resolution of the clinical status of patients with an initial elevated PSA at baseline was confirmed in the majority (82%, 2,217/2,718) with 4-year follow-up. Cancer was confirmed in 944 cases (34.7%); 933 (34.3%) had negative biopsies; and 340 (12.5%) had lower PSA values.

Table 5: False-Positive Rate by ERSPC Participating Countries

	Italy	Belgium	Finland	Sweden	Netherlands
Screening frequency, years	4–7[a]	4	4	2	4
PSA threshold	3 ng/ml	3 ng/ml	4 ng/ml	3 ng/ml	3 ng/ml
False-positive rate, %	10.5	11.0	13.0	22.3	26.1

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PSA, prostate specific antigen.
[a]Screening frequency was 7 years initially, then 4 years.
Source: Kilpelainen et al, 2011. (74)

Table 6: False-Positive Rate by Participant Age in ERSPC Trial

	Participant Age, Years				
	< 55	**55–59**	**60–64**	**65–69**	**≥ 70**
Prevalence round false-positive rate, %	3.5	6.4	11.1	14.5	20.6

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer.
Source: Kilpelainen et al, 2011. (74)

Interval Cancers

Cancers detected outside the screening study protocol (between screening intervals) are known as interval cancers. Technically, they are missed cancers and represent a measure of the adequacy of the frequency of the screening process. (76) These cancers were identified by linkages to national cancer registries. The occurrence of interval cancers are less of a concern with the annual screening frequency in the PLCO trial, but they are potentially an issue with the longer frequencies of 2 and 4 years employed in the European trials.

In the PLCO trial, after 4 years of follow-up with annual screening of men age 55 to 74 years, 1,902 men were diagnosed with PC. Of these cancers, 1,603 (84%) were classified as screen-detected, 204 (11%) as interval cancers, and 95 (5%) occurred in non-participants, men never being screened. (77) In the ERSPC trial, after 9-year follow-up and detection of 5,990 PCs, 4,235 (71%) PCs were screen-detected and 1,755 (29%) were detected either outside of the screening protocol or in men never screened. (45)

Countries within the ERSPC trial, however, employed varied screening frequencies. A comparison of interval cancers occurring with different screening frequencies was made between Goteborg, the Swedish centre employing 2-year screening intervals for men 50 to 65 years of age randomized before consent, and Rotterdam, the Dutch centre employing 4-year screening intervals for men 55 to 75 years of age randomized after consent. (76) For comparability, the study comparison was restricted to men age 55 to 65 years. Interval cancers were also evaluated as being potentially life-threatening or aggressive cancers, defined as stage M1 (distant metastasis) or N1 (nodal involvement), total serum PSA greater than 20 ng/ml, or a tumour grade GS greater than 7.0.

At the 10-year study review point, the mean follow-up was 7.38 months for the 4,202 screened men in the Goteborg study (2-year interval) and 7.16 months for the 13,301 men screened in the Rotterdam study (4-year interval) (see Table 7). (76) A total of 521 PCs (12.4%) and 1,061 PCs (8.0%) were screen-detected in the Goteborg and Rotterdam trials, respectively. The PC detection rates in the control groups were 6.8% in the Goteborg study and 2.5% in the Rotterdam trial. Thirty-one interval cancers (0.74%) occurred in the Goteborg trial and 57 (0.43%) occurred in the Rotterdam trial. Most of the screen-detected and interval cancers in both countries were low stage (T1 or T2) or low grade (GS < 8). However, there were a large number of PCs detected in both countries for which the metastatic status was unknown. The 10-year cumulative incidence between the countries was significantly different for total PCs (8.4% vs. 13.14%; $P < 0.001$) but not for interval PCs (0.43% vs. 0.74%; $P = 0.51$) or aggressive interval PCs detected (0.15% vs. 0.12%; $P = 0.72$). (76)

Table 7: Interval and Screen-Detected Prostate Cancers by Stage and Grade

		Interval Cancers, n		Screen-Detected Cancers, n	
		Rotterdam (Total = 57)	Goteborg (Total = 31)	Rotterdam (Total PCs/Screened Men = 1,061/13,301)	Goteborg (Total PCs/Screened Men = 521/4,202)
T-stage	T1	38	19	536	388
	T2	14	12	432	117
	T3, T4	5	0	93	14
M-stage	M0	45	20	949	366
	M1	2	4	2	0
	MX	10	7	110	155
Gleason score	2–6	34	22	798	420
	7	12	6	209	89
	8–10	3	2	48	12
	unknown	8	1	6	0

Abbreviations: M0, no distant metastasis; M1, distant metastasis present; MX, distant metastasis cannot be evaluated; PC, prostate cancer; T, tumour stage.
Source: Roobol et al, 2007. (76)

Prostate Cancer Treatment

As noted, in all of the screening trials, treatment of screen-detected PCs was not defined by protocol but was left to the discretion of the treating general practitioner or urologist in line with local clinical practices or guidelines. The primary treatments provided to study group participants in the 2 biggest trials, the PLCO (48) and the ERSPC (55) trials, are outlined in Table 8. In the PLCO trial, more patients received some form of primary treatment (87% of both the screen and control groups) than in the ERSPC trial (71% of the screen group and 77% of the control group). Treatments provided to the study groups within a trial should be balanced in order to avoid outcome differences that may be attributable more to treatment differences than screening practices. The treatments were balanced in the PLCO trial but were significantly different ($P < 0.001$) between the trial arms in the ERSPC trial. (78)

Table 8: Primary Treatments of Prostate Cancers Between Trials and Study Arms

	American PLCO RCT (Age 55–74 Years)		European ERSPC RCT (Core Age 55–69 Years)	
	Screen Group, % (n = 4,250)	Control Group, % (n = 3,815)	Screen Group, % (n = 6,963)	Control Group, % (n = 5,396)
Prostatectomy	40	36.6	33.7	23.9
Radiotherapy	21.2	20.8	19.6	14.5
Radiation and hormone therapy	18.4	21.3	8.7	19.2
Hormone therapy	7.1	8.6	8.8	19.6
Active surveillance	NR	NR	23	16
No known curative	11.5	10.6	NR	NR

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized controlled trial.
Sources: For PLCO, Schroder et al, 2012 (55); for ERSPC, Andriole et al, 2012. (48)

In the ERSPC trial, surgery and active surveillance were more commonly performed in the screened group than the control group. Hormone therapy alone was more commonly provided in the control group than the screened group (19.6% vs. 8.8%). The treatment imbalance was examined further with a comparison of the impact of imbalances in surgery and hormone therapy (androgen deprivation therapy [ADT]) on PC mortality rates in 3 trials. (79) The difference in surgery rates between the screen group and the control group in the PLCO (3.7%), ERSPC (9.8%), and Goteborg (7.5%), were not consistent with the varying reduction in relative risk for PC mortality in the 3 trials (see Table 9). The greatest treatment imbalance in the overall ERSPC trial was not associated with the greatest impact on reduction in PC mortality risk.

Table 9: Treatment Imbalance Between Study Arms and Impact on Prostate Cancer Mortality

Trial	Follow-Up	PC Mortality RR (95% CI)	Difference in Surgery Rates Between Screen and Control Groups
PLCO	13 years	1.09 (0.87–1.36)	3.7%
ERSPC	11 years	0.79 (0.6–0.91)	9.8%
Goteborg	14 years	0.56 (0.39–0.82)	7.5%

Abbreviations: CI, confidence interval; ERSPC, European Randomized Study of Screening for Prostate Cancer; PC, prostate cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk.
Source: Haines et al, 2013. (79)

The similarity of the PC mortality rates in the screening arms (41/10,000 patients) and divergent rates in the control groups (38, 52, and 78/10,000 patients) across the trials suggested other potential imbalances with the treatment of control patients, namely the use of ADT. (79) In the PLCO trial, patients treated only with ADT were similar in the screen group and the control group (7.1% vs. 8.6%) and ADT treatment was balanced across tumour prognostic subgroups.

