Title: Prostate Specific Antigen (PSA) for Prostate Cancer Screening: A Clinical Review

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Context and policy issues:

Prostate cancer is the most common tumor in men, and is one of the leading causes of cancer death in men. Prostate cancer can be slow growing and some prostate cancers may not be clinically significant (no risk of progression). Prostate cancer incidence increases with increasing age.

The aim of screening for prostate cancer is to diagnose the disease early and to enable early treatment. Screening for prostate cancer can be done by testing for prostate specific antigen (PSA) in the blood. PSA is a glycoprotein and is produced primarily by the prostate gland. PSA may increase with prostate cancer, but can also be increased in benign prostatic hyperplasia, and transiently increased following a digital rectal exam or biopsy. PSA is an inexpensive reproducible test which is minimally invasive. Another method to screen for prostate cancer is by a digital rectal exam (DRE). If a screening test is suspicious, transrectal ultrasound (TRUS) guided biopsy is done to diagnose prostate cancer.

It has been suggested that the decrease in prostate cancer mortality rate that has been reported in the 1990s may be due to increased PSA screening. It is unclear whether there is an advantage to PSA screening for prostate cancer and therefore a review of the evidence is necessary to determine the effectiveness of PSA screening.

Research question:

What is the clinical effectiveness and accuracy of the PSA test for prostate cancer screening?
Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 3, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, meta-analyses, health technology assessment and randomized controlled trials.

Summary of findings:

Systematic reviews

Three systematic reviews were found examining prostate cancer screening. These systematic reviews describe results of randomized controlled trials (RCTs) and more detail on the RCTs is provided below.

A 2006 Cochrane review examined the effect of prostate cancer screening on mortality and quality of life. Randomized controlled trials were included that compared screening for prostate cancer to no screening. Two RCTs were identified; the first screened men aged 69 years or younger and had 1494 men in the screening group and 7532 men in the control group. There were four screening rounds in this study conducted every 3 years. DRE only was conducted in the first two screening rounds, and both DRE and PSA was conducted in the following two screening rounds. If DRE was abnormal or if PSA was > 4.0 ng/ml, participants underwent TRUS. The second RCT was conducted in males aged 45 to 80 years and had 31,133 men in the screening group and 15,353 men in the control group. PSA and DRE were conducted in the first round of screening, and follow-up screening was a PSA test. PSA > 3.0 ng/ml or an increase in over 20% from the last screen was the criteria for TRUS. The meta-analysis conducted found that there was no statistically significant difference in screening versus control groups for prostate cancer mortality (relative risk 1.01, 95% CI 0.80 – 1.29). DRE is not distinguished from PSA for screening for prostate cancer in this systematic review as both RCTs used both methods for screening. The authors concluded that there is not enough evidence on prostate cancer screening.

A systematic review published in 2002 from the Institute for Clinical Evaluative Sciences (ICES) investigated the evidence for PSA screening. Clinical trials, guidelines and evidence-based summaries were included. Three RCTs were identified. The European Study of Screening for Prostate Cancer (ERSPC) is an ongoing study in 10 centers which will include men aged 55 to 70 years of age. No data from this study was reported in this systematic review. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) is also an ongoing study and no data was reported. This is an American study and will include men aged 55 to 74 years of age. The third RCT identified is a 1999 report of a Quebec trial, which included men aged 45 to 80 years of age. There were 8137 men in the screened group and 38,056 in the control group. There were 367 cases of prostate cancer in the screened group (4.5%). This study found that prostate cancer mortality rates were lower in the screened group (15 / 100,000 man-years) compared to the unscreened group (48.7/100,000 man-years). This results in an odds-ratio of 3.25 in favor of screening. This study had cross-over (men in the control group underwent screening), and when an intention-to-treat analysis was conducted, there was no significant difference in prostate cancer mortality rate. An observational study from Austria was also reported in this systematic review. This study examined prostate cancer mortality rates in a
region of Austria where screening was freely offered to men aged 45 to 75 years compared to the mortality rates in all other regions in Austria. After 4 years of the free screening, there was a 32% decrease in prostate cancer mortality rates compared to expected mortality. There was a 42% decrease after 5 years and a 33% decrease after 6 years. The mortality rate did not change in the other regions where prostate cancer screening was not freely offered. Overall, this systematic review concluded that there is a lack of high-quality evidence on screening for prostate cancer with PSA.

In 2002, the US Preventive Services Task Force published a systematic review on prostate cancer screening. RCTs and case-control studies were included. The Quebec study (also included in the SR above) was included and it found that the prostate cancer mortality rate was similar in the screened and unscreened group. Both DRE and PSA were used for screening in the Quebec RCT. The case-controlled studies included investigated the relationship between DRE and prostate cancer and did not include PSA. Therefore, this study is not relevant to the research question.

