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COCHRANE REVIEW

Screening for prostate cancer: an updated Cochrane systematic review

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OBJECTIVE

- To determine whether screening for prostate cancer reduces prostate cancer-specific mortality, impact on all-cause mortality and patient health-related quality of life.

MATERIALS AND METHODS

- An update to our 2006 Cochrane systematic review was performed by re-running an updated search of several databases, including MEDLINE and the Cochrane CENTRAL Register of Controlled Trials.
- Articles were included if they were a randomized controlled trial (RCT) examining screening vs no screening for prostate cancer. Data was collected and analysed according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS

- Five RCTs with a total of 341 351 participants were included in this updated Cochrane systematic review. All involved PSA testing, although the interval and threshold for further evaluation varied across trials. The age of participants was 50–74 years, with durations of patient follow-up of 7–15 years.
- The methodological quality of three of the studies was assessed as posing a high risk of bias.
- Meta-analysis of the five included studies indicated no statistically significant difference in prostate cancer-specific mortality between men randomized to screening and control [relative risk (RR) 0.95, 95% CI 0.85–1.07]. Sub-group analyses indicated that prostate cancer-specific mortality was not affected by age at which participants were screened. A pre-planned analysis of a 'core' age group of men aged 55–69 years from the largest RCT *(*European Randomised Study of Screening for Prostate Cancer*)* reported a significant 20% relative reduction in prostate cancer-specific mortality; (95% CI 0.65–0.98; absolute risk 0.71 per 1000 men). The number of men diagnosed with prostate cancer was significantly greater in men randomized to screening, compared with those randomized to control (RR 1.35, 95% CI 1.06–1.72).
- Harms of screening included high rates of false-positive results for the PSA test, over-diagnosis and adverse events associated with transrectal ultrasonography guided biopsies such as infection, bleeding and pain.

CONCLUSIONS

- Prostate cancer screening did not significantly decrease all-cause or prostate cancer-specific mortality in a combined meta-analysis of five RCTs.
- Any benefits from prostate cancer screening may take >10 years to accrue; therefore, men who have a life expectancy of <10–15 years should be informed that screening for prostate cancer is not beneficial and has harms.

KEYWORDS

prostate cancer, screening, systematic review

INTRODUCTION

Prostate cancer is the second most prevalent cancer in men worldwide [1]. Globally, it is a less prominent cause of cancer death, contributing 5.8% of cancer deaths in men [1]. For most men prostate cancer is slow growing and does not result in clinical signs or symptoms during their lifetime [2,3]. However, in some men prostate cancer progresses and is a leading cause of cancer morbidity and mortality.

While the intention of screening for prostate cancer is to decrease mortality and increase health-related quality of life (HRQL), the true benefit of screening for prostate cancer remains uncertain [4]. Use of the DRE as a screening tool is limited due to poor reliability, sensitivity, and the inability to palpate the entire prostate gland, especially for small tumours that have not reached the prostatic capsule [5]. The PSA test produces high false-negative and false-positive results, depending on thresholds used to define abnormality, and may detect prostate cancers that are unlikely to cause future health problems even if left untreated (over-diagnosis) [5]. Recent data has suggested that the PSA test does not attain the likelihood ratios (i.e. the likelihood of a given test result in a person with the disease compared with the likelihood that the same result would be apparent in a person without the disease) for a screening test, regardless of what threshold value for the PSA is assigned [6].

In 2006 we first published our Cochrane systematic review on screening for prostate cancer [4]. It concluded that there was insufficient evidence to either support, or refute, screening for prostate cancer. In 2009 two high profile randomized controlled trials (RCTs) of prostate cancer screening were published [7,8]. In this version of our Cochrane systematic review we update our literature search to identify studies published from 2006 onwards to examine whether screening reduces prostate cancer-specific and all-cause mortality in men [9].

MATERIALS AND METHODS

LITERATURE SEARCH METHODS AND INCLUSION CRITERIA

Electronic searches of the PROSTATE register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CANCERLIT and the NHS Economic Evaluation Database were performed in our original Cochrane systematic review [4]. An updated search of the electronic databases was performed with the same search strategy in July 2010 [9]. All RCTs, and quasi-RCTs of screening vs no screening for prostate cancer were eligible for this review. Screening interventions included PSA test, DRE and TRUS-guided biopsy. No language restrictions were placed on studies considered for inclusion in this review and published or unpublished sources were considered.

