Screening for prostate cancer with prostate specific antigen and treatment of early-stage or screen-detected prostate cancer: a systematic review of the clinical benefits and harms

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ABSTRACT

Background and Objective: Prostate cancer screening with prostate-specific antigen (PSA) was first conducted widely in Canada in the early 1990s. The Canadian Task Force on Preventive Health Care (CTFPHC) recommendations were last published in 1994 at which point there was insufficient evidence to recommend screening men over 50 years of age with PSA. This review will evaluate the current evidence on the effect of PSA screening on mortality which will be used by the CTFPHC to develop an updated prostate cancer screening recommendation. In addition, treatment effectiveness will be reviewed to help inform the recommendation on screening.

Methods: A search was conducted to update the 2011 United States Preventive Services Task Force (USPSTF) evidence reviews which addressed benefits and harms of screening and treatment of prostate cancer. GRADE was used to assess the strength of evidence. Meta-analysis was not performed on the screening studies due to methodological and clinical heterogeneity, whereas meta-analysis was conducted on the treatment studies.

Results: Six RCTs were identified that examined the effect of PSA screening for prostate cancer on mortality, with two trials reporting a reduction in prostate cancer-specific mortality, and four showing no effect. Harms of screening included overdiagnosis and false-positives, as well as harms of biopsy following positive screening. The meta-analysis of treatment studies showed a reduction in prostate cancer-specific mortality with prostatectomy, radiation therapy, and radiation therapy in combination with hormone therapy. No treatment effect was reported with hormone therapy alone. Harms of treatment included erectile dysfunction and urinary incontinence following treatment with prostatectomy and radiation therapy.

Limitations: The screening RCTs varied in their screening interval, age range, follow-up period, and PSA threshold for biopsy. Quality of the studies also varied, with three having a low risk of bias and three with a high risk of bias. Of the low risk of bias studies, one study did not have an unscreened population for comparator, but rather compared population based screening to opportunistic screening. This trial reported no effect of screening and therefore the effect of screening may be underestimated.

Discussion: The results of this systematic review underline the methodological and clinical inconsistencies across the prostate cancer screening evidence base and the conflicting conclusions about the effectiveness of PSA screening. Although the pooled analyses of treatment for prostate cancer show a reduction in prostate cancer-specific mortality with prostatectomy and radiation therapy, there are substantial harms associated with these treatments. The inconsistent results of screening with PSA on prostate cancer-specific mortality, the harms associated with screening and treatment, and the overdiagnosis rates should be considered when developing recommendations on PSA screening.

INTRODUCTION

In Canada, prostate cancer is the most commonly diagnosed non-skin cancer in men; 23,600 newly diagnosed cases were estimated in 2013, with incidence generally increasing with age.[2] For the same year, 4,000 deaths due to prostate cancer were estimated.[1] Prostate-specific antigen (PSA) is a protein produced by the prostate gland.[3] In Canada, measurement of serum PSA levels via PSA testing became widespread in 1990-1991.[4] The purpose of the PSA screening test is to identify prostate cancer earlier, thereby reducing mortality.[5]

The Canadian Task Force on Preventive Health Care (CTFPHC) last reviewed the evidence on prostate cancer screening and treatment in 1994 at which point there was "…insufficient evidence to include prostate-specific antigen screening in the periodic health examination of men over 50 years of age".[6] This recommendation was based on evidence from observational studies. Since that time, several large randomized controlled trials and systematic reviews of these trials have been published. Most recently, in January 2013, The Cochrane Collaboration published a review on screening for prostate cancer and reported that PSA screening did not significantly reduce mortality due to prostate cancer based on 5 RCTs. The United States Preventive Services Task Force (USPSTF) review published in 2011 reported no reduction in prostate cancer-specific mortality with PSA screening.[7]

The purpose of the current review was to evaluate the current evidence on the effect of PSA screening and prostate cancer treatment on prostate cancer-specific and all-cause mortality, in order to inform updatedCTFPHC recommendations on screening for prostate cancer.

METHODS

The analytical framework upon which this review was based is found in Figure 1. There are key questions for both screening for and treatment of prostate cancer, and additional questions to aid in the contextualizing of the information. The guideline that will use this systematic review as a basis will focus on screening. The treatment questions are included to help inform the screening recommendation. Further, the benefits and harms of treatment will be examined in the context of screening to help determine the effectiveness of screening and early detection of prostate cancer.