Primary ADT treatment of patients in the screen and control groups, however, differed greatly in the ERSPC (8.8% vs. 19.6%) and Goteborg (7% vs. 22.6%) trials. The proportion receiving ADT therapy was higher for patients in the ERSPC control group than in the screening group for all PC risk levels (low, intermediate, and high) categories (see Table 10). Treatment with ADT was particularly divergent for the high-risk cancers (29.5% of the control group and 14.7% of the screen group).

Table 10: Hormone Therapy Treatment Imbalance in ERSPC Screening Arms

Risk Category		ADT Treated	
		Screen Group	Control Group
Low risk	T1 or T2 and GS ≤ 6	2.0%	3.9%
Intermediate risk	T1 or T2 and GS = 7, or T3 and GS ≤ 7	6.4%	8.0%
High risk	T1, T2 or T3 and GS ≥ 7, or T4 and any GS and M1, or PSA >100	14.7%	29.5%

Abbreviations: ADT, androgen-deprivation therapy; ERSPC, European Randomized Study of Screening for Prostate Cancer; GS, Gleason score; M1, distant metastasis present; PSA, prostate-specific antigen; T, tumour stage.
Source: Haines et al, 2013. (79)

B) Systematic Reviews of Primary RCTs of PSA-Based Population Screening for Prostate Cancer

Five systematic reviews (80-84) were identified involving PSA screening programs for PC. The characteristics of these reviews are summarized in Table 11.

Table 11: Systematic Reviews of Prostate Cancer Screening Trials

Author, Year	Reviewer Country	Affiliation of Lead Author	Review Sponsor/ Funder	Type of Report	Search Period	Outcomes of Interest
Chou et al, 2011 (80) Lin et al, 2011 (85)	United States	Oregon Health and Science University	AHRQ for USPSTF	SR; Update to 2002 and 2008 AHRQ reviews for USPSTF	2002 to July 2011	PC mortality, all-cause mortality, harms of PSA screening, benefits of treating early stage or screen-detected cancers
Djulbegovic et al, 2010 (81)	United States	Urology and Prostate Disease Center, University of Florida	None declared	SR-MA	January 2005 to July 2010	PC mortality, all-cause mortality, PC diagnosis, screening and stage at diagnosis, FP and FN results, harms of screening, QOL, cost-effectiveness
Ilic et al, 2013 (82;86)	Australia	Department of Epidemiology and Preventive Medicine, Monash University Melbourne	Cochrane Collaboration	Update to 2006 and 2010 Cochrane reviews	Up to June 2012	Primary: PC mortality, all-cause mortality. Secondary: incident PC by stage and grade at diagnosis, metastatic disease at follow-up, QoL, harms of screening
Lee et al, 2013 (83)	Korea	Department of Laboratory Medicine and Genetics, Soonchunhyang University	National R&D Program for Cancer Control, Ministry of Health and Welfare	SR of SRs, RCT	Since January 2009	PC mortality, all-cause mortality, PC diagnosis, stage at diagnosis
Lumen et al, 2011 (84)	Belgium	Department of Urology, Ghent University Hospital	None declared	SR	Up to April 2011	PC mortality, all-cause mortality, PC diagnosis, PC incidence, stage and grade

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; FN, false negative; FP, false positive; MA, meta-analysis; PC, prostate cancer; QoL; quality of life; RCT, randomized control trial; SR, systematic review; USPSTF, U.S. Preventive Services Task Force.

The primary outcome measures being evaluated in the reports was the same in all studies, namely PC mortality and all-cause mortality. The studies selected for eligibility in the systematic reviews varied depending on the reviewers' inclusion and exclusion criteria and timeframes (see Table 12).

Meta-analyses were performed in all of the review studies except the Chou et al (80) evidence review. That 2011 evidence review, conducted by the Agency for Healthcare Research and Quality for the U.S. Preventive Services Task Force (USPSTF), was an update to the 2002 and 2008 USPSTF evidence reviews on PC screening. The review identified 5 RCTs: 2 that were rated as fair quality (40;45) and 3 as poor quality. (43;46;51) Two prior meta-analyses (81;86)

were also reviewed. The reviewers in this study decided against pooling the trial results given the diversity of the trials' design, operation, evaluation, and settings.

The Ilic et al (82) 2013 systematic review and meta-analysis, an update to the 2006 and 2010 Cochrane reviews, included 5 RCTs on PC screening (341,342 participants). Subgroup analyses of PC mortality were conducted, comparing studies judged to have a low or high risk of bias and for men of different ages (≥ 45 years, ≥ 50 years, ≥ 55 years).

The Djulbegovic et al (81) 2010 systematic review and meta-analysis included 6 RCT studies of screening trials for PC (387,286 participants). Subgroup analyses of PC mortality were conducted for men of 4 age groups (50–54, 55–59, 60–64, and 65–69 years), mostly from the ERSPC trial.

The Lee et al (83) 2013 systematic review included 6 RCTS of PC screening. Subgroup analyses on PC mortality were conducted for overall study bias (low risk, high risk), different study follow-up periods (< 10 years, ≥10 years), and age group and study follow-up (≤ 55 years and 7- or 10-year follow-up).

The Lumen et al (84) 2011 systematic review included 8 studies, of which 7 were screening RCTs for PC (571,594 participants) and 1 was a comparative study of the screened population in the Rotterdam site of the ERSPC trial and a population in Northern Ireland where routine screening was not conducted. (87) Subgroup analyses on PC mortality were conducted for length of follow-up (< 8 years), PSA screening contamination in the usual care group (> 33%), and participation in the screen group (< 75%).

Table 12: Studies Included in Systematic Reviews of Prostate Cancer Screening Trials

Author, Year	Review Type	Studies Included in Systematic Reviews							
		Quebec, Labrie et al (46)	PLCO, Andriole at al (40)	Stockholm (Sweden), Kjellman et al, (43)	Norrkoping (Sweden), Sandblom et al (51)	Goteborg (Sweden), Hugosson et al (53)	ERSPC (all countries), Schroder et al (45)	ERSPC (France), Jegu (66)	Rotterdam and Ireland, van Leeuwen et al (87)
Chou et al, 2011 (80) Lin et al, 2011 (85)	SR	X	✓	✓	✓	✓	✓	X	X
Djulbegovic et al, 2010 (81)	SR-MA	✓	✓	X	✓	✓	✓	✓	X
Ilic et al, 2013 (82;86)	SR-MA	✓	✓	✓	✓	X	✓	X	X
Lee et al, 2013 (83)	SR-MA	✓	✓	X	✓	X	✓	✓	X
Lumen, 2011 (84)	SR-MA	✓	✓	X	✓	✓	✓	✓	✓

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; MA, meta-analyses; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SR, systematic review.

Summary Estimates of Disease-Specific and All-Cause Mortality From Systematic Reviews

In all the trials of population-based screening programs included in the systematic reviews, the primary outcome of interest was PC mortality. Table 13 provides a summary of the PC and all-

cause mortality risk estimates from the systematic reviews in which meta-analyses were performed. None found a statistically significant reduction in relative risk of PC mortality or all-cause mortality in the screened group compared to the usual-care group. In the pooled estimates, relative risk for all-cause mortality was also not significantly reduced in any of the reviews. The absolute risk difference (ARD) in PC mortality ranged from 3 to 8/1,000 across the systematic reviews. The impact of PSA screening on relative risk of PC mortality were evaluated further through subgroup analyses based on length of study follow-up, age of participants, and judgment of overall study bias.

Of the 4 reviews, 2 (83;84) examined the effect of length of study follow-up on PC mortality. The Lumen et al (84) study found a significant reduction in relative risk for PC mortality when trials with less than 8 years follow-up were excluded (RR, 0.76; 95% CI, 0.58–0.98). Lee et al (83) did not find a significant relative risk reduction in PC mortality when correcting for length of follow-up. For follow-up shorter than 10 years, the relative risk was 1.04 (95% CI, 0.85–1.27) and, for follow-up greater than 10 years, it was 1.06 (95% CI, 0.89–1.27).