SUMMARY OF OUTCOMES ASSESSED

The primary outcomes assessed were prostate cancer-specific and all-cause mortality. Secondary outcomes measures included:

- incident prostate cancers by stage and grade at diagnosis;
- metastatic disease at follow-up;
- HRQL;
- harms of screening (including both adverse outcomes from false-positive and/or false-negative results and their impact upon resulting treatment procedures); and
- costs associated with screening programmes.

STUDY QUALITY

In this updated review assessment of risk of bias was conducted according to The Cochrane Collaboration's tool for assessing risk of bias, as described in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Risk of bias in the present review was assessed independently by two authors against the following key criteria:

- sequence generation;
- allocation concealment;
- 'blinding' of participants, personnel and outcome assessors;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias (defined as inappropriate data analysis).

Overall risk of bias for each study was summarised as 'low', 'unclear' or 'high' for each study dependent on the risk of bias across each of the key criteria.

STATISTICAL ANALYSIS

Statistical analysis was performed according to the statistical guidelines referenced in the Cochrane Handbook for Systematic Reviews of Interventions and facilitated by Revman [10,11]. For dichotomous outcomes the measure of effect was expressed as a relative risk (RR) and absolute risk (AR) with 95% CIs. Results were analysed using a fixed-effects model. Sub-group analyses were performed according to screening intervention and age. Sensitivity analyses were performed to investigate the impact of risk of bias of included studies. Heterogeneity was assessed by graphical interpretation of the Forest plot and with the I^2 statistic. An I^2 value of >75% was considered to be an indicator of considerable heterogeneity [10].

RESULTS

LITERATURE SEARCH

The updated search in July 2010 yielded 366 citations, of which 106 were selected for full-text review. In all, 11 manuscripts, representing five studies, met the inclusion criteria for this review;

- European Randomised Study of Screening for Prostate Cancer (ERSPC) [8,12]
- Norrkoping [13,14]
- Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [7,15]
- Quebec [16–18]
- Stockholm [19,20]

Of the five included studies, three were identified through the updated search (ERSPC, PLCO and Stockholm) and added to our earlier review.

STUDY QUALITY

The risk of bias for each study was assessed as follows;

- **ERSPC** – low risk of bias (allocation concealment was unclear, limited data was given on the details of allocation concealment in the trial reports. However, an early pilot study indicates that adequate allocation concealment was used during the study) [21].
- **Norrkoping** – high risk of bias (due to high risk associated with the allocation sequence generation and lack of allocation concealment).
- **PLCO** – low risk of bias (a high risk of bias was given in the incomplete outcome data domain; however, this was graded as such because only 67% of the participants were

FIG. 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

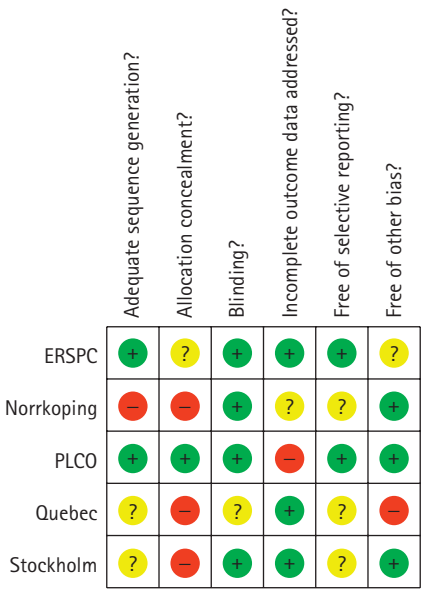
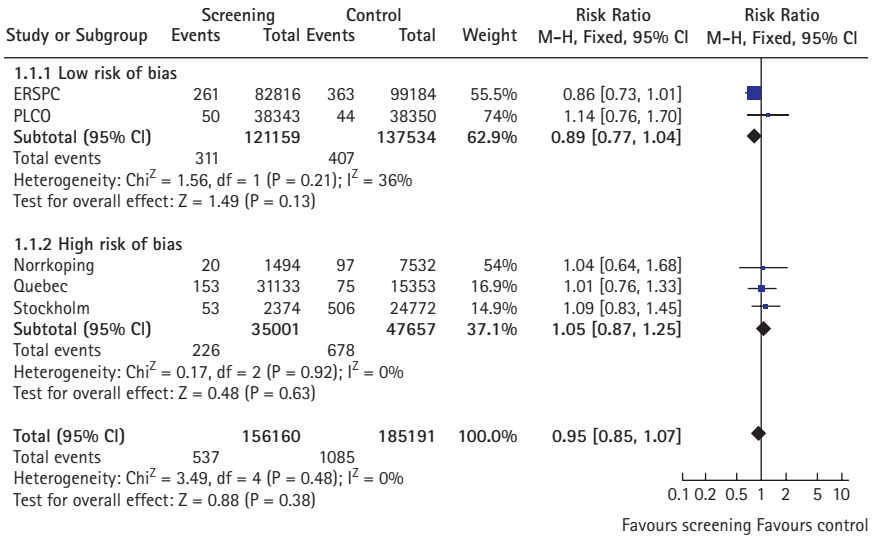


FIG. 2. Prostate cancer-specific mortality (sub-group analysis risk of bias).



followed-up at 10 years. In all, 98% of participants were followed-up at 7 years).

