Screening for Prostate Cancer: Reflecting on the Quality of Evidence from the ERSPC and PLCO Studies

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Abstract

The first Cochrane systematic review examining the evidence on screening for prostate cancer was first published in 2006. The 2006 version of the Cochrane review identified two randomised controlled trials (RCTs), drawing the conclusion that there was insufficient evidence to either support, or refute, the use of screening versus no screening in reducing prostate cancer-specific morality. The most recent version of the review, published in 2013, assessed evidence from five RCTs. Based on the evidence from the five RCTs, the authors of the 2013 version concluded that screening did not significantly reduce prostate cancer-specific mortality. Of the five trials included in the 2013 Cochrane review, only two were assessed as being a low risk of bias—the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial. This chapter discusses the differences between the ERSPC and PLCO trials, and examines what issues may contribute to their conflicting results. It also aims to contextualise results from this most recent Cochrane systematic review and discuss the critique of the Cochrane systematic review raised by Schroder in the chapter entitled, "ERSPC, PLCO studies and critique of Cochrane review 2013".

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The evidence base informing the merits of screening for prostate cancer has changed significantly since the first Cochrane systematic review was published in 2006 (Ilic et al. 2006). That version of the review identified two randomised controlled trials (RCTs), both assessed as having methodological weaknesses, concluding that there was insufficient evidence to either support or refute the use of screening, compared to no screening, for reducing prostate-specific cancer mortality. The most recent version of this review, published in 2013, identified five RCTs and concluded that a meta-analysis of those five studies did not significantly decrease prostate cancer specific mortality (Ilic et al. 2013). This chapter aims to contextualise results from this most recent Cochrane systematic review and discuss the critique of the Cochrane systematic review raised by Schroder in the chapter entitled, 'ERSPC, PLCO studies and critique of Cochrane review 2013'.

Each of the five studies included in the 2013 version of the Cochrane systematic review were assessed for their risk of bias. Seven domains are available for assessment under Cochrane's 'risk of bias' tool. These domains include selection bias (sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other biases (Higgins et al. 2011). All five trials included in the 2013 version of the Cochrane systematic review were assessed against these domains, with the exception of performance bias—since blinding of participants and study personnel to the intervention received is redundant in screening trials.

Three of the studies included in the 2013 Cochrane review were assessed as posing a 'high' risk of bias, whilst the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trials were assessed as posing a 'low' risk of bias. Whilst there is consensus on the rating of the three trials, which were rated as posing a 'high' risk of bias, Schroder raises the point that some of the domains used in assessing this risk of bias, such as allocation concealment, may not be applicable to screening trials. The Cochrane 'risk of bias' tool permits each domain to be assessed and assigned a judgement of 'low', 'high' or 'unclear' risk, with evidence from published data to support this assessment (Table 1). Both the ERSPC and PLCO studies are assessed as 'low' risk of bias for sequence generation (selection bias). The ERSPC study has been assessed as 'unclear' risk of bias for the allocation concealment domain, since information regarding the allocation process itself was not present in published data. If the investigator or patient is able to identify the impending treatment allocation, then the value of the randomisation has been compromised, thereby increasing the chances of imbalances between prognostic factors between the two groups and selection bias upon the trial (Forder et al. 2005).

Table 1 Risk of bias for the ERSPC and PLCO studies as described by the 2013 Cochrane systematic review of screening for prostate cancer (Ilic et al. 2013)

Bias	Authors' judgement	Support for judgement
ERPSC study		
Random sequence generation (selection bias)	Low risk	The study was a multicentre trial across nine European countries that randomly assigned men to screening or control groups 'Within each country, men were assigned to either the screening group or the control group… on the basis of random number generators'
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the publication '…randomization procedures differed among countries and were developed in accordance with national regulations'
Blinding (performance bias and detection bias)	Low risk	Outcomes were evaluated in a blinded manner 'Causes of death were evaluated in a blinded fashion… or on the basis of official causes of death. The causes were classified by the independent committees'
Incomplete outcome data (attrition bias)	Unclear risk	Data from the Portugal study centre were excluded from all analyses due to discontinuation. Data from the France centre of the trial were not included in mortality analyses due to short duration of follow-up, and were not included in primary analyses of additional outcomes—although data were provided '…the primary analysis was planned at the outset on the basis of follow-up of at least 10 years, which was reached with data through 2008. The current analyses include follow-up data through 2008…regarding the core age group analysis'
Selective reporting (reporting bias)	Low risk	Objectives of the ERSPC include cancer specific mortality and quality of life outcomes. Mortality is reported but quality of life is not descriptively reported in this publication. Measures relating to quality of life are currently being reviewed and will form the basis of future publications '…an evaluation of the effect on quality of life is pending'
Other bias	Unclear risk	Main data analysis is based on the core age group (55–69 years). There are differing age groups across the eight reported sites in the publication 'The benefit of screening was restricted to the core age group of subjects who were between the ages of 55 and 69 years at the time of randomizations'