Subgroup analyses examining the effect of age on relative risk of PC mortality were performed in 3 of the reviews. (81-83) Two did not find a significant effect of age on the relative risk of PC mortality: Ilic et al (82) using 3 age groups (≥ 45 years, ≥ 50 years, ≥ 55 years) and Lee et al (83) using 2 age categories (< 55 years, > 55 years). Djulbegovic et al, (81) comparing 5 age groups from the ERSPC trial (50–54, 55–59, 60–64, 65–69, 70–74 years), found a significant reduction in relative risk of PC mortality for one group—men 65 to 69 years of age (RR, 0.74; 95% CI, 0.56–0.99).

Two of the reviews (82;83) evaluated the effects of the estimated overall risk of study bias (low and high) on relative risk reduction for PC mortality. Although both studies found that the PC mortality relative risk was lower in the studies with low risk of bias than in studies with high risk of bias, neither difference was statistically significant.

Table 13: Summary Estimates of All-Cause and Prostate-Specific Mortality From Systematic Reviews

Author, Year	All-Cause Mortality			Prostate Cancer Mortality		
	RCTs (Men), n	RR (95% CI)	*P* Value	RCTs (Men), n	RR (95% CI)	*P* Value
Djulbegovic et al, 2010 (81)	4 (256,019)	0.99 (0.97–1.02)	0.44	5 (302,500)	0.88 (0.71–1.09)	0.25
Ilic et al, 2013 (82)	5 (341,342)	1.00 (0.96–1.03)	0.84	5 (341,342)	1.00 (0.86–1.17)	0.99
Lee et al, 2013 (83)	5 (266,750)	0.99 (0.98–1.01)	0.50	4 (313,236)	0.93 (0.81–1.07)	0.31
Lumen et al, 2011 (84)	4 (206,393)	0.90 (0.75–1.08)	0.32	7 (318,631)	0.88 (0.72–1.06)	0.18

Abbreviations: CI, confidence interval; n, number; RCT, randomized control trial; RR, relative risk.

Summary Estimates of Prostate Cancer Detection From Systematic Reviews

All of the reviewers evaluated the rate of PC detection with the screening programs. A summary of these results is outlined in Table 14. In all reviews, a statistically significantly higher detection rate for total PCs was reported for the screening group compared to the control group. In the Ilic et al review, (82) the detection of PC cases was much higher for men age 50 years or older (RR, 1.59; 95% CI, 1.54–1.64) than for those 55 years of age or older (RR, 1.12; 95% CI, 1.08–1.17).

A significant stage shift to a greater detection of stage 1 or localized, non-palpable cancers was reported by the 3 reviews examining this trend. The detection of advanced cancers was defined and evaluated differently by the reviewers. In the Ilic et al review, (82) the detection of advanced tumours, defined as clinical stage T3 or T4 with nodal involvement (N1) or metastasis (M1), was significantly reduced in the screening group (RR, 0.80; 95% CI, 0.73–0.87). In the Lumen et al review, (84) tumours with a Gleason score of 8 or higher were not significantly less likely to be detected in the screening arm (RR, 0.91; 95% CI, 0.73–1.14). Fewer metastatic tumours were also detected in the screening group, but not significantly less often than in the control group (RR, 0.63; 95% CI, 0.38–1.05).

Table 14: Summary Estimates of Prostate Cancer Detection From Systematic Reviews of Screening Trials

Author, Year		Screen Group		Control Group		ARD	RR	95% CI
		PCs/Men, n	Rate/1,000	PCs/Men, n	Rate/1,000			
Djulbegovic et al, 2010 (81)								
PCs	All	10,328 / 159,372	65	7,968 / 181,428	44	21	1.46	1.21–1.77
Stages	Stage 1	3,789 / 155,317	24	1,971 / 177,426	11	13	1.95	1.22–3.13
	Stage 2	5,114 / 155,317	33	4,035 / 177,426	23	10	1.39	0.99–1.95
	Stage 3, 4	701 / 155,317	5	975 / 177,426	5	0	0.94	0.85-1.04
Ilic et al, 2013 (82)								
Localized	T1, T2, N0, M0	10,107 / 112,725	90	7,671 / 135,229	57	33	1.79	1.19–2.70
Advanced	T3, T4, N1, M1	868 / 112,725	8	1460 / 135,229	11	-3	0.80	0.73–0.87
Patient age	≥ 50 years	8,023 / 84,310	95	6,276 / 106,715	59	36	1.59	1.54–1.64
	≥ 55 years	3,906 / 40,714	96	5,260 / 63,117	83	13	1.12	1.08–1.17
Lee et al, 2013 (83)								
PCs	All	11,715 / 167,804	70	8,802 / 183,727	48	22	1.45	1.13–1.85
Stages	Stage 1	3,749 / 153,823	23	1,907 / 169,894	11	12	1.67	0.95–2.94
	Stage 2	5,093 / 153,823	33	3,943 / 169,894	14	19	1.39	1.33–1.45
	Stage 3, 4	677 / 153,823	4	843 / 169,894	5	-1	0.94	0.85–1.04
Lumen et al, 2011 (84)								
PCs	All	12,447 / 179,639	69	14,413 / 345,469	42	27	1.55	1.17–2.06
Localized	T1, T2	8,832 / 155,317	57	5,850 / 177,426	33	24	1.81	1.15–2.86
Metastatic		281 / 177,259	2	1,360 / 320,686	4	-2	0.63	0.38–1.05
Gleason score	≤ 6	7,682 /177,259	43	5,601 / 320,686	17	26	2.32	1.39–3.88
	≥ 8	820 / 177,259	5	1,863 / 320,686	6	-1	0.91	0.73–1.14

Abbreviations: ARD, absolute risk difference; CI, confidence interval; M0, no distant metastasis; M1, distant metastasis present; n, number; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; PC, prostate cancer; RR, relative risk; T, tumour stage.

C) Outcomes in Primary RCTs of PSA-Based Population Screening for Prostate Cancer

Mortality Outcomes

The primary outcome of interest in all the PSA-based screening trials was the effect of PSA screening on PC mortality.

Single Sites – North America

The Quebec trial reported PC mortality but not all-cause mortality in the 8-year (46) and 11-year (41) study follow-up. Disease-specific mortality was evaluated across various combinations of screened participants in both the screen and control groups, resulting in statistically significant reductions in PC mortality. However, an intention-to-treat analysis was not performed for PC mortality relative risk reductions in the 8-year follow-up and, when it was performed in the 11-year follow-up, the relative risk reduction was not statistically significant. All-cause mortality was not reported for any study subgroups.

Single Sites – European Studies

The mortality outcomes of 3 RCTs involving PSA screening for PC conducted in 3 Swedish cities—Norrkoping, (44;51) Stockholm, (43) and Goteborg, (53) with 15, 12.9, and 14 years median follow-up, respectively—are outlined in Table 15. The reduction in relative risk of PC mortality was not significant in the Norrkoping or Stockholm trials but was significant in the Goteborg trial (RR, 0.56; 95% CI, 0.39–0.82). The Goteborg trial results (for 2 of the 3 cohorts) were also included in the ERSPC trial.

Table 15: Mortality Outcomes in Single-Site European Trials of PSA Screening for Prostate Cancer

	Norrkoping (44;51) 15-Year Follow-Up		Stockholm (43) 12.9-Year Follow-Up		Goteborg (53) 14-Year Follow-Up	
	Screen Group	**Control Group**	**Screen Group**	**Control Group**	**Screen Group**	**Control Group**
Participants, n	1,494	7,532	2,374	24,772	9,952	9,952
PC cases, n (%)	85 (5.7)	292 (3.9)	208 (8.7)	1,972 (8.1)	1,138 (11.4)	718 (7.2)
PC/1,000 men	57	39	88	80	114	72
PC/1,000 P-YR (95% CI)	NR	NR	4.0 (3.4–4.7)	5.2 (5.0–5.4)	NR	NR
PC deaths, n	20	97	53	506	44	78
Deaths/1,000 P-YR (95% CI)	NR	NR	1.72 (1.32–2.26)	1.57 (1.44–1.71)	NR	NR
RR (95% CI)	1.16 (0.78–1.73)		1.10 (0.83–1.46)		0.56 (0.39–0.82)	
ARD			0.15/1,000 P-YR		0.40% (95% CI, 0.17–0.64)	
Total deaths, n	NR	NR	933	9,822	1,981	1,982
Deaths/1,000 P-YR (95% CI)	NR	NR	30.4 (28.5–32.4)	30.5 (29.9–31.1)	NR	NR
RR (95% CI)	NR		0.98 (0.92–1.05)		NR	
ARD	NR		0.1 /1,000 P-YR		NR	

Abbreviations: ARD, absolute risk difference; CI, confidence interval; n, number; NR, not reported; PC, prostate cancer; P-YR, person year; RR, relative risk.

