COCHRANE COLUMN

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This month we feature the Cochrane Review assessing the effects of screening in reducing prostate-specific and all-cause mortality.

The aim of the Column is to highlight Cochrane Reviews of relevance to public health, and to stimulate debate on relevance, feasibility and acceptability. The Cochrane Collaboration (http://www.cochrane.org) is an international, non-profit organization that prepares and disseminates up-to-date systematic reviews on the effects of healthcare interventions in order to help people make well-informed decisions. Systematic reviews aim to answer focused healthcare questions by systematically identifying and evaluating all relevant research studies and synthesizing their results.

If you are interested in contributing to the Cochrane Column or the Cochrane Collaboration, contact me at the South African Cochrane Centre.

Screening for prostate cancer

Dragan Ilic,1 Denise O’Connor1, Sally Green1 and Timothy Wilt2

Prostate cancer is a common cause of cancer in men worldwide. There is debate around the effectiveness of screening methods for prostate cancer—around the digital rectal examination (DRE) and prostate specific antigen (PSA) test.

A recent Cochrane Review was conducted in order to identify the efficacy of screening in reducing prostate-specific and all-cause mortality. Randomized and quasi randomized controlled trials of screening vs no screening for prostate cancer were eligible for inclusion. Electronic searches of databases and hand-searching of selected journals were performed. Authors independently selected trials according to a pre-determined inclusion checklist. Included trials were assessed independently by the authors for methodological quality and susceptibility of bias against pre-determined criteria. Data were independently extracted from studies by authors. An intention-to-screen (ITS) analysis was performed by the authors in the event that the original study did not perform an ITS analysis.

Two trials, one randomized controlled trial (RCT) and one quasi randomized trial, met the inclusion criteria for the review. The Quebec RCT recruited 46 193 men aged between 45 and 80 years from Quebec, Canada. Participants randomized to the screening group were invited by letter to receive an annual screen including a DRE and PSA test. A transectral ultrasound (TRUS) biopsy was performed in men with an abnormal DRE or PSA elevated above 3.0 ng/ml. Men assigned to the control group were assumed to receive usual care. The Norrkoping trial recruited 9026 men aged between 50 and 69 years from Norrkoping, Sweden. Every sixth man was allocated to the screening group, with men in the control group assumed to receive usual care. Participants in the screening group received DRE alone for the first two rounds of screening, however, combination PSA and DRE was used for the next two rounds of screening. TRUS biopsies were conducted in men with a PSA above 4.0 ng/ml. The methodological quality of both studies were assessed to have a high risk of bias due to a combination of unclear allocation concealment, potential unblinded outcome assessment, cross-over between screening and control groups and failure to report results according to ITS analysis.

At 11 years follow-up the authors of the Quebec study reported the relative risk of death from prostate cancer to be 0.39 (95% CI: 0.19–0.65) in men who are screened. However, an ITS analysis of the data determined the relative risk of death from prostate cancer to be 1.01 (95% CI: 0.76–1.33). From the data reported in the Norrkoping study, an ITS analysis at 15 years follow-up determined the relative risk of death from prostate cancer to be 1.04 (95% CI: 0.64–1.68). A pooled analysis of these two ITS-analysed studies produced a relative risk of death from prostate cancer of 1.01 (95% CI: 0.80–1.29). Neither study assessed the impact of screening upon quality of life, costs or the potential harms of screening. The findings of this Cochrane Review suggest that there is insufficient evidence to either support or refute the use of screening for prostate cancer. The availability of data from the European Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) in upcoming years will provide a higher level of evidence for practice.


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Commentary: Screening for prostate cancer

Jenny Donovan and Richard Martin

Screening for prostate cancer is one of the most controversial healthcare topics worldwide. This competently conducted review reinforces this controversy. A high quality searching strategy identified nearly 100 potential studies, but there were only two published randomized trials: Quebec and Norrkoping. Two other ongoing studies were identified [European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO)]. The two published trials of screening both exhibited many methodological weaknesses and so the review authors reanalysed the data using an ITS approach and also a meta-analysis. The conclusions were that there were no statistically significant differences in prostate cancer mortality between men randomized to screening or control in either study alone or both studies together. These findings and the many serious methodological weaknesses in the studies mean that there is insufficient evidence to support or refute the use of screening to reduce prostate cancer mortality.