- **Quebec** – high risk of bias (due to high risk of bias associated with lack of allocation concealment and analysing data not using the intention-to-treat principle)
- **Stockholm** – high risk of bias (due to high risk associated with lack of allocation concealment and uncertainty with sequence generation). This study also has low external validity as it had a one-time screen for prostate cancer, with biopsy only performed if the PSA value was >10 ng/mL. None of the cancers eventuating in this population were detected by PSA testing.

Further information detailing the risk of bias for each study is given in Table 1 and Fig. 1.

TRIAL CHARACTERISTICS

Five studies, randomizing 341 351 men, provided information relating to prostate cancer-specific mortality. Additional reported outcomes included prostate cancer diagnosis, all-cause mortality, stage at diagnosis and treatment follow-up. The ERSPC and PLCO studies provided data on number of biopsies performed and harms associated with screening (e.g. infection/bleeding from TRUS-guided biopsies). The studies differed considerably in their design, screening methodologies, frequencies, thresholds and analysis thus limiting the value of strict reliance on pooled estimates. Detailed trial characteristics are described in Table 2.

PROSTATE CANCER-SPECIFIC MORTALITY

Prostate cancer screening did not result in a statistically significant reduction in prostate cancer-specific mortality when all populations of all studies were analysed and combined in meta-analysis according to intention-to-screen analysis. Meta-analysis of the five included RCTs identified the RR of prostate cancer-specific mortality to be 0.95 (95% CI 0.85–1.07; Fig. 2). The ERSPC study showed a significant benefit for screening in reducing prostate cancer-specific mortality among a 'core' subgroup of men aged 55–69 years at baseline (RR 0.80, 95% CI 0.65–0.98). Overall risk of bias was graded as high for this outcome due to the high risk of bias associated with the Quebec, Stockholm and Norrkoping studies. Meta-analysis of the ERSPC and the PLCO studies (which were the only two studies assessed as a low risk of bias) produced a RR of 0.89 (95% CI 0.77–1.04). Subgroup analysis identified no significant difference in prostate cancer-specific mortality regardless of whether men were screened from 45 years of age (RR 1.01, 95% CI 0.76–1.32), 50 years of age (RR 0.88, 95% CI 0.75–1.02), or 55 years of age (RR 1.11, 95% CI 0.88–1.39; Fig. 3).

ALL-CAUSE MORTALITY

Prostate cancer screening did not result in a statistically significant reduction in all-cause mortality. A meta-analysis of the two studies providing information on all-cause mortality in the ERSPC (which was provided through author contact) and Stockholm studies showed no difference in all-cause mortality between screening and control groups (RR 1.00, 95% CI 0.98–1.02).

DIAGNOSIS OF PROSTATE CANCER

Prostate cancer screening increased the number of men diagnosed with prostate cancer. The number of men diagnosed with prostate cancer across both screening and control groups was reported by four of the included studies. A meta-analysis of the ERSPC, Norrkoping, PLCO and Stockholm trials indicates that screening is associated with a 35% increase in the number of men diagnosed with prostate cancer (RR 1.35, 95% CI 1.06–1.72). Both the ERSPC and PLCO were assessed as a low risk of bias. The Norrkoping and Stockholm studies were graded as a high risk of bias. Sensitivity analysis showed no meaningful difference in results with the exclusion of the Norrkoping and Stockholm studies.

HARMS OF SCREENING

The direct harms of prostate cancer screening were generally considered minor in severity and transient in duration. In all, 20 437 positive PSA tests were recorded in the ERSPC study, with a further 17 543 biopsies taken. Of the biopsies performed, 5900 (8.2%) men in the screening group were diagnosed with

TABLE 1 Methodological quality summary: review of authors' judgements about each methodological quality item for each included study