Multicentre Trials

The results of the 2 largest multicentre trials, based on the 13-year follow-up in the American PLCO (48) and the 11-year follow-up in the European ERSPC (55) trials, are detailed in Tables 16a and 16b. The relative risk of death from any cause was not significantly reduced in either trial. The relative risk of all-cause mortality in the PLCO trial (excluding deaths from prostate, lung, and colorectal cancer) was 0.97 (95% CI, 0.93–1.10). The cause of death was detailed in the 10-year follow-up and, of the 3,953 deaths (not including the 92 PC cases or an unspecified number of lung or colorectal cancer deaths), 1,648 were deaths from ischemic heart disease, stroke, and other circulatory diseases. (88) In the ERSPC trial, the relative risk for all-cause mortality (excluding PC deaths) was 0.99 (95% CI, 0.97–1.10). The relative risk of death from PC in the screening group was significantly reduced in the ERSPC trial (RR, 0.79; 95% CI, 0.67–0.92) and increased but not significantly in the PLCO trial (RR, 1.09; 95% CI, 0.87–1.36).

Table 16a: Outcomes in the PLCO and ERSPC Trials

	PLCO RCT		ERSPC RCT	
	Screen Group	**Control Group**	**Screen Group**	**Control Group**
Men randomized, n	38,343	38,350	72,891	89,352
Total PC cases, n	4,250	3,815	6,584	4,960
Crude PC incidence	11.1%	9.9%	9.0%	5.6%
PC incidence /10,000 P-YR	108.4	97.1	98.3	58.7
PC deaths, n	158	145	299	462
Crude PC mortality rate	0.4%	0.37%	4.5%	9.3%
PC mortality rate /10,000 P-YR	3.7	3.4	3.5	4.4
Total deaths, n	5,783[a]	5,982[a]	13,917	17,256
All-cause mortality rate/10,000 P-YR	NR	NR	182	185

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; n, number; PC, prostate cancer; PLCO , Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; P-YR, person year; RCT, randomized controlled trial.
[a] Deaths due to lung or colorectal cancers were not included in total deaths for the PLCO trial.
Sources: For PLCO, Schroder et al, 2012 (55); for ERSPC, Andriole et al, 2012. (48)

Table 16b: Mortality Outcomes in the PLCO and ERSPC Trials

	Prostate Cancer RR (95% CI)	**Prostate Cancer ARD 95% CI (Screen – Control)**	**All-Cause Mortality RR (95% CI)**
PLCO RCT	1.09 (0.87–1.36)	3.4–3.7/10,000	0.96 (0.93–1.10)
ERSPC RCT	0.79 (0.67–0.92)	-4.4 to -3.5/10,000	0.99 (0.97–1.10)

Abbreviations: ARD, absolute risk difference; ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized controlled trial; RR, relative risk.
Sources: For PLCO, Schroder et al, 2012 (55); for ERSPC, Andriole et al, 2012. (48)

As described earlier, the countries in the ERSPC trial had varying age criteria for eligibility in their trials. Some countries allowed younger ages for trial entry and screening programs in different countries were terminated at different ages. In Finland, screening was no longer performed for those over 71 years and in the Netherlands screening was no longer performed in those over 75 years of age. Although the main ERSPC trial analysis included all participants,

the decision at the beginning of the trial was that those age 55 to 69 years were the ideal or core group. The trial results were therefore presented for the core group and the total group, which included the broader age range of 50 to 74 years. For both age groupings, the mortality rates for PC in both trial arms were very low in comparison to the all-cause mortality rates (see Table 17). (55)

The relative risk for all-cause death was not significantly reduced in the core age group (RR, 0.99; 95% CI, 0.97–1.01) or in the all-ages group (RR, 1.00; 95% CI, 0.98–1.02). The relative risk for PC mortality in the screening group was significantly reduced for both the core age group (RR, 0.79; 95% CI, 0.68–0.91) and all-ages group (RR, 0.83; 95% CI, 0.72–0.94), although the reduction was greater for the core age group.

Table 17: Prostate Cancer and All-Cause Mortality Rates in the ERSPC Trial Arms

	Core Age Group (55–69 Years)		All Ages (50–74 Years)	
	Screen Group	Control Group	Screen Group	Control Group
PC mortality rate/ 10,000 P-YRs	3.9	5.0	4.2	5.0
All-cause mortality rate /10,000 P-YRs	182	185	191	192

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PC, prostate cancer; P-YR, person-year.
Source: Schroder et al, 2012. (55)

Results from the 7 countries that completed the ERSPC trial were also reported individually, in addition to the pooled ERSPC analyses (see Table 18). (55) The relative risk for PC mortality in the screening group was reduced in all countries except Spain but was significantly lower only in the Netherlands (RR, 0.71; 95% CI, 0.52–0.96) and Sweden (RR, 0.56; 95% CI, 0.38–0.83). The relative risk reduction for PC mortality was not significant for Finland, which contributed almost half of the PC deaths in the pooled results (46% [139/299] in the screen arm and 51% [237/462] in the control arm). Across countries, PC mortality rates in the screening groups had much less variability (1.8–5.3/10,000) than in the control groups (0.8–9.5/10,000). Sweden's control group had the highest PC mortality rate (9.5/10,000), almost double that of Finland (4.7/10,000). The follow-up in the Finnish trial (11 years) was the same as in the Netherlands (11 years) but shorter than in Sweden (14 years).

In a breakdown by 5-year age categories for the ERSPC trial, few deaths occurred among men 50 to 54 years old—6 in the screening arm and 9 in the control arm (see Table 19). Although the relative risk of death from PC in the screening group was reduced in all age groups except for men over age 70, the reduction was significant only for 65 to 69 year olds (RR, 0.67; 95% CI, 0.53–0.86). The absolute risk difference (screen minus control) for PC mortality between the study groups for this age group was –3.3 (95% CI, –5.2 to 1.5) or 3.3 fewer deaths per 10,000 person-years of follow-up.

Table 18: Prostate Cancer Mortality for ERSPC Participating Countries (Core Age Group, 55–69 Years)

Country, Median Follow-Up, Years	Screening Arm					Control Arm					RR (95% CI)	ARD/10,000 P-YRs (Screen – Control)
	PC Cases	Cumulative Incidence %	PC Deaths	P-YRs	Rate /10,000 P-YRs	PC Cases	Cumulative Incidence %	PC Deaths	P-YRs	Rate /10,000 P-YRs		
Netherlands, 11.0	2,478	11.7	69	186,082	3.7	1,152	5.4	97	184,999	5.2	0.71 (0.52–0.96)	–1.5
Belgium,12.1	504	9.7	22	48,270	4.6	405	7.8	25	47,102	5.3	0.86 (0.48–1.52)	–0.7
Sweden,14.0	1,139	11.4	39	73,663	5.3	715	7.2	70	74,031	9.5	0.56 (0.38–0.83)	–4.2
Finland,11.0	2,838	8.9	139	333,535	4.2	3,175	6.6	237	504,263	4.7	0.89 (0.72–1.09)	–0.5
Italy,10.7	394	5.3	19	72,315	2.6	267	3.6	22	71,691	3.1	0.86 (0.46–1.58)	–0.5
Spain,10.6	88	4.8	2	10,969	1.8	33	1.8	1	11,819	0.8	2.15 (0.20–23.77)	1.0
Switzerland, 8.2	497	9.6	9	39,398	2.3	237	4.6	10	39,147	2.6	0.89 (0.36–2.20)	–0.3