(continued)

Table 1 (continued)

Bias	Authors' judgement	Support for judgement
PLCO study		
Random sequence generation (selection bias)	Low risk	Individual randomisation was performed within blocks stratified according to centre, age and sex 'The randomization scheme uses blocks of random permutations of varying lengths and is stratified by SC (study centre), gender and age. Random assignment is implemented using compiled software and encrypted files loaded on SC microcomputers'
Allocation concealment (selection bias)	Low risk	Concealment was achieved through a central system 'As each person is successfully randomized into the trial, data including name, gender, date of birth and study arm are automatically stored in encrypted data tables'
Blinding (performance bias and detection bias)	Low risk	Possible cancer specific deaths were reviewed by blinded reviewers 'Reviewers of these deaths were unaware of study-group assignments for deceased subjects'
Incomplete outcome data (attrition bias)	Low risk	Data on mortality and diagnosis are available for the 10-year follow-up, but follow-up data on 13-year outcomes are not complete 'As of December 31, 2009 (the cutoff date for this analysis), the vital status of 92 % of the trial participants was known at 10 years and of 57 % of the participants at 13 years'
Selective reporting (reporting bias)	Low risk	Study protocol is available and the study's pre-specified outcomes have been reported. '…there is evidence of harms, in part associated with the false-positive tests, but also with the overdiagnosis inseparable from PSA screening, especially in older men'
Other bias	High risk	Data on contamination were provided (estimated to be 40–52 %)

There are important differences between the ERSPC and PLCO studies, including contamination and compliance issues. The impact of these biases cannot be addressed under the theme of selection, performance, attrition, detection bias or reporting bias; hence why the category of 'other sources of bias' is available (Higgins et al. 2011). Published data on the PLCO estimated contamination to be 40–52 % between groups; therefore, it was judged to pose a high risk of bias for that domain. Risk of bias for each study is determined by the empirical evidence across these domains. Additionally, the risk of bias across each outcome (prostate cancer specific mortality, all-cause mortality, diagnosis of prostate cancer and prostate tumour stage), with sensitivity analysis demonstrating no meaningful

Table 2 Summary of findings from the Cochrane systematic review on screening for prostate cancer (Ilic et al. 2013)

Outcomes[b]	Illustrative comparative risks[a] (95 % CI)		Relative effect (95 % CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Screening				
All-cause mortality	21 per 100	21 per 100 (20–22)	RR 1 (0.96–1.03)	294,856 (4 studies[c,d])	⊕⊕⊕⊖ moderate[e,f,g]	
Prostate cancer specific mortality	7 per 1,000	7 per 1,000 (6–8)	RR 1 (0.86–1.17)	341,342 (5 studies[c,d])	⊕⊕⊕⊖ moderate[g,h,i,j]	
Prostate cancer diagnosis	68 per 1,000	88 per 1,000 (69–112)	RR 1.3 (1.02–1.65)	294,856 (4 studies[c,d])	⊕⊕⊖⊖ low[e,j,k,l]	
Tumour stage (localised T1-T2, N0, M0)	6 per 100	10 per 100 (7–15)	RR 1.79 (1.19–2.7)	247,954 (3 studies[m,n])	⊕⊕⊖⊖ low[j,o,p,q]	
Tumour stage (advanced T3-4, N1, M1)	11 per 1,000	9 per 1,000 (8–9)	RR 0.8 (0.73–0.87)	247,954 (3 studies[m,n])	⊕⊕⊕⊖ moderate[o,p,r]	