There is a lack of high quality evidence on prostate cancer screening, and although there were two RCTs (ERSPC and PLCO) in progress at the time of the SR, the design of these studies were flawed (some men in the control groups received screening) so these RCTs may not provide sufficient evidence regarding the efficacy of prostate cancer screening.

**Randomized controlled trials**

A Canadian RCT was published in 2004 on the 11-year follow-up of a prostate cancer screening trial. This is one of the two RCTs that were mentioned in the Cochrane systematic review and is the Quebec trial referred to in the other systematic reviews. However, the trial reported in the ICES systematic review is based on the data obtained from the 1999 report, and additional data has been made available since then. Of the 31,133 men aged 45 to 80 years invited for PSA and DRE screening, 7348 were screened (23.6% acceptance rate). There were 15,353 men in the control group, although 1122 were screened on their own, leaving 14,231 men in the control group. Ten men in the screened group and 74 men in the control group died from prostate cancer, resulting in a prostate cancer death rate incidence of 19.8/100,000 man-years in the screened group and 52.3/100,000 man-years in the control group (p < 0.002). The relative risk was 0.38 which is a significant reduction in death due to prostate cancer (62%; p = 0.0025). The majority of cancers diagnosed were localized (99.4%) with only one cancer diagnosed as metastatic. Overall, this study showed a decrease in prostate cancer death rates with prostate cancer screening.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is currently underway. This is a large multi-centre trial that was started in 1993 to look at prostate cancer mortality rates in screened and unscreened men. Final results of this trial are expected in 2008. Participants were screened by PSA, DRE and TRUS. Men with a PSA $\geq 4.0$ ng/ml (and later, PSA $\geq 3.0$ ng/ml) and men with suspicious DRE and TRUS results were recommended for biopsy. This screening protocol was used in the several reports from individual centers involved in the ERSPC. Individual reports from sections of the ERSPC are discussed in further detail.

The Rotterdam section of ERSPC published a report in 2005. In this section, 17,636 men aged 55 to 74 years old were randomized to the screening group and 17,513 were in the control group. There were three rounds of screening in addition to the initial prevalence screen. Men with PSA results $> 4.0$ ng/ml were indicated for sextant transrectal biopsy following the initial
prevalence screening round, and in subsequent rounds a PSA level of > 3.0 ng/ml became the cut point for biopsy. In the screening group, there were 818 cancers detected after prevalence screening, 63 after the first round, 336 after the second round, 8 after the third screening round and 44 interval cancers. In the control group, there were 336 cancer diagnosed. This study found that the cancers detected in the screening group had more favorable prognostic stages and grades compared to the cancers in the control group. There were more men with metastatic cancer in the control group (8%) compared to the screening group (0.6%) (p = 0.001). The authors concluded that screening for prostate cancer is favorable.

Another RCT from the Rotterdam section was published in 2006 with the same group of patients. This report states that 19,970 men were in the screening group and 21,166 men were in the control group. As in the above study, biopsy was administered to men with a PSA level of > 4.0 ng/ml in the first screening round, but this was changed to PSA > 3.0 ng/ml in the later rounds. There were 1339 men diagnosed with prostate cancer in the screening group and 298 men in the control group. This was a significant difference in cancers in the screening group (67.1/1000 men) and the control group (14.1/1000 men) (p < 0.0001). There was less nodular metastasis and distant metastasis in the screening group (1.5% and 1%) compared to the control group (4% and 8.7%) (p < 0.0001 for both). Men were younger at diagnosis in the screening group (67 years) compared to the control group (69 years) (p < 0.0001) and PSA levels were lower (5.5 ng/ml versus 11.7 ng/ml; p < 0.0001). The authors concluded that screening results in diagnosis of prostate cancers with a better prognosis.

Specificity of prostate cancer screening was reported in a 2007 report from the Finnish section of the ERSPC. In the first screening round, there were 30,194 men aged 55 to 67 years invited for screening and 20,794 received screening for prostate cancer (69% acceptance). Of these, 18,825 were negative during the screening round (PSA < 3.0 ng/ml or PSA 3.0 – 3.9 ng/ml with a negative DRE or a free PSA level ≥ 0.16). Of the 1969 men with a positive screening result, 508 were confirmed with prostate cancer by biopsy. Biopsy was negative in 1358 men, and 102 men did not have a biopsy. The authors calculated specificity as proportion of men who were screened negative among all the men who were found to be negative for prostate cancer. Therefore, the specificity was found to be 93.3% (18,825 / 18,825 + 1358; 95% confidence interval 92.9% – 93.6%). This calculation, however, assumes that all men that screened negative were truly free from disease and there were no false negatives. The specificity was 91.2% (95% CI 90.8% - 91.6%) in the second screening round. The authors concluded that the specificity for prostate cancer screening by PSA testing is acceptable.