Abbreviations: ARD, absolute risk difference; CI, confidence interval; ERSPC, European Randomized Study of Screening for Prostate Cancer; PC, prostate cancer; P-YR, person-year; RR, relative risk.
Source: Schroder et al, 2012. (55)

Table 19: Prostate Cancer Mortality by Participant Age in the ERSPC Trial

Age, Years	Screening Arm			Control Arm			RR (95% CI)	ARD/10,000 P-YRs, Screen – Control (95% CI)
	PC Deaths	P-YRs	Rate/10,000 P-YRs	PC Deaths	P-YRs	Rate/10,000 P-YRs		
≤ 54	6	66,010	0.9	9	64,334	1.4	0.65 (0.23–1.83)	−0.5 (−1.7 to 0.7)
55–59	94	378,539	2.5	144	480,748	3.0	0.81 (0.62–1.15)	−0.5 (−1.2 to 0.2)
60–64	106	226,339	4.7	136	261,588	5.2	0.92 (0.71–1.18)	−0.5 (1.8 to 0.7)
65–69	99	159,355	6.2	182	190,717	9.5	0.67 (0.53–0.86)	−3.3 (−5.2 to 1.5)
≥ 70	59	44,402	13.3	51	45,285	11.3	1.18 (0.81–1.72)	2.0 (−2.6 to 6.6)
Core ages (55–69)	299	764,233	3.9	462	933,053	5.0	0.79 (0.68–0.91)	−1.0 (−1.7 to −0.4)
All ages (50–74)	364	874,644	4.2	522	1,042,672	5.0	0.83 (0.72–0.94)	−0.8 (−01.4 to −0.2)

Abbreviations: ARD, absolute risk difference; CI, confidence interval; ERSPC, European Randomized Study of Screening for Prostate Cancer; PC, prostate cancer; P-YR, person-year; RR, relative risk.
Source: Schroder et al, 2012. (55)

Screen Detection Rates of Prostate Cancer

Prostate Cancer Detection in the PLCO Trial

The PC detection rates at follow-up were reported for the PLCO trial (see Table 20). (45) At 7-year follow-up there was a significantly increased PC detection rate (RR, 1.22; 95% CI, 1.16–1.29) in the screening arm (3,452 PC cases) compared to the control arm (2,978 PC cases). Among the total PCs detected in the screening arm, 154 were detected in those never screened, 374 outside of the protocol and 875 after the end of the screening program. The significant excess detection of PC cases in the screening arm continued at the 10-year follow-up (RR, 1.17; 95% CI, 1.11–1.22). At the 13-year follow-up, the detection rate per 10,000 person-years was 108.4 in the screen group and 97.1 in the control group, and the higher detection remained statistically significant (RR, 1.12; 95% CI, 1.07–1.17). (48)

Prostate Cancer Stage and Grade Migration

Clinically localized disease (stage T1 or T2) was the most commonly detected PC in both the screening (95.5%) and control (93.8%) groups. A clinical stage of T3 or T4 was less common in the screening group (88 cases, 3.5%) than the control group (113 cases, 4.6%). Gleason scores at biopsy were largely low grade (GS < 7) in both the screening group (66%) and the control group (60%). However, the detection of intermediate-grade tumours (GS = 7) was almost 1 in 4 in both the screen group (815 cases, 23.6%) and the control group (779 cases, 26.2%). High-grade tumours (GS = 8–10) were less commonly detected in the screen group (289 cases, 8.4%) than the control group (341 cases, 11.5%). At 13-year follow-up there were fewer high-grade PCs (GS = 8–10) in the screen arm (401 cases) than the control arm (454 cases), but the relative risk reduction was not significant (RR, 0.89; 95% CI, 0.77–1.11).

Table 20: Prostate Cancer Detection in the PLCO Trial

	Screen Group, n (%)	Control Group, n (%)
Men randomized (age 55–74 years)	34,343	38,350
Total PCs detected at 10 years	**3,452 (10.1)**	**2,974 (7.8)**
At baseline	549	NA
Detected at years 1–5	1,500	NR
Outside of screening	374	NA
After screening	875	NA
Never screened	154	NA
PCs detected by tumour (T) stage		
T1	18 (0.5)	15 (0.5)
T2	3,297 (95.5)	2,790 (93.8)
T3	49 (1.4)	56 (1.9)
T4	73 (2.1)	79 (2.7)
Unknown	15 (0.4)	34 (1.1)
PCs detected by tumour grade		
GS = 2–4	222 (6.4)	137 (4.6)
GS = 5–6	2,047 (59.3)	1,656 (55.7)
GS = 7	815 (23.6)	779 (26.2)
GS = 8–10	289 (8.4)	341 (11.5)
Unknown	79 (2.3)	61 (2.1)

Abbreviations: GS, Gleason score; NA, not appropriate; NR, not reported; PC, prostate cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.
Source: Andriole et al, 2012. (48)

Prostate Cancer Detection in the ERSPC Trial

PC detection rates for participants in the core age group (55–69 years) in the ERSPC trial are outlined in Table 21. (55) The cumulative rate of PC detection was significantly greater in the screening group than the control group at both 9 years of follow-up (RR, 1.88; 95% CI, 1.81–1.96) and 11 years (RR, 1.68; 95% CI, 1.62–1.75). At 11-year follow-up, the absolute risk difference was an additional 3.97 cases per 1,000 person-years or an additional 34.8 cases per 1,000 men.

The breakdown of PC detection by participating countries, also for the core age group, is outlined in Table 22a (using data from journal supplemental tables). (55) Of the 7,938 PC cases detected in the screening arm at the end of the study follow-up, 5,455 cases (68.7%) had been screen-detected, and 2,483 cases (31.3%) had been detected either between screening intervals or in unscreened individuals. In each country, the PC detection rate was greater in the screen group than the control group. Although the overall PC detection rate in the screening arms of the ERSPC and PLCO trials were similar (9.6% vs. 10.1%), individual European countries, notably the Netherlands (11.7%) and Sweden (11.4%), had higher detection rates in their screening groups (see Table 22b).

In the ERSPC control groups, the PC detection rate at 11-year follow-up was variable, ranging from 1.8% in Spain and 3.6% in Italy to 7.2% in Sweden and 7.8% in Belgium (see Table 22b). This variation suggests that usual screening or testing practices also varied across these

countries. The effect of the timing of randomization (before or after consent, as shown in Table 3) might also influence these differences but appears inconsistent. The PC detection rate in control arms might be expected to be higher in countries where randomization occurred after consent, as controls would be informed of screening and more likely to participate in opportunistic screening. The difference in PC detection between the trial arms, however, was not lower for countries where control participants were aware of screening (6.3% in the Netherlands) than in countries where they were not (4.2% in Sweden). The PC detection rate in the PLCO trial control group (7.8%) was higher than that reported for the global ERSPC results (6.0%) but was similar to the rate in Sweden (7.2%) and higher than in Finland (6.6%). The PC detection differences between the study arms was narrower in the PLCO trial than in the ERSPC trial overall (2.3% vs. 3.6%). For individual ERSPC countries, the PC detection difference between study groups was the same (2.3%) for Finland as for the PLCO trial and much higher for the Netherlands (6.4%) and Sweden (4.4%).