Item	Judgement	Description
ERSPC study		
1. *Adequate sequence generation?*	Yes	The study was a multi-centre trial across seven European counties 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'.
2. *Allocation concealment?*	Unclear	Method of concealment was not described in the publication. It is also unclear whether method of concealment differed among study sites given that different randomization procedures were implemented across the different sites. '. . . randomization procedures differed among countries and were developed in accordance with national regulations'.
3. *Blinding?*	Yes	It is not possible to blind participants and clinicians to the screening intervention. Causes of death were evaluated in a blinded manner. Causes of death were obtained from registries and individual chart reviews. A committee analysed causes of death at each centre, with an independent data and safety committee reviewing the trial. There was no information on blinding for other outcome measures (e.g. diagnosed cancers). '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'.
4. *Incomplete outcome data addressed?*	Yes	Withdrawals from two participating sites were not included due to short duration of follow-up and discontinuation in the overall ERSPC study. Missing data is likely to be balanced across groups and unlikely to introduce bias. 'The results of analyses from two participating countries were not included in this analysis . . . data from their analyses were not included because of the short duration of follow-up'.
5. *Free of selective reporting?*	Yes	Objectives of the ERSPC include cancer-specific mortality and HRQL outcomes. Mortality is reported but HRQL is not descriptively reported in this publication. Measures relating to HRQL are currently being reviewed and will form the basis of future publications. 'No deaths were reported as a direct complication associated with a biopsy procedure'.
6. *Free of other bias?*	Unclear	Main data analysis is based on the core age group (55–69 years). There are differing age groups across the seven sites. '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'.
Norrkoping		
1. *Adequate sequence generation?*	No	Men were randomized to the screening group from a list of dates of birth. '. . . men were randomly allocated to be screened by assigning every sixth man from a list of dates of birth'.
2. *Allocation concealment?*	No	There was no description of allocation concealment.
3. *Blinding?*	Yes	It is not possible to blind participants and clinicians to the screening intervention. Prostate cancer mortality was obtained from a national cancer registry and cross-referenced against patient notes. There is no clear description of blinding during outcome assessment; however the outcomes (mortality, diagnosis) are unlikely to be influenced by lack of blinding. 'All cases of prostate cancer detected in the screened as well as the unscreened cohort were also registered in the South-East Region Prostate Cancer Register'.
4. *Incomplete outcome data addressed?*	Unclear	Withdrawals were cited, but it is unclear how the data for those men who migrated was available. There was no missing data for mortality, but some for number of men diagnosed, due to migration and death. 'The screened cohort diminished from 1492 men at the start of the study to 1118 in 1996 due to migration and death'.
5. *Free of selective reporting?*	Unclear	Insufficient information to permit judgement.
6. *Free of other bias?*	Yes	Data presented to allow analysis according to intention-to-screen principle.
PLCO		
1. *Adequate sequence generation?*	Yes	Individual randomization was performed within blocks stratified according to centre, age and sex. Although the method used to generate allocation sequence was not mentioned in the trial report, it was done so in an earlier publication. '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 (study centre) microcomputers'.
2. *Allocation concealment?*	Yes	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'.