Search strategy

Our search updated those conducted for the USPSTF reviews for screening and treatment of prostate cancer.[7,8] We searched Medline, Medline In-process and Other Non-Indexed Citations, The Cochrane

Control Trial Registry, EMBASE and PubMed for studies published between July 2011 and November 2012 (treatment) and July 2011 to November 2013 (screening). Our search was limited to languages of English and French but was not limited by study design. We also searched reference lists of on-topic systematic reviews. Our search identified 6704 unique citations of which 40 new papers met the inclusion criteria for this review and as such were added to the studies included in the USPSTF reviews.[7,8] A separate search was conducted for contextual questions. We searched Medline, EMBASE and psycINFO for studies published between January 2007 and November 2012. The search strategy is reported in Appendix 1. To ensure that all the harms of screening of interest to the Prostate Working Group were available the ERSC undertook a separate search. The databases searched included Medline, The Cochrane Library and Embase for Januray 2000 to November 2013 (Appendix 1).

Selection

The titles and abstracts of papers considered for the key questions were reviewed independently by two members of the synthesis team (JB, UA, RW, MK); any article marked for possible inclusion by either team member went on to full-text rating. Full-text inclusion, quality assessment and data extraction were also completed by two team members. All disagreements were resolved through discussions. The inclusion results were reviewed by a third investigator (DFL). Data were extracted by one investigator (JB, UA, DFL) using a standard format with this extraction being checked by a second investigator (RW, MK). The exceptions to this process were studies related to the contextual questions and grey literature, for which title and abstract screening and data extraction were done by one investigator (DFL). There was no assessment of the quality of the evidence used to answer the contextual questions. The flow diagram of included studies in reported in Appendix 2.

Inclusion/Exclusion Criteria

Screening

For inclusion in this review the population of interest was men asymptomatic for prostate cancer (although men with chronic, mild lower urinary tract symptoms were included). The intervention of interest was one or more PSA measurements, with or without additional methods such as digital rectal examination. The comparison was to no screening/usual care in the asymptomatic general primary care population. Men who had previous PSA screens were not excluded. The outcomes for effectiveness were all-cause or prostate cancer-specific mortality, or harms associated with screening. Harms of screening included false positives, overdiagnosis/overtreatment, and post biopsy harms such as infection, bleeding, composite medical harms, and hospitalization. Study design for assessing

effectiveness of screening was limited to randomized control trials (RCTs).There were no limitations on study design for the harms outcomes.

Treatment

The population of interest was men treated for screen-detected prostate cancer. Because most studies do not describe whether the prostate cancer was screen detected, studies of localized (T1 or T2) prostate cancer were also included (as most screen-detected cancer is localized).[8] The treatments of interest were radical prostatectomy, radiation therapy, hormonal therapy, cryotherapy, and high-intensity focused ultrasonography (HIFU). Control treatments defined in the included studies were: observation (no immediate treatment), deferred treatment (no initial treatment for 6 months following diagnosis), and conservative management (non-curative treatment which could include hormone therapy or palliative therapy). Because of the lack of detail in the studies, it is unclear if these control treatments were active surveillance (continued PSA monitoring) or watchful waiting (monitoring for symptom progression). The outcomes of interest were all-cause mortality, prostate cancer-specific mortality, and harms associated with prostatectomy, radiation therapy, hormonal therapy, cryotherapy, and HIFU. The harms of interest included mortality, reduced quality of life or function, increased urinary incontinence, bowel dysfunction, erectile dysfunction, surgical complications, and 30 day post-surgical complications. Acceptable study designs included RCTs and cohort studies. If no RCTs, cohort studies, or large (n>1,000) uncontrolled studies were available, smaller uncontrolled studies were used. For harms, uncontrolled observational studies were included if they reported on perioperative harms.

Quality Assessment

The strength of the evidence supporting the key questions was assessed through the GRADE system which grades the quality of evidence as high, moderate, low or very low. Each of the four levels reflects the likelihood that further research will impact the estimate of effect (e.g., high quality: further research is unlikely to change confidence in the estimate of effect).[9,10] A GRADE quality rating is based on an assessment of five conditions: (1) limitations in study designs (risk of bias), (2) inconsistency (heterogeneity) in the direction and/or size of the estimates of effect, (3) indirectness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, (4) imprecision of results (few events/observations, wide confidence intervals), and (5) indications of reporting or publication bias. Each of these components is rated as high, low or unclear risk of bias. In order to achieve a high or low risk of bias for a particular component we looked for explicit statements from the