Table 21: Prostate Cancer Detection Over Time in the ERSPC Trial, Core Age Group (55–69 Years)

	Screen Group			Control Group			RR (95% CI)	ARD/1,000 P-YR (95% CI)	ARD/ 1,000 Men
	n	P-YRs	Rate/1,000 P-YR	n	P-YRs	Rate/1,000 P-YR			
Men randomized	72,891			89,352					
Prostate cancers detected									
1–9 year follow-up	6,043	580,502	10.41	4,044	731,204	5.53	1.88 (1.81–1.96)	4.80 (4.49–5.12)	37.6
8–9 year follow-up	1,410	113,850	12.38	1,174	145,293	8.08	1.56 (1.44–1.69)	4.30 (3.51–5.10)	6.2
1–11 year follow-up	6,584	669,501	9.83	4,960	845,666	5.87	1.68 (1.62–1.75)	3.97 (3.68–4.26)	34.8
Total	6,963	720,643	9.66	5,396	907,392	5.95	1.63 (1.57–1.69)	3.71 (3.44–3.99)	35.1

Abbreviations: ARD, absolute risk difference; CI, confidence interval; ERSPC, European Randomized Study of Screening for Prostate Cancer; P-YR, person–year; RR, relative risk.
Source: Schroder et al, 2012. (55)

Table 22a: Prostate Cancer Detection by ERSPC Countries, Core Age Group (55–69 Years)

	ERSPC Participating Countries							
	Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total
Randomization period	1993–2000	1991–2003	1994	1996–1999	1996–2000	1996–1999	1998–2003	
Median follow-up, years	11.1	12.1	14.0	11.0	10.7	10.7	8.2	11.0
Men randomized, n	43,368	10,359	19,911	80,379	14,972	3,702	10,309	182,000
Screen interval	4 years	4–7 years	2 years	4 years	4 years	4 years	4 years	
Screen arm participants, n	21,206	5,188	9,957	31,970	7,497	1,840	5,158	82,816
Total PCs detected in screen arm	2,487	504	1,139	2,838	394	88	497	7,938
Screen detected, n	2,040	214	896	1,,631	202	78	394	5,455
Interval or non-attender, n	438	290	243	1,207	192	10	103	2,483
Control arm participants, n	21,162	5,171	9,954	48,409	7,475	1,862	5,151	99,184
Total PCs detected in control arm	1,152	405	715	3,175	267	33	237	5,984

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; n, number; PC, prostate cancer.
Source: Schroder et al, 2012. (55)

Table 22b: Differences in Prostate Cancer Detection Between Trial Arms in ERSPC Countries and PLCO Trial

	Prostate Cancer Detection								
	Netherlands	**Belgium**	**Sweden**	**Finland**	**Italy**	**Spain**	**Switzerland**	**Total ERSPC**	**PLCO**
Screen group, %	11.7	9.7	11.4	8.9	5.3	4.8	9.6	9.6	10.1
Control group, %	5.4	7.8	7.2	6.6	3.6	1.8	4.6	6.0	7.8
Difference (Screen – control), %	6.3	1.9	4.2	2.3	1.7	3.0	5.0	3.6	2.3

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Trial.
Source: Schroder et al, 2012. (55)

PC Stage and Grade Migration

In the ERSPC trial, the majority of the PCs were also clinically localized tumours (stage T1 or T2) in both the screening arm (86%) and the control group (74%) (see Table 23). (55) Fewer tumours were at an advanced clinical stage (T4) in the screen arm (1.3%) than the control arm (6.2%). There were also fewer aggressive tumours (GS = 8–10) in the screen group (8.2%) than the control group (15.9%).

The 3 risk grouping of the detected cancers, based on PSA level, tumour grade, and stage, was favourable for the screen group in all groupings. The screen group had more low-risk PCs than the control group (60.3% vs. 42.4%) and fewer intermediate-risk (21.5% vs. 26.7%) and high-risk (7.4% vs. 12.5%) tumours. Missing information on risk grouping, however, was consistently higher in the control arm for all measures of tumour risk.

Table 23: Prostate Cancer Stage and Grade Detection in the ERSPC Trial

	Screen Group		Control Group	
	n (metastatic)	%	n (metastatic)	%
Total PCs detected	6,963		5,396	
Tumour (T) stage (metastatic)				
T1 (M1 or PSA > 100)	4,136 (32)	59.4	2,613 (45)	48.4
T2 (M1 or PSA >100)	1,848 (40)	26.5	1,379 (83)	25.6
T3 (M1 or PSA >100)	589 (95)	8.5	865 (226)	16.0
T4 (M1 or PSA >100)	88 (54)	1.3	206 (152)	3.8
Missing	302	4.3	333	6.2
Tumour grade (metastatic)				
GS ≤ 6 (M1 or PSA >100)	4,528 (58)	65.0	2,564 (57)	47.5
GS = 7 (M1 or PSA >100)	1,433 (104)	20.6	1,488 (146)	27.6
GS = 8–10 (M1 or PSA >100)	574 (29)	8.2	857 (270)	15.9
Missing	428	6.1	487	9.0
Risk group (stage, grade, and PSA level)				
Low (T1 or T2 and GS ≤ 6)	4,198 (58)	60.3	2,249	42.4
Intermediate (T1, T2 and GS = 7) or (T3 and GS ≤ 7)	1,495	21.5	1,442	26.7
High (T1,T2, or T3 and GS = 8–10; or T4 and any GS, M1, or PSA > 100; or any stage and M1 or PSA > 100)	515	7.4	673	12.5
M1 or PSA > 100	180	2.6	424	7.9
Missing	575	8.3	608	11.3

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer.GS, Gleason score; M1, distant metastasis present; n, number; PC, prostate caner; PSA, prostate-specific antigen.

Source: Haines et al, 2013. (79)

An intermediate or proxy outcome measure of the effectiveness of a screening program is the decreasing rate of advanced PCs in the screening arm over the conduct of the trial. The PC stage and grade detection rates for individual countries participating in the ERSPC trial are outlined in Appendix 3, Table A2. (55) Detection rates of any PC and high-grade PCs (GS = 8–10) during screening visits were compared among 6 countries (Sweden, Finland, Netherlands, Italy, Spain, and Belgium). (89) PC detection rates in the prevalence round (first visit) were

found to vary considerably among the countries, from 163 (Italy) to 507 (Netherlands) per 10,000 men (see Table 24). The detection rate of high-grade PCs also varied considerably among the countries, with the highest detection rate again in the Netherlands. The detection of high-grade PCs decreased in the second visit in 2 countries, Finland (from 22.6 to 15.4/10,000) and the Netherlands (from 41.1 to 13.6/10,000) but was only significantly reduced in the Netherlands ($P < 0.001$). The significant decline in high-grade PC detection in the Netherlands was also associated with the highest overall PC detection rate at the first visit.

Table 24: Detection of High-Grade Prostate Cancer by Screening Rounds of ERSPC Countries

	Men Screened, n		Prostate Cancer Detection Rate/10,000 Screened Men		High-Grade Cancer Detection Rate/10,000 Screened Men	
Country (Screen Interval)	**Visit 1**	**Visit 2**	**Visit 1**	**Visit 2**	**Visit 1**	**Visit 2**
Sweden (2-year)	5,858	4,687	246	203	5.1	6.4
Finland (4-year)	20,793	16,243	258	306	22.6	15.4
Netherlands (4-year)	19,970	12,529	507	439	41.1	13.6
Italy (4-year)	5,106	3,894	163	128	15.7	15.4
Spain (4-year)	2,416	1,708	166	228	16.6	23.4
Belgium (4- to 7-year)	4,567	1,364	252	587	10.9	29.3
Total	58,710	40,425	331	335	26	12.6

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; n, number.
Source: Van Der Kwast et al, 2006. (89)

A detailed review of detection rates of PC (overall and advanced) with PSA screening was reported separately for Finland (see Table 25). (63) A total of 5,451 PC cancers were detected in 12-year follow-up involving 3 screening rounds with 4-year intervals. The cumulative incidence rate ratio was significantly increased in the screen group over the control group for all PCs (RR, 1.46; 95% CI, 1.4–1.5) and for localized PCs (RR, 1.63; 95% CI, 1.5–1.7).

Advanced cancer was defined as a PC with a T3 or T4 clinical stage, regional node involvement (N1), or metastasis (M1). Although the cumulative incidence of advanced PCs was significantly lower in the screen group than the control group (RR, 0.69; 95% CI, 0.6–0.8), the reduction was significant only for 67-year-old men (RR, 0.57; 95% CI, 0.5–0.7). The incidence of low-grade PCs (GS < 7) was significantly higher in the screen group than the control group (RR, 1.82; 95% CI, 1.7–1.9), but the incidence of intermediate-grade (RR, 1.02; 95% CI, 0.9–1.1) and high-grade (RR, 0.89; 95% CI, 0.8–1.0) PCs was not significantly different between the groups.