TABLE 1 Continued

Item	Judgement	Description
3. *Blinding?*	Yes	It is not possible to blind participants and clinicians to the screening intervention. Data on diagnosed cancers and mortality were obtained by patient reported questionnaire and followed up by telephone (unblinded). This data was supplemented by linkage to the National Death Index. Death certificates were obtained to confirm deaths and determine cause. Possible cancer specific deaths were reviewed by blinded reviewers. 'Reviewers of these deaths were unaware of study-group assignments for deceased subjects'.
4. *Incomplete outcome data addressed?*	No	Data on mortality and diagnosis is available for the 7-year follow-up. However, follow-up data on 10-year outcomes is not complete. 'At 7 years, vital status was known for 98% of men in the two groups. At 10 years, vital status was known for 67% of the subjects'.
5. *Free of selective reporting?*	Yes	Findings are consistent with pre-specified outcomes in an earlier publication. Screening related risks (not specified in the earlier publication) are briefly described in this trial report. The authors state that outcomes relating to HRQL is currently under review and will be published upon completion.
6. *Free of other bias?*	Yes	Data was analysed according to the intention-to-screen principle.
Quebec		
1. *Adequate sequence generation?*	Unclear	No sequence generation process is mentioned. Authors only state that men were randomly assigned to groups. '. . . men were randomly allocated either to the group invited for annual screening or to the control group not invited for screening at a ratio of 2:1 in favor of screening'.
2. *Allocation concealment?*	No	No mention of allocation concealment.
3. *Blinding?*	Unclear	It is not possible to blind participants and clinicians to the screening intervention. Blinding of outcome assessment was not clearly described. 'The information on cause-specific death was obtained from the Death Registry of the Health Department of the Province of Quebec'.
4. *Incomplete outcome data addressed?*	Yes	Withdrawals from both the screening and control groups were cited.
5. *Free of selective reporting?*	Unclear	Insufficient information to permit judgement.
6. *Free of other bias?*	No	Data was not analysed according to the intention-to-screen principle. A total of 31 133 men were randomized to receive screening for prostate cancer, but only 23% of participants in this group actually complied with the randomization and were screened. Similarly ≈7% of men randomized to the control group were screened for prostate cancer. '. . . all screened men were compared to all unscreened men irrespective of the original randomization group'.
Stockholm		
1. *Adequate sequence generation?*	Unclear	The authors only state that patients were randomly selected for screening. No additional information is provided on the method of randomization. '. . . 2400 (men) were randomly selected and invited to participate in a prostate cancer screening study. The 24 202 remaining men served as a control group'.
2. *Allocation concealment?*	No	No method of allocation concealment was described.
3. *Blinding?*	Yes	It is not possible to blind participants and clinicians to the screening intervention. There was no specific mention of blinding of outcome assessors. Outcomes (mortality and diagnosis) and outcome measurement are unlikely to be influenced by lack of blinding. Outcomes were obtained from a national cancer registry, with urologists independently reviewing medical records to assign cause of death. 'From the Cause of Death register we collected information on date of death and the underlying cause of death. . . three senior urologists independently reviewed the medical records and assigned the cause of death'.
4. *Incomplete outcome data addressed?*	Yes	No missing outcome data for mortality or number diagnosed. However, there was discrepancy between population sizes, from Swedish census record 1998 and Statistics Sweden records. 'The file containing the registration number of the original 26 602 men could not be retrieved. We reconstructed the cohort . . . This comprised 27 204 men, that is 602 (2%) more than the original source population'.
5. *Free of selective reporting?*	Unclear	Insufficient information to permit judgement.
6. *Free of other bias?*	Yes	Data was analysed according to the intention-to-screen principle.