Two reports from the Finnish section of the ERSPC were published in 2004. The first reported on sensitivity of PSA testing for prostate cancer screening. There were 30,195 men invited for screening, and 69% accepted. There were 20,790 men who were in the group that received screening and 48,458 in the control group. A PSA level of < 3.0 ng/ml or a PSA level < 4.0ng/ml with an additional negative test (DRE or free PSA) constituted a negative screening result. There were 2882 men that had positive screening results and 543 of these men were diagnosed with prostate cancer. In addition, there were 24 interval cancers in the screening group. In the control group, there were 539 cases of prostate cancer diagnosed. Sensitivity was the incidence of interval cancers (cancer in men who screened negative) compared to the cancer incidence in the control group. Sensitivity of PSA < 3.0 ng/ml was calculated to be 89% (95% CI 84% - 93%) and PSA < 4.0 ng/ml with an additional negative test was calculated to be 87% (95% CI 82% - 92%). This may not be an accurate estimation of sensitivity, as interval cancer incidence was used and all participants were not given the diagnostic test. The authors' concluded that sensitivity was acceptable and that PSA is a valid screening test for prostate cancer. The second study from the Finnish group reported on prostate cancer detection rates in

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the second screening round. There were 4407 men in the second round of screening, and 461 had a positive screening result (PSA ≥ 4.0 ng/ml) and 72 had a PSA result between 3.0 ng/ml and 3.9 ng/ml and a low free PSA percentage. These 533 men were referred for biopsy, 502 underwent biopsy, and 97 cancers were diagnosed. This corresponds to a detection rate of 2.2%. The authors concluded that compliance for the screening was acceptable and that the detection rate was lower than the initial screening round, which are both characteristics of an effective screening program.

The Spanish section of ERSCP published a report in 2003. Initially, the acceptance rate was 23%, however, some were excluded for various reasons (i.e. previous prostate cancer). There were 4276 men aged 45 to 70 years included, with 2416 men in the screening group (mean age 58.5) and 1862 in the control group (mean age 58). The PSA level for referral for biopsy changed throughout the study, starting at > 4.0ng/ml and finally the criteria was set at PSA > 2.99 ng/ml or a PSA level of 1 – 2.99 ng/ml and a low free PSA level. Biopsies were conducted in 166 men, and 40 cancers were diagnosed for a detection rate of 1.7%. The majority of the cancers that were diagnosed were localized (88.6%) with 11.4% metastatic or advanced cancers diagnosed. The authors concluded that detection rates can be increased with early screening.

The Swedish section of the ERSPC published a report in 2007 about PSA testing and the risk of being diagnosed with prostate cancer. There were 7516 out of 9972 invited (acceptance rate of 75%) men in the screening group and 9973 men in the control group. DRE, TRUS and lateral sextant biopsies were recommended for men with a PSA level of ≥ 3 ng/ml. There were 810 cases of prostate cancer diagnosed in the screening group, and 442 cases in the control group. There was a 1.83 fold increased risk of prostate cancer diagnosis in the screening group compared to the control group. There were 24 men in the screening group and 47 men in the control group that were diagnosed with metastatic cancer (p = 0.0084), which is a 48.9% decrease in risk of advanced prostate cancer diagnosis in the screening group. Overall, this study found a decrease in prostate cancer metastasis with PSA screening. An earlier report from the Swedish group was published in 2004 with the same patient population. There were 640 cases of prostate cancer diagnosed in the screening group and 244 diagnosed in the control group. This study concluded that screening for prostate cancer with PSA is effective at diagnosing early stage prostate cancers. An earlier report from the same group (2003) had 5853 men who were included in the PSA screening group (acceptance rate of 59.7%). Six hundred and sixty of these men were recommended for DRE, TRUS and biopsy based on a PSA level of > 3 ng/ml. DRE, TRUS and biopsy was conducted in 611 of these men, and 145 cases of prostate cancer were diagnosed for a detection rate of 2.5%. The majority of the cancers detected were localized (93%) and the authors concluded that early stage and low grade prostate cancers can be detected with PSA screening.