Table 25: Prostate Cancer Detection in the Finnish Prostate Cancer Screening Trial

	Screen Arm	Control Arm	RR	95% CI	*P* Value
Total men randomized, n	31,866	48,278			
P-YRs	292,474	449,885			
Total PCs, n	2,655	2,796			
PC incidence rate	8.3%	5.8%			
PC incidence/1,000 P-YRs	9.1	6.2	1.46	1.4–1.5	< 0.001
Incidence localized (T1–2, N0, M0) PC/1,000 P-YRs	7.5	4.6	1.63	1.5–1.7	< 0.001
Incidence advanced (T3–4 or N1 or M1) PC/1,000 P-YRs (all ages)	1.1	1.5	0.69	0.6–0.8	< 0.001
55-year-olds			0.84	0.6–1.2	0.33
59-year-olds			0.79	0.6–1.0	0.09
63-year-olds			0.83	0.6–1.1	0.14
67-year-olds			0.57	0.5–0.7	< 0.001
Incidence low-grade (GS < 7) PC/1,000 P-YRs	5.8 (5.3%)	3.2 (3.0%)	1.82	1.7–1.9	< 0.001
Incidence intermediate-grade (GS = 7) PC/1,000 P-YRs	1.9 (1.7%)	1.8 (1.7%)	1.02	0.9–1.1	0.72
Incidence high-grade (GS = 8-10) PC/1,000 P-YRs	0.8 (0.8%)	0.9 (0.7%)	0.89	0.8–1.0	0.16

Abbreviations: CI, confidence interval; GS, Gleason score; M0, no distant metastasis; M1, distant metastasis present; N0, no regional lymph node involvement; N1, regional lymph node involvement; PC, prostate cancer; P-YR, person-year; RR, relative risk; T, tumour stage.
Source: Kilpelainen et al, 2010. (63)

Metastatic Disease

The rate of screen detection of metastatic PC in PSA screening trials was first evaluated in Goteborg, Sweden, (56) and later reported for 4 countries in the ERSPC trial that had collected information on metastatic status for both study arms throughout the study follow-up (Netherlands, Sweden [Goteborg], Finland, and Switzerland). (90)

In the Swedish report, advanced PC was defined as metastatic, non-curable disease. Bone scans were recommended at diagnosis if PSA levels were greater than 20 ng/ml or when symptoms were suggestive of bone metastasis at diagnosis. Patients with PSA above 100 ng/ml at diagnosis were also considered to have metastasis, even if not proven with bone scans. In practice, only patients with tumours potentially treated with curative intent were subject to nodal staging. During the 10-year follow-up of biennial screening, 1,252 PC cases were detected: 810 in the screening arm and 442 in the control arm. The number of metastatic PC cases detected at diagnosis, either by imaging or by elevated PSA levels, was 24 (20 by imaging and 4 by PSA) in the screening arm and 47 (37 by imaging and 10 by PSA) in the control arm ($P = 0.0084$). It was also noted that of the 24 metastatic cases diagnosed in the 9,972 men randomized to screening, 13 cases occurred in the 2,456 men who did not participate in screening.

The report involving 4 ERSPC countries evaluated the incidence of metastatic PC among men age 55 to 69 years, both at initial diagnosis and progression during the overall 12-year median follow-up. The analysis included 36,270 men randomized to the screening arms and 40,543 men in the control arms. (90) Follow-up was variable for the countries—12.0 years in the

Netherlands, 14.9 years in Sweden, 12.9 years in Finland, and 9.1 years in Switzerland. Metastatic disease status was assigned after an obvious bone scan or x-ray; in doubtful cases, computed tomography or magnetic resonance imaging were used. If imaging was not reported, men with PSA above 100 ng/ml were considered to have metastatic disease.

During follow-up, 10.9% of men in the screening arm were diagnosed with a PC (3,940 cases) and 6.8% in the control arm (2,744 cases). In the screen group, 256 (6.5%) of the PC cases were metastatic, 121 (3.1%) at diagnosis and 135 (3.4%) progressed to metastasis during follow-up. In the control arm, 410 of the PC cases (14.9%) were metastatic: 280 (10.2%) at diagnosis and 130 (4.7%) progressing to metastasis during follow-up. The cumulative incidence of metastatic PC in the screening and control arms was 0.67% and 0.86% respectively ($P < 0.001$). At 12-year follow-up, the relative risk of metastatic disease overall was significantly reduced in the screening group compared to the control group (RR, 0.70; 95% CI, 0.60–0.82), with risk curves separating 5 years after randomization. The relative risk reduction was significant for metastatic cases detected at diagnosis (RR, 0.50; 95% CI, 0.41–0.62) but not for PCs progressing to metastasis during follow-up (RR, 1.2; 95% CI, 0.91–1.47).

CONCLUSIONS

None of the systematic reviews of the randomized controlled screening trials for PC found a statistically significant reduction in relative risk of PC mortality or overall mortality with PSA-based population screening programs. The evidence from the primary trials on the benefit of PSA screening programs for PC mortality was conflicting. Prostate cancer mortality reductions were found to vary by country, by screening program, and by age of men at study entry. PSA screening programs in some but not all of the European countries participating in the ERSPC trial found a statistically significant reduction in relative risk for PC mortality, for some age groups, although the absolute risk difference was small. The American PLCO screening trial found a non-statistically significant increase in relative risk for PC mortality. Both trials had methodological limitations potentially influencing their results—differential treatment of participants in the ERSPC trial arms and high rates of PSA screening in the usual-care or control arm in the PLCO trial.

The PSA screening trials were consistent in that none demonstrated a relative risk reduction in all-cause mortality and all found a statistically significant increase in the detection of PCs in the screening arms, with the majority of detected cancers being low risk and organ confined. The detection of high-risk PCs at initial diagnosis was reduced in screening groups, but the much higher rate of intermediate-risk tumours was similar in the study arms. In addition, although the detection of metastatic PCs at diagnosis declined with subsequent screening, the progression of low-grade PC to metastasis during follow-up did not decline, a finding that potentially limits the effectiveness of screening programs. Overall, although the probability of having a PC detected through screening for men was significantly increased, their risk of dying from PC was low and their risk of dying from other causes was much higher—notably from other cancers and cardiovascular events.

Both the American and the European screening trials compared the effectiveness of PSA-based population screening programs for PC against usual local practice, and major differences in screening, diagnosis, and treatment practices therefore limit the generalizability of these screening trials. There was no evidence of a PC mortality benefit in the American PLCO trial, which investigated a PSA-based screening program in a setting where, unlike the European trials, opportunistic screening was already common practice. Given that opportunistic PSA screening practices in Ontario, Canada, are similar to those in the United States, it is unlikely that the introduction of a formal PSA-based screening program in Ontario would result in PC mortality reductions.

The high prevalence of PSA testing in Ontario and the positive attitudes of men and their physicians about the value of the test suggest that Ontario may, in essence, already have an informal PSA screening program. However, because of the uncertain benefits and known harms of PSA screening, many professional societies are recommending (as outlined in the following section) that a shared decision-making approach be adopted for men who seek PSA testing and that this process include adequate discussion of the benefits and harms of PSA screening.

CURRENT GUIDELINES ON PSA TESTING FOR PROSTATE CANCER

In light of current evidence, guidelines from professional bodies reflect different perspectives, providing guidance for public health decisions on population-wide PSA screening and for clinical decisions on PSA testing for individuals.