TABLE 2 Characteristics of included studies

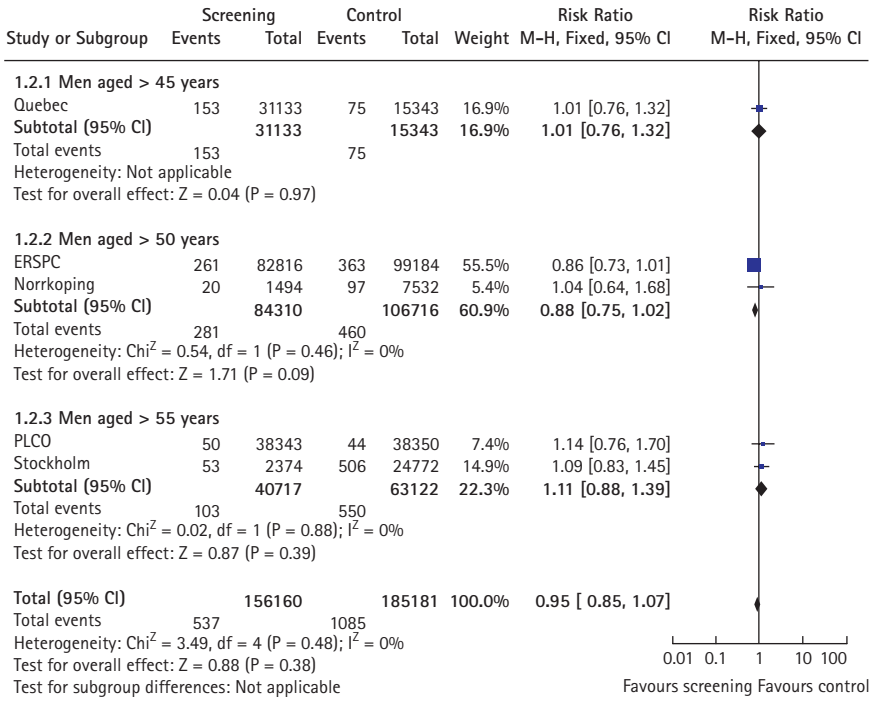
Item	Description
ERSPC study	
Methods	The ERSPC programme was a randomized, multi-centre trial across nine European countries (The Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, Portugal and France). Each country used different recruitment and randomization procedures. Participants were randomized 1:1 in all sites apart from Finland, which undertook a 2:3 randomization process. Duration of follow-up was dependent on site of randomization. The trial reports data on seven countries (data from Portugal and France was not included in this follow-up period).
Participants	The core age group for male participants was 55–74 years. In Sweden, study investigators included men aged 50–54 years, and investigators in the Netherlands, Italy, Belgium, and Spain included men up to the age of 74 years at entry. In Switzerland, men aged 55–69 years were included, with screening up to the age of 75 years. In Finland, men were recruited at the ages of 55, 59, 63, and 67 years. Men with a diagnosis of prostate cancer were ineligible for the study.
Intervention	Participants in the screening group were offered a combination of PSA testing, DRE and TRUS biopsy. Most sites used a PSA value of 3.0 ng/mL as the threshold and indication for biopsy. In Finland a PSA value of 4.0 ng/mL was used as the threshold – men with a PSA value of 3.0–3.9 ng/mL underwent a DRE until 1998. In Italy a PSA value of 4.0 ng/mL was the defined threshold, but men with a PSA value of 2.5–3.9 ng/mL underwent a DRE and TRUS. In the Belgian and Dutch sites a combination of DRE and PSA (with a threshold of 4.0 ng/mL) was used until 1997, from which PSA testing alone was used. In Belgium the PSA threshold value was 10.0 ng/mL. The screening interval at six of the seven sites was 4 years; Sweden used a 2-year interval. There was a 7-year interval between first and second screening rounds in Belgium.
Outcomes	Primary outcome was prostate cancer mortality. Also reported was number of prostate cancers diagnosed.
Notes	In all, 82.2% of men in the screening group were screened at least once. The median duration of follow-up was 8.8 and 9.0 years in the screening and control groups, respectively. No deaths were reported as a direct complication from the biopsy procedure. The rate of over-diagnosis in the screening group was estimated to be up to 50%.
Norrkoping	
Methods	RCT in Norrkoping, Sweden. Participants were men residing in the city of Norrkoping identified from a national population register. The study reports on a 15-year follow-up of participants on prostate cancer outcome.
Participants	Participants were male inhabitants of Norrkoping aged 50–69 years. Every sixth man was randomly allocated to the screening group from a list of date of births obtained from the national population register to screening. The remaining men served as controls. Only men aged ≤69 years were invited to the fourth screening round in 1996. There was no mention on any other specific exclusion criteria (e.g. previous diagnosis of prostate cancer or with symptoms).
Intervention	Interventions were screening every 3 years vs control (not invited for screening). The first and second rounds of screening were performed only by a DRE. The first screening round DREs were performed by a GP and a urologist. In the second and subsequent rounds the DRE was performed by a GP only. The third and fourth rounds of screening included a DRE and a PSA test. TRUS biopsy was performed if the DRE was deemed abnormal or if the PSA value was >4.0 ng/mL.
Outcomes	Primary outcome was prostate cancer mortality at 15-years follow-up. Also reported was clinical stage and choice of therapy in men diagnosed with prostate cancer across both screened and control groups, and number of prostate cancers diagnosed.
Notes	
PLCO	
Methods	The PLCO study was a RCT across 10 study centres in the USA. Each study centre used recruitment sources and strategies appropriate to the local situation. Participants were randomized 1:1. The study reports on a 7–10-year follow-up of participants for prostate cancer outcome.
Participants	Participants were men aged 55–74 years. Men with a history of prostate, lung or colorectal cancer were excluded, together with participants currently receiving cancer treatment. In 1995, men who had undertaken more than one PSA blood test in the previous 3 years were also excluded.
Intervention	Participants in the screening group were offered annual PSA testing for 6 years and annual DRE for 4 years. A PSA value of 4.0 ng/mL was determined to be positive for prostate cancer. DREs were performed by physicians, qualified nurses or physician assistants. Men with positive PSA results, or abnormal DREs, were advised to seek diagnostic evaluation.
Outcomes	Primary outcome was prostate cancer mortality at 7- and 10-years follow-up. Also reported was number of prostate cancers diagnosed.
Notes	The median (range) duration of follow-up was 11.5 (7.2–14.8) years.The rate of compliance for PSA testing and DRE in the screening group were 85% and 86%, respectively. The rate of PSA testing in the control group increased from 40% to 52% over the trial period. Similarly, the rate of DRE in the control group ranged from 41% to 46%.
Quebec	
Methods	RCT in Quebec, Canada. Participants were men identified from electoral roles and allocated 2:1 in favour of screening. The study reports on an 11-year follow-up of participants on prostate cancer outcome.
Participants	Participants were male inhabitants of Quebec city aged 45–80 years. Men with a previous diagnosis of prostate cancer or previously screened and referred to the study clinic for consultation were not eligible.