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Patient or population: adult male patients
Settings: primary or secondary care
Intervention: screening for prostate cancer
CI Confidence interval; *RR* vRisk ratio
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate
[a]The basis for the *assumed risk* (e.g. the median control group risk across studies) is provided in footnotes. The *corresponding risk* (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95 % CI)
[b] Information on costs, quality of life, metastatic disease at follow-up and harms of screening was limited and could not be meta-analysed; available information is summarised in the text
[c] ERSPC study data includes all ages (not just 'core' age group defined by trialists)
[d] PLCO study data is at 10 years of follow-up for this outcome
[e] Risk of bias was 'high' or 'unclear' for allocation concealment in three studies; 'high' or 'unclear' for random sequence generation in two studies; 'low' for blinding in all four studies; 'unclear' for incomplete outcome data in two studies; 'unclear' for selective reporting in 1 study and 'high' or 'unclear' for other bias in two studies
[f] $I^2 = 62$ %; $\text{Chi}^2 = 7.99$ ($P = 0.05$)
[g] Norrkoping study data for this outcome only included men who had been diagnosed with prostate cancer up to 12/31/1999, in whom mortality was then followed until 12/31/2008
[h] Risk of bias was 'high' or 'unclear' for allocation concealment in four studies; 'high' or 'unclear' for random sequence generation in three studies; 'unclear' for blinding of outcome assessment in one study; 'unclear' for incomplete outcome data in two studies; 'unclear' for selective reporting in two studies and 'high' or 'unclear' for other bias in three studies
[i] $I^2 = 46$ %; $\text{Chi}^2 = 7.40$ ($P = 0.12$)
[j] Wide 95 % CI
[k] $I^2 = 98$ %; $\text{Chi}^2 = 162.78$ ($P < 0.00001$)
[l] Screening intervention and screening interval varied between and even within some studies; the method of diagnosis also varied
[m] PLCO study data is provided at 13 years of follow-up for this outcome
[n] ERSPC study data includes only 'core' age group, as defined by trialists
[o] Risk of bias was 'high' or 'unclear' for allocation concealment in two studies; 'high' for random sequence generation in one study; 'low' for blinding in all three studies; 'unclear' for incomplete outcome data in two studies; 'low' for selective reporting in all three studies and 'high' or 'unclear' for other bias in two studies
[p] Tumour stage was unknown for some participants diagnosed with prostate cancer in all 3 studies
[q] $I^2 = 99$ %; $\text{Chi}^2 = 288.85$ ($P < 0.00001$)
[r] $I^2 = 0$ %; $\text{Chi}^2 = 1.34$ ($P = 0.51$)

difference in prostate cancer specific mortality, all-cause mortality and diagnosis of prostate cancer. Sensitivity analysis demonstrated a reduction in effectiveness of detecting localised prostate cancer with the removal of one high risk of bias study (Ilic et al. 2013).

Schroder highlights that it is not sufficient to state whether a bias is present or absent, but that it is necessary to quantify it and its potential impact with respect to the overall level of bias. The 2013 version of the Cochrane review utilised for the first time the GRADE framework, which was applied to assess the quality of evidence across all outcomes, and reported in a summary of findings Table 2 (Ilic et al. 2013). According to the GRADE framework, RCTs begin the grading process as high-quality evidence, with several factors influencing whether it is ultimately rated as high, medium, low or very low (Guyatt et al. 2011). Evidence may be modified higher if it demonstrates a large magnitude of effect, dose response and/or confounders are likely to minimise the effect. Evidence may be modified lower if there is likely publication bias and serious risk of bias, inconsistency, indirectness and/or imprecision. Risk of bias using the GRADE framework quantified a moderate quality of evidence for prostate cancer specific, all-cause mortality and tumour stage (advanced), with a low quality of evidence for prostate cancer diagnosis and tumour stage (localised).

Overall findings of the Cochrane systematic review determined that four of the five studies did not report a significant benefit in screening for prostate cancer (Ilic et al. 2013). A meta-analysis of the five studies concluded no evidence of benefit in the reduction of prostate cancer specific mortality (RR = 1.00 (95 %CI 0.86, 1.17)), with sensitivity analysis of the ERPSC and PLCO studies (as the only "low" risk of bias studies) resulting in a similar result (RR = 0.96 (95 %CI 0.70, 1.30)) (Ilic et al. 2013). Potential reasons for the contradictory results between the ERSPC and PLCO studies have also been highlighted within the summary of main results and characteristics of included studies table of the 2013 Cochrane systematic review.

Given the clinical and statistical heterogeneity of studies included in the Cochrane systematic review, a meta-analysis may not be appropriate (Ilic et al. 2013); in which case a descriptive analysis may be more suitable. Although the ERSPC study has been designed as a multicentre study, the potential for clinical heterogeneity within the study sites should also be explored. Variation in the recruitment of patients with respect to age and follow-up and between site variation in their use of PSA/DRE and PSA thresholds would be suggestive markers of clinical heterogeneity present in the ERSPC study (Ilic et al. 2013). This clinical heterogeneity within the ERSPC study itself may in part contribute to the variation in results, as only two of the sites (Netherlands and Sweden) demonstrated a statistically significant reduction in the risk of prostate cancer specific mortality.

Several types of systematic reviews are available under the Cochrane framework including reviews of interventions, diagnostic test accuracy, methodology or overview of review. In his concluding remarks, Schroder raises the possibility that the quality requirements for screening trials are different from the quality requirements for treatment trials. Much like other screening reviews (including

screening for breast, lung and colorectal cancer), screening for prostate cancer (be it by prostate-specific antigen (PSA) test and/or digital rectal examination (DRE)), is an intervention study. The potential impact of systematic bias remains constant, regardless of whether the intervention is one of screening or treatment.

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