The need to weigh the benefits with the risks of early detection is acknowledged in many guidelines on PSA testing for prostate cancer. A number of professional societies and associations are recommending that, for men interested in PSA testing, a shared decision-making approach be adopted and that men be involved in adequate discussion of the benefits and harms of screening. Organizations emphasizing this approach include the American Cancer Society, (91) American Urological Association, (92) European Association of Urology, (93) Canadian Cancer Society, (94) Canadian Urological Association, (95) U.S. Preventive Services Task Force (USPSTF), (96) American College of Family Physicians, (97) and American Society of Clinical Oncology. (98)

The public health or population perspective on screening is addressed by the U.S. Preventive Services Task Force and the Canadian Task Force on Preventive Health Care. In its last published guidelines, in 1994, the Canadian task force concluded there was insufficient evidence to include PSA screening in the periodic health examination for men over age 50 years. (99) The Canadian task force is currently reviewing its guideline, with a report expected in mid-2014. The USPSTF recommended against PSA screening in its 2012 report, concluding that the harms outweigh the benefits for the target population of all asymptomatic men regardless of age or risk factors. (96)

At the same time, the USPSTF recognized that PSA screening is commonly used in clinical practice and that some men will continue to request screening and some physicians will continue to offer it. (96) The USPSTF also acknowledged that clinical decisions involve more considerations than evidence alone. The American task force stressed that the decision to initiate or continue PSA screening should reflect an explicit understanding of the possible benefits and harms but that it should also respect patients' values and preferences. Physicians were also advised not to offer or order PSA screening unless they were prepared to engage in shared decision-making that enables patients to make an informed choice about the test.

Several national societies of urology specialists—the Canadian Urological Society, American Urological Society, and European Association Urology—have recently issued guidelines regarding the utility of routine PSA screening for PC. Their recommendations are summarized in Table 26.

Table 26: Recommendations by Urological Societies on PSA Testing for Prostate Cancer

Society, Year	Recommendation Summary
American Urological Association, 2013 (92)	• does not recommend routine PSA screening in men age < 40 years. • does not recommend routine PSA screening in men age 40–54 years at average risk • recommends shared decision-making in men age 55–69 years • states that, to reduce harms, a routine screening interval of 2 years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening • does not recommend PSA screening in men age > 70 years or in men with life expectancy < 10–15 years
Canadian Urological Association, 2011 (95)	• recommends PSA screening be offered to all men age 50 years or older with a life expectancy of at least 10 years • states that harms and benefits of PC screening must be explained to each patient so they understand the factors to be considered in the shared decision-making about screening
European Association of Urology, 2013 (93)	• does not recommend mass screening for PC but does recommend early detection in well-informed men

Abbreviations: PC, prostate cancer; PSA, prostate specific antigen.

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APPENDICES

Appendix 1: Literature Search Strategies

Search date: September 24, 2013
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase, All EBM Databases (see below)

Q: What are the risks and benefits of using prostate-specific antigen (PSA) to screen for prostate cancer?
Limits: 2008-current; English
Filters: case reports, editorials, letters, comments and conference abstracts removed

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2013>, EBM Reviews - ACP Journal Club <1991 to September 2013>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2013>, EBM Reviews - Cochrane Central Register of Controlled Trials <August 2013>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2013>, EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2013>, Embase <1980 to 2013 Week 38>, Ovid MEDLINE(R) <1946 to September Week 2 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 23, 2013>
Search Strategy:

#	Searches	Results
1	exp Prostatic Neoplasms/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	96910
2	exp prostate tumor/ use emez	146036
3	(prostat* adj2 (cancer* or neoplas* or tumo?r*)).ti,ab.	187956
4	or/1-3	268416
5	exp Mass Screening/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	105557
6	exp "Early Detection of Cancer"/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	7364
7	exp early diagnosis/ use emez	64302
8	exp screening/ use emez	419316
9	screen*.ti,ab.	1048218
10	or/5-9	1325597
11	exp Prostate-Specific Antigen/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	20086
12	exp prostate specific antigen/ use emez	34756
13	(prostate specific antigen* or PSA or kallikrein or semenogelase or gamma seminoprotein or seminin).ti,ab.	90124
14	or/11-13	105308
15	4 and 10 and 14	12928
16	Case Reports/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt.	4146104
17	Case Report/ use emez or Comment/ use emez or Editorial/ use emez or Letter/ use emez or conference abstract.pt.	4175349
18	or/16-17	7057520
19	15 not 18	10711
20	limit 19 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	9533
21	limit 20 to yr="2008 -Current" [Limit not valid in DARE; records were retained]	4098
22	remove duplicates from 21	2496

Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Randomized Trials of PSA Screening for Prostate Cancer

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
All-cause mortality							
2 RCTs (48;55)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not evaluated	None	High
Prostate cancer mortality							
2 RCTs (48;55)	Serious limitations (–1)[a]	Serious limitations (–1)[b]	No serious limitations	No serious limitations	Not evaluated	Other considerations (+1)[c]	Moderate
Prostate cancer detection							
2 RCTs (48;55)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not evaluated	None	High
High-risk prostate cancer detection							
2 RCTs (48;55)	Serious limitations (–1)[d]	Serious limitations (–1)[e]	No serious limitations	Serious limitations (–1)[f]	Not evaluated	None	Low

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PC, prostate cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; RCT, randomized controlled trial.

[a]The rate of contamination in the control group was very high in the ERSPC trial, potentially attenuating the mortality risk reductions in the screening group. The treatment differences of screen-detected PCs in the ERSPC trial arms may have decreased mortality in the screen arm or increased mortality in the control arm.

[b]The effect of screening on prostate cancer mortality risk was in opposite directions in the 2 trials: significantly reduced in the ERSPC trial and increased but not significantly in the PLCO trial.

[c]Both trials were large, well-conducted multicentre trials with data monitoring committees, independent cause of death committees, and independent analytical teams.

[d]The trials defined high risk differently and tumour risk measures, particularly metastasis, were generally not consistently evaluated in the trial groups over time.

[e]The detection rates of high-risk tumours were not consistent between countries: significantly reduced in the screen group compared to the control group in some reports and not in others.

[f]The majority of the prostate cancers detected in the trials were low-grade localized tumours, and the low occurrence, variable definition, and incomplete investigations resulted in unreliable estimates of high-risk or aggressive tumours.

Appendix 3: PC Stage and Grade Detection by ERSPC Countries

Table A2: PC Stage and Grade Detection by ERSPC Countries, Core Age Group (55–69 Years)

	Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total	M1 or PSA > 100
Men in screen arm, n	**21,206**	**5,188**	**9,957**	**31,970**	**7,497**	**1,840**	**5,158**	**82,816**	
Screen arm PCs, n	**2,028**	**420**	**759**	**2,838**	**374**	**69**	**475**	**6,963**	
Stage T1	1,149	110	523	1,801	115	41	397	4,136	32
Stage T2	639	121	181	686	131	21	69	1,848	40
Stage T3	219	32	32	284	14	5	3	589	95
Stage T4	17	2	11	53	2	1	2	88	54
Stage missing	4	155	12	14	112	1	4	302	8
GS ≤ 6	1,422	144	548	1,842	198	41	333	4,528	58
GS = 7	393	29	157	645	96	14	99	1,433	104
GS = 8–10	116	17	47	293	59	6	36	574	29
Grade missing	97	230	7	58	21	8	7	428	
Men in control arm, n	**21,162**	**5,171**	**9,954**	**48,409**	**7,475**	**1,862**	**5,151**	**99,184**	
Control arm PCs, n	**896**	**311**	**507**	**3,175**	**257**	**24**	**266**	**5,396**	
Stage T1	428	88	231	1,689	25	12	139	2,613	45
Stage T2	224	100	180	738	55	8	74	1,379	83
Stage T3	187	26	60	576	8	3	5	865	226
Stage T4	42	6	20	130	0	1	7	206	152
Stage missing	15	91	16	42	169	24	0	333	15
GS ≤ 6	444	22	244	1,610	108	10	126	2,564	57
GS = 7	265	4	158	945	55	8	53	1,488	146
GS = 8–10	163	4	96	487	72	5	30	857	270
Grade missing	24	281	9	133	22	1	17	487	48

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; GS, Gleason score; M1, distant metastasis present; PC, prostate cancer; PSA, prostate specific antigen; T, tumour stage.

Source: Schroder et al, 2012. (55)

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