Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials

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CRD summary
This review found that screening for prostate specific antigen with or without digital rectal examination increased prostate cancer diagnosis but did not reduce mortality. The authors concluded that current evidence did not support the routine use of screening. The review was well-conducted and the conclusions appear reliable.

Authors' objectives
To assess the benefits and harms of screening for prostate cancer.

Searching
The authors searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 2005 to July 2010 to identify trials published since a Cochrane review on this topic. Search terms were reported. Abstracts of three relevant conferences (details listed in the paper) were screened. The authors also searched for narrative reviews and systematic reviews to identify additional trials. Studies were considered irrespective of language and publication status.

Study selection
Randomised controlled trials (RCTs) of screening of asymptomatic men for prostate cancer versus no screening were eligible for the review. Screening was defined as testing for prostate specific antigen, with or without digital rectal examination. Trials with participants previously diagnosed with prostate cancer were excluded.

Predefined outcomes of interest were all-cause mortality, death from prostate cancer, diagnosis of prostate cancer, effect of screening on age at diagnosis, false positive and false negative results, harms of screening, quality of life, and cost-effectiveness.

Minimum age for screening in the included trials ranged from 45 to 55; the maximum age ranged from 64 to 80. Digital rectal examination was used in four of the six trials.

Study selection was performed by two independent reviewers. Disagreements were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed based on method of randomisation, allocation concealment, blinding, analysis by intention to screen, contamination of the control arm and completeness of follow-up.

Validity assessment was performed by two independent reviewers. Disagreements were resolved by a third reviewer.

Data extraction
Data on numbers of events and participants in each trial arm were extracted to calculate relative risks (RRs) and associated 95% confidence intervals (CIs).

Data extraction was performed by two independent reviewers. Disagreements were resolved by a third reviewer.

Methods of synthesis
Pooled relative risks were calculated by meta-analysis using a Mantel-Haenszel random-effects model. An inverse variance model was used for outcomes for which event rates were not available from all trials. Heterogeneity was assessed based on clinical characteristics of the trials, as well as by $\chi^2$ and $I^2$. 

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Predefined subgroup analyses based on age and stage at diagnosis, and sensitivity analyses based on methodological quality parameters, were performed.

Risk of publication bias was assessed using Begg and Egger funnel plots.

**Results of the review**

Six RCTs with 387,286 participants (range 9,026 to 162,243) were included in the review. Median follow-up time ranged from four to 15 years. Methodological limitations were common; only three trials reported blinding of outcome assessors and only one reported adequate allocation concealment. Possible reporting bias was also identified as an issue. Quality of evidence for individual outcomes, assessed using the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system, ranged from moderate to very low.

Screening was associated with an increased probability of receiving a diagnosis of prostate cancer (RR 1.46, 95% CI 1.21 to 1.77; five RCTs; n=340,800 men; statistical heterogeneity was significant for this outcome) and of being diagnosed at the earliest stage (stage I RR 1.95, 95% CI 1.22 to 3.13; four RCTs; n=332,743 men). Screening did not significantly affect death from prostate cancer (RR 0.88, 95% CI 0.71 to 1.09; five RCTs; n=302,500 men) or all-cause mortality (RR 0.99, 95% CI 0.97 to 1.01; four RCTs; n=256,019 men).

There were no data on effects of screening on quality of life and limited data on potential harms of screening.

Results for publication bias were not reported separately because the method was considered unreliable for reviews with fewer than 10 trials.

Results of other analyses were reported in the paper.

**Cost information**

One trial reported that screening costs in the 1990s were £1,640 (UK pounds sterling) per detected cancer and £2,343 per detected and cured cancer.

**Authors’ conclusions**

The evidence did not support the routine use of screening for prostate cancer with prostate specific antigen, with or without digital rectal examination.

**CRD commentary**

The review question and inclusion criteria were clear. The authors searched a range of relevant sources without restriction by language or publication status, and they attempted to assess risk of publication bias. Study selection, quality assessment and data extraction were conducted in duplicate, which minimised the risk of reviewer errors or bias.

Trial validity and overall strength of evidence were assessed using appropriate criteria, and the results were used in the analysis. Trials were pooled by meta-analysis and heterogeneity was investigated.

This was a well-conducted systematic review and the authors’ conclusions appear reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that patients should be informed of existing uncertainties to help with decisions about screening on an individual basis.

**Research:** The authors stated that challenges for future clinical trials include: the choice of an appropriate screening threshold and interval; the risk of contamination between the screening and control arms; and compliance with recommendations for biopsy. They also stated that a number of ongoing trials (listed in the paper) will provide further evidence of the benefits and harms of screening.
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**Other publications of related interest**

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