authors as to what they did or did not do methodologically. In the absence of information we assessed that component as 'unclear'. To determine the overall risk of bias we placed a higher value on random sequence generation, allocation concealment and blinding. As well, components assessed as unclear were considered equivalent with high risk of bias. The Cochrane Risk of Bias tool was used to assess risk of bias in the RCTs, and the Newcastle Ottawa Scale was used for the cohort studies. Therefore RCTs which in GRADE begin with a high quality rating may be downgraded if there were serious or very serious concerns across the studies related to one or more of the five conditions. Quality ratings can also be upgraded based on an assessment of three conditions: (1) large effect size, (2) dose response effect, and (3) plausible confounding. All groups of observational studies begin with a low quality rating which were further downgraded based on assessments of the same five criteria. All other types of evidence were assigned a very low quality rating.

Data Analysis

For the benefits of PSA-based screening, the results were synthesized descriptively using median with ranges, since the studies were methodologically and clinically too different from each other to allow for a quantitative synthesis of data. The results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial[11] for the outcome of prostate cancer-specific mortality were separated based on screening interval, as all centers except Sweden used a 4 year screening interval while the Swedish center (Göteborg)[12] used a 2 year screening interval. For the harms of PSA-based screening, the results were reported descriptively using proportions (%) with 95% confidence intervals, since the data were primarily obtained from uncontrolled or modelling studies.

For benefits and harms of treatments of localized prostate cancer, the preferred measure was the number of events from each intervention group (radical prostatectomy, radiotherapy, hormonal therapy) compared to control group in the meta-analysis. The DerSimonian and Laird random effects models with inverse variance method were utilized to generate the summary measures of effect in the form of risk ratio for each outcome. The risk ratio was used as a summary statistic because only a few studies reported the time-to-event data or hazard ratios, and adjustment of various factors along with length of follow-up varied across studies reporting hazard ratios. In this situation, it was necessary to utilize the number of events data to maximize the number of included studies in quantitative synthesis and to provide statistical stability. For studies where events data were not reported for each intervention arm, we contacted the authors. Two of the studies reported survival, and therefore the

number of deaths was estimated from the survival proportion/percentage provided using Kaplan-Meier curves.[13,14]

To compare the direction and magnitude of effect obtained from risk ratios (RR) using events data for mortality outcomes, we also pooled adjusted hazard ratios (HR's) reported in papers using DerSimonian and Laird random effects models with inverse variance method, and no significant differences were found between results obtained from risk ratios and hazard ratios. The Cochrane's Q (α=0.10) and I^2 statistic were employed to quantify the statistical heterogeneity between studies, where $p<0.10$ indicated a high level of statistical heterogenity between studies. Sensitivity analyses were performed on the type of intervention, study design, and study risk of bias to evaluate statistical stability and effect on statistical heterogeneity.

In order to investigate the clinical relevance of the results, the number needed to screen/treat (NNS/NNT) and the absolute risk reductions were generated. NNS/NNT were calculated by taking the inverse of the risk difference between the control and intervention groups.[15] The direction of effect was presented with the corresponding 95% confidence interval.[16] NNS/NNT were only presented when the estimate of effect (RR) showed a statistically significant effect.

RESULTS

Key question 1: Benefits of screening for prostate cancer

Six RCTs were identified that addressed the benefits of screening on prostate cancer-specific mortality, all-cause mortality, other-cause mortality (causes other than prostate, colorectal, or lung cancer), or all-cause mortality in those patients diagnosed with prostate cancer.[11,12,17-20] An overview of these trials is reported in Table 1. These trials were included in the 2011 USPSTF systematic review[21] (and two now have additional years of follow-up[11,17]) and the 2013 Cochrane review[5] on screening for prostate cancer. One of these trials is a sub-study (Göteborg, Sweden) of the ERSPC trial and was assessed as higher quality than the ERSPC.[11,12] In addition, this study had a different protocol than the other ERSPC sub-studies and was originally its own study and later added to the ERSPC. Therefore the results of the Göteborg study are reported separately and removed from the larger trial data. The estimates for prostate cancer specific-mortality in the ERSPC study are those excluding the Göteborg centre.