The ERSPC study from Switzerland published a report in 2003 and 2004 on their results of PSA screening. Patients with PSA > 3.0 ng/ml or PSA level of 1 ng/ml – 3 ng/ml and a low free PSA are recommended for DRE and TRUS guided transrectal sextant biopsy. Men aged 55 to 70 years old were invited to participate and 3562 men were randomized to the screening group and 3562 men were in the control group. The acceptance rate for screening was 38.8%. There were 395 men in the screening group with PSA > 3ng/ml and 372 of these men had a biopsy. Eighty-nine cancers were detected in this group for a detection rate of 2.5%. There were 251 men with a PSA of 1 ng/ml to 3 ng/ml and a low free PSA; 227 underwent biopsy and 31 cancers were detected. Overall, there was a prostate cancer detection rate in the PSA screened group of 3.4%. The authors concluded that a prostate cancer screening RCT is feasible, although there is not enough evidence to recommend a mass screening program.
The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer screening trial is a large multi-centre trial to examine cancer screening. The final results of this trial are not due until 2008. Men aged 55 to 74 years were included in this study, and 38,350 were in the screening group and 38,355 were in the control group. Screening was conducted with PSA and DRE, and the majority of men received both screening tests. There were 34,233 men who received a PSA screening test (acceptance rate of 89%) and 34,104 who received both PSA and DRE. Follow-up was recommended for men with a PSA level of 4.0 ng/ml. Positive PSA results were found in 2717 men, and 1112 of these men underwent biopsy. Prostate cancer was diagnosed in 489 of these men, for a detection rate of 18%. No conclusions were drawn from this study, and the end results hope to address the change in prostate cancer mortality due to screening.

The feasibility of a prostate cancer screening program was studied in 2004 in men aged 50 to 69 years. There were 1494 men randomly assigned to the screening group and 7532 men were included in the control group. The first and second screening rounds were done with DRE only, and the third and fourth rounds also included PSA. The acceptance rates ranged from 70% to 78% in the different screening rounds. Men were referred for biopsy if they had a PSA level > 4ng/ml. Due to relocation and death, there were diminishing numbers of men who attended the screening rounds. There were 895 men who attended the third round and 446 who attended the fourth round. Seventeen cancers were detected in the third round and 6 detected in the fourth round. There were also 29 interval cancers detected after these screening rounds. In total, including the screening rounds that only included DRE, there were 43 cancers detected from screening and 42 interval cancers. Cancers detected in the screening group were more localized than the control group (p < 0.001) and fewer metastatic cancers were detected in the screened group compared to the control group (p < 0.001). The authors concluded that screening can efficiently detect localized prostate cancer.

**Limitations**

Although there are a number of RCTs included, the majority of these trials are part of a larger trial (ERSPC) which has not been completed. These smaller studies do not address changes in prostate cancer mortality due to a prostate cancer screening program. All of the RCTs used both DRE and PSA for prostate cancer screening, and therefore it is difficult to determine the effectiveness of PSA alone for prostate cancer screening. A possible limitation to all the RCTs is that the reference standard test (biopsy) is not administered to all men who are screened. To determine whether PSA is a good screening test for prostate cancer, sensitivity and specificity should be calculated by comparing PSA results with the results of the reference standard test for diagnosis. Because the reference standard is TRUS guided biopsies, this is typically not conducted on men with negative screening tests, and therefore determining sensitivity and specificity is difficult. Clearly, biopsy should not be performed unless a suspicious screening test result occurs; however, this can introduce bias into the results. The three systematic reviews included all state that there is a lack of high-quality evidence for prostate cancer screening.

**Conclusions and implications for decision or policy making:**

The RCTs on prostate cancer screening used both DRE and PSA, and therefore, the usefulness of PSA screening alone is difficult to determine. The RCTs reported varying levels of acceptance for prostate cancer screening, from 23% to 89%. It is unclear why the acceptance rate was much higher in some studies compared to other studies. The rate of prostate cancer...
detection in groups that were screened ranged from 1.7% to 18%. Only one RCT\textsuperscript{21} reported on prostate cancer mortality rates as a result of prostate cancer screening. This study reported a reduction in prostate cancer mortality with prostate cancer screening. A systematic review, however, suggests that there are flaws with this study, and when an intention to treat analysis was conducted, no differences in prostate cancer mortality was found.\textsuperscript{4} The other studies did not report on prostate cancer mortality rates and PSA screening. The large RCTs (ERSPC and PLCO) that are currently underway are expected to report on prostate cancer mortality rates, and this data is due to be available in 2008. The studies that looked at the characteristics of prostate cancer in the screened and control groups all found that the cancers that were diagnosed in the screened groups were more localized and there were fewer cases of metastatic cancers compared to the control group.

It has been suggested that the majority of prostate cancers detected by screening are not clinically important and would not result in significant disease.\textsuperscript{5} Therefore, it is uncertain how useful PSA screening is for detection of prostate cancer. It is unclear the best age for PSA screening for prostate cancer. The RCTs included men of varying ages, with the largest age interval being 45 years to 80 years and the smallest interval being 55 years to 67 years. There does not appear to be a suggested age group for PSA screening. Overall, there is a lack of high quality data on the effects of PSA screening for prostate cancer, and perhaps the larger RCTs that are currently being conducted will provide the information that is needed to determine whether the PSA test is effective for prostate cancer screening.

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References:


10. Roemeling S, Roobol MJ, Gosselaar C, Schröder FH. Biochemical progression rates in the screen arm compared to the control arm of the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Prostate* 2006;66(10):1076-81.