TABLE 2 Continued

Item	Description
Intervention	Interventions were annual screening vs control (not invited for screening). The firstst screening round included a PSA test and a DRE. TRUS biopsy was performed in cases with PSA values of >3.0 ng/mL and/or abnormal DRE (except for first 1002 men who had all three procedures performed). Follow-up screening included a PSA test. TRUS biopsy was only performed if the PSA value was >3.0 ng/mL for the first time or increased by >20% from last measurement.
Outcomes	Primary outcome was prostate cancer mortality at 11-years follow-up. Also reported was prostate cancer death incidence rates in screened vs unscreened cohorts, and clinical stage and choice of therapy in men diagnosed with prostate cancer.
Notes	Crossover and contamination were issues for this pragmatic trial. The compliance and contamination rate within both the screening and control groups was described. From a total of 31 133 men randomized to the screening group, 7348 (23.6%) were actually screened (i.e. all 31 133 men were invited to be screened but only 23.6% took up the invitation and actually were screened). Similarly, of the 15 353 randomized to the control group, 1122 (7.3%) were screened for prostate cancer at the study site. There was no report of any other withdrawals or whether participants in the control group were screened somewhere other than the study site; hence it is possible that >7.3% of the control group were actually screened. The data was re-analysed by this review's authors according to the intention-to-screen principle.
Stockholm	
Methods	RCT in Stockholm, Sweden. Male participants living the catchment area of Stockholm South Hospital were identified through census records. The study reports on a 15-year follow-up of participants on prostate cancer outcome.
Participants	Participants were all men aged 55–70 years living in the catchment area of Stockholm South Hospital. Men with an earlier diagnosis of prostate cancer were excluded from the study.
Intervention	Interventions were one-time screening vs control (not invited for screening). The screening consisted of DRE, PSA test and TRUS. TRUS-guided biopsies were taken if abnormal findings occurred during the DRE and/or TRUS. A repeat TRUS was performed if the PSA value was >7 ng/mL.
Outcomes	The primary outcome was prostate cancer mortality at 15-years follow-up. Also reported was 'any' cause mortality (including attendees and non-attendees), 'other' cause mortality (including attendees and non-attendees), and number of prostate cancers diagnosed.
Notes	The median follow-up was 12.9 years overall. The mean (range) follow-up for the screened group was 12.9 (0.2–15.7) years and for the control group was 13.0 (0.7–15.7) years.

prostate cancer; with 1755 of these men (29.3%) diagnosed with prostate cancer outside of the screening protocol. The false-positive rate for men who had an elevated PSA value (different PSA thresholds were used to define elevated but typically was defined as >3.0 ng/mL) and subsequently underwent a biopsy was 75.9% in the ERSPC study. The main harm of screening is the rate of over-diagnosis in the screening group; which was estimated to be up to 50% (ERSPC). This results in unnecessary treatment and harms which are frequent, often persist and are at least moderate in severity. No deaths were reported as a direct complication (from issues such as septicaemia or bleeding) from the biopsy procedure. Complication rates associated with TRUS-guided sextant biopsies from the Netherlands site have been previously published [22]. In this site, complication rates from 5802 first-time TRUS-guided sextant biopsies were evaluated. The most common complications assessed as 'minor' were haematospermia (50.4% of participants who underwent a biopsy) and haematuria for >3 days (22.6%). The most common side-effects assessed as 'major'

FIG. 3. Prostate cancer-specific mortality (sub-group analysis age).



complications were pain after biopsy (present in 7.5% of men biopsied) and fever (3.5%).

The PLCO study similarly reported on adverse events for screening and treatment. Pain or bleeding was associated with a rate of 0.3 per 10 000 screenings with DRE. The PSA test had a complications rate of 26.2 per 10 000 screenings (primarily dizziness, bruising and haematoma; with three episodes of fainting). Medical complications from the diagnostic procedures occurred in 68 of 10 000 evaluations after a positive result from screening. These complications were primary infection, bleeding, clot formation and urinary difficulties.

DISCUSSION

A meta-analysis of the five included studies in this review identified that screening does not significantly decrease prostate cancer-specific mortality, and is associated with a high degree of over-diagnosis. Given the variation in study design and quality across the five included studies, it could be argued that pooling studies is not appropriate. However, assessment of the five studies individually using intention-to-screen analysis also indicates no decrease in prostate-specific cancer mortality. The only exception was the ERSPC study, which reported a benefit for screening in men aged 55–69 years. In this specific subgroup it was identified that 1410 men needed to be invited to screening and 48 additional men subsequently diagnosed with prostate cancer needed to receive early intervention to prevent one additional prostate cancer death at 10 years. The known harms associated with screening (false-positives with PSA testing, complications associated with TRUS-guided biopsies, over-diagnosis and treatment-related harms) suggests that any small mortality benefit of screening at 10 years would be challenged by the occurrence of these harms that occur early and may persist.