This review thus confirms a lack of robust evidence. It is an important message, but not a particularly interesting one. In part, the lack of evidence reflects the difficulties of conducting research in this area, particularly because of contamination between arms (due to screening activity in the arm randomized to no screening) and selection biases. The key issues remain unresolved: the identification of life-threatening tumours (because prostate cancer is slow growing in most men, the majority dies with rather than of prostate cancer), appropriate screening protocols and intervals, and the comparative effectiveness of treatments for screen-detected disease. The first two will be addressed in the ERSPC and PLCO studies. There is one other comprehensive study underway that is not mentioned in the review: the CAP (Comparison Arm for the ProtecT (Prostate testing for cancer and Treatment)) study. This UK-based cluster randomized trial allocates men aged 50–69 years in general practices to either (i) intensive population-based PSA testing followed by entry of men with localized prostate cancer into the ProtecT treatment trial comparing radical surgery, radical conformal radiotherapy and active monitoring, or (ii) standard (unscreened) practice. Over 400,000 men will be recruited by 2008 to provide an unbiased estimate to the effect of testing on prostate cancer-specific and all-cause mortality, investigate the impact on morbidity and health status, and develop a probabilistic model of the cost-effectiveness of prostate cancer screening. In combination, these three ongoing studies should provide robust and comprehensive evidence about prostate cancer screening over the next decade or two. This review has confirmed that we must await the publication of these studies before implementing screening.

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References


Commentary: Screening for prostate cancer

CF Heyns

This Cochrane review examines trials we know about already, and in this instance the review presents conclusions which have already been provided by other critical reviews. Ilic and associates used stringent criteria to select and re-analyse two studies of screening for prostate cancer, and rejected the conclusions of the original studies. However, I question their decision to re-analyse the data according to the ITS principle. For example, in the Quebec study, only 23% of the men randomized to screening actually were screened, while ~7% of the control group was screened. Because of this low screening rate and crossover contamination it could be argued that the authors of the Quebec study were justified in comparing the outcome of those who actually underwent screening with those who did not.

The methods of prostate cancer screening have not remained static, and are still evolving, with controversy about the following:

(i) the age group to be screened (50–70 years is generally accepted, but 45 or even 40 has been recommended);
(ii) the PSA cut-off level for performing a biopsy (varying from 5.5 ng/ml in elderly men, to as low as 2.5 ng/ml in some centres);
(iii) the interval of PSA testing (varying from 1 to 4 years);
(iv) the number of biopsy cores (varying from 6 to 18 or more, with some authors advocating ‘saturation’ biopsy of >40 cores).

Using lower PSA cut-offs and taking more biopsy cores will increase the detection rate, and this may occur especially among men in the control arm of a randomized study who choose to undergo screening. Therefore, analysis by ITS will produce erroneous conclusions unless such men are meticulously excluded.

There are daunting challenges of conducting randomized studies of screening for prostate cancer. PSA is not a perfect tumour marker, but it is better than most other screening tests for any type of cancer. The use of PSA testing in asymptomatic men has led to a dramatic stage migration, which is probably why most doctors and patients continue to opt for PSA testing—simple common sense dictates that it is better to detect cancer at an early (curable) rather than advanced ( incurable) stage. However, there is a risk of over-diagnosis and over-treatment, and the challenge is to differentiate between men who require aggressive treatment and those who do not.

The conclusion drawn by this Cochrane Review is not new or unique. Eminent leaders in research on prostate cancer screening accept that there is insufficient evidence to introduce prostate cancer screening as a general healthcare policy. However, there is no doubt that early prostate cancer can be detected by PSA testing and individual patients can be cured. The problem lies in predicting whether a given individual will benefit from an aggressive approach leading to significant gains in survival without major losses in quality of life. Nonetheless, there is general consensus that PSA testing cannot be refused to well-informed men who have decided to accept the uncertainties about the risk-to-benefit ratio of early prostate cancer detection and treatment.1

Among the problems of future research on prostate cancer screening are how to measure quality of life and how to define cost-effectiveness. A cynic may argue that prostate cancer screening, even if it is successful in reducing mortality, will prolong survival in men who are no longer economically productive, and will therefore only cause an additional drain on pension funds—therefore a priori not cost-effective.

Reference


A summary of Cochrane Reviews relevant to health promotion and public health is available on http://www.vichealth.vic.gov.au/cochrane/