Notably, participant cross-over between groups was an issue in several of the included trials and will continue to be an important factor for consideration in future analyses. The rate of compliance for PSA testing and DRE in the screening group of the PLCO study were 85% and 86%, respectively. The rate of PSA testing in the control group of the PLCO study increased from 40% to 52% over the trial period, with the rate of DRE in the control group also increasing to 46%. In the Quebec study, only 23% of men randomized to the screening group complied with the randomization, with 7% in the control group being screened.

For men who express an interest in prostate cancer screening, including those with risk factors such as family history of prostate cancer and African ethnicity [23], clinicians should adopt a shared-informed approach to decision making. Men should be informed of the lack of benefit to at least 10 years, and demonstrated adverse effects when deciding whether or not to undertake screening for prostate cancer. Any benefits from prostate cancer screening may take up to 10 years to accrue [24,25]. Men who have an anticipated life expectancy of <10–15 years (either due to age or co-morbid conditions) should be informed that testing for prostate cancer is unlikely to be beneficial given harms associated with testing. Prostate cancer screening also increases by up to two-fold the number of cancers detected many of which would never cause problems during a man's lifetime even if left untreated [26–28]. Several fundamental issues should be addressed when considering screening for prostate cancer. Screening for prostate cancer is primarily performed using the DRE and PSA testing, yet the specificity and sensitivity of both these methods are not ideal [6]. The consequences of heightened anxiety and further examinations through biopsies and the considerable side-effects associated with various prostate cancer treatments, must be appreciated [29]. This predicament is further compounded by the inability to understand whether identified neoplasms are clinically significant. Some slow growing tumours may never threaten a man's life, as is represented by the discrepancy between the incidence and death attributed to prostate cancer [1].

Before obtaining a PSA test men should be informed about the known harms that are frequent, both immediate and long term vs the lack of benefit at 10 years, and the requirement that any potential future benefit may take up to 20 years to accrue [25,30]. Clinicians may adopt either a 'reactive' or 'proactive' method to counselling patients on prostate cancer screening, depending on their attitudes to screening; i.e. clinicians in favour of screening men of certain age will adopt a 'proactive' nature to counselling opposed to those who wait for the patient to raise the topic of screening. We think that rather than counselling all men (proactive), counselling should be targeted to men who ask about screening or those who have previously screened in order to provide updated information. This approach permits clinicians to focus time, effort and resources on areas of greatest concern to their patients and where there is greatest evidence of effectiveness. Facilitating this process with the aid of appropriate patient education materials will promote informed patient choice [31], while minimizing workload burden among primary care providers and permitting primary care clinicians to focus on other preventive healthcare strategies of proven effectiveness for other health conditions.

Findings from this review support further research across various health disciplines. Further long-term follow-up from existing trials is required to gain a better understanding of the adverse events, HRQL and economic impact of screening. A longer follow-up period of existing trials for prostate cancer-specific mortality will also provide more robust evidence that can better inform any net benefit of screening for prostate cancer. Future research could incorporate time-to-event analysis, to incorporate the longer duration of follow-up from the included trials.

Any additional trials should aim to provide high-quality data on the impact of prostate cancer screening on HRQL, potential harms, adverse events and an economic evaluation in addition to mortality across different populations as yet unrepresented in RCTs (e.g. Asia). Additionally, such studies should be conducted using appropriate, or justified, selection of participants, adequate allocation concealment, adequate blinding of assessors, completeness of follow-up and analysis of data according to intention-to-screen principles when possible. Prostate cancer-specific mortality is also highly dependent on the effectiveness of treatment regimes. Further research is required from long-term high-quality trials to inform the effectiveness of current treatment regimens including radical prostatectomy, radiotherapies and active surveillance.

Recent evidence suggests that the PSA test does not have the required characteristics to be used as a widespread screening test for prostate cancer [6]. If the PSA test is to be used as a screening tool, greater evidence is needed to establish recognised threshold

values for a 'negative' and 'positive' test results to ensure that patients do not undergo unnecessary invasive investigations; and similarly are able to be referred for further investigations when warranted. A systematic review of diagnostic test accuracy synthesising the current evidence would inform the broader understanding of the PSA test, its characteristics and value as a screening and diagnostic tool. Whilst the PSA test may be prostate specific, it is not specific to prostate cancer; therefore, continued research into alternative prostate-specific markers is required.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HRQL**, health-related quality of life; **RCT**, randomized controlled trials; **RR**, relative risk; **AR**, absolute risk; **ERSPC**, European Randomised Study of Screening for Prostate Cancer; **PLCO**, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.