The six RCTs varied in the interval of screening, the screening test (some included digital rectal exam or transrectal ultrasonography as well as PSA), the PSA cut-off for biopsy, the age group included for

screening, and the follow-up time (study characteristics reported in Appendix 3). In addition, the control group in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) trial included opportunistic screening. For these reasons, data from these studies were not pooled, but instead, the results were synthesized descriptively using median with ranges in the form of rate ratios. Table 2 reports the overall findings of these studies and GRADE ratings. Risk of bias for each of these studies also was assessed (Appendix 4, Appendix 5) and overall risk of bias was serious. The assessment indicated a high risk of bias for the Quebec, Norrköping, and the Stockholm studies, with lower risk of bias for the other studies. Göteborg was assessed with the lowest risk of bias.

Two of these trials found a reduction in prostate cancer-specific mortality (ERSPC and Göteborg; very low quality evidence), whereas four found no difference between the screening and control groups (PLCO, Quebec, Norrköping, Stockholm; very low quality evidence). The absolute risk reduction was calculated to be 0.08% for ERSPC and 0.34% for Göteborg, corresponding to number needed to screen (NNS) of 1221 (95% CI: 676-6337) and 293 (95% CI 177-799; Table 2). The NNS is not reported for the other trials given the absence of an effect. No difference in overall, all-cause, or other cause mortality was found in any of the trials (PLCO, ERSPC, Norrköping, Stockholm; low quality evidence; Table 2 [Evidence Set 1]; Quebec did not report all-cause mortality and Göteborg data for all-cause mortality could not be separated from ERSPC and therefore is included in the ERSPC data).

Key question 1b: Differential screening based on risk factors

Results were presented by age for the PLCO and ERSPC trials for prostate cancer-specific mortality (Table 3). No differences based on age (< 65 years and ≥ 65 years) were reported in the PLCO trial. The ERSPC trial reported RR for prostate cancer-specific mortality in 5 year age groups starting at ≤54 years to ≥ 70 years of age. In this ERSPC subgroup analysis, the only significant difference was seen in the 65-69 year age group (RR 0.67 [95% CI: 0.53-0.86]). To allow comparison with the PLCO trial, data was analyzed by <65 years and ≥ 65 years. The significant difference seen in the 65-69 year age group is maintained when this group is combined with the ≥ 70 year age group. It is important to note however that these data include the results from the Göteborg study which were removed from the overall results for the ERSPC study in key question 1. No evidence was identified that addressed the question of whether other specific risk factors such as ethnicity, family history, or previous PSA values require different screening recommendations.

Key question 2: Harms of screening for prostate cancer

Harms of screening identified as clinically relevant included overdiagnosis (detection of cancers that if left untreated would not result in symptoms or death), false positives, and harms associated with biopsy (Evidence Set 2). The quality of the evidence on harms of screening identified in the observational studies was assessed as very low. The results were reported descriptively using proportions (%) with 95% confidence intervals, since the data were primarily obtained from uncontrolled or modelling studies. Overdiagnosis was estimated in modeling studies and was from 40.45% and 42% of men screened for screening every four years using a PSA threshold of 3 ng/mL[22-24] and was 54% with a threshold of 4ng/mL.[25] An overdiagnosis rate for screening every year with a PSA threshold of 4 ng/mL was estimated at 42% [25] and 56% (Table 4).[25] The overdiagnosis rate for a single screen was also reported, but may not be relevant as screening is likely occur at intervals as opposed to once.

False positive results for men screened at least once using a 3 ng/mL PSA threshold was reported to be 19.82% (11.51% - 28.13%) in one study[26] and using a 4 ng/mL PSA threshold was reported to be 11.30% (9.92% - 12.67%) in two studies (Table 5).[26,27]

Harms related to biopsy following positive PSA results included hematuria, infection, hospitalization, and death (Table 6). Hematuria (which occurred less than 30 days after biopsy) was reported in 14 uncontrolled observational studies and the mean rate was 23.61% (0.8% - 84%). Infection (< 30 days) was reported in 6 studies and the rate was 1.08% (0.005% to 2.4%). Hospitalization occurred in a mean of 2.07% of patients (1.59% - 2.54%) reported in 24 studies and death in 0.169% (0.089% - 0.249%) in eight studies. The ERSPC reported a biopsy rate of 27.0% (ranging from 12.0% - 46.0% in the different study sites.[11]

Key question 3: Benefits of treatment for prostate cancer

The GRADE evidence profiles and Forest Plots for studies assessing the benefits of treatments for prostate cancer are reported in Evidence Set 3, as well as subgroup analysis by control group definition. Study characteristics are reported in Appendix 6. Risk of bias was assessed using the Cochrane risk of bias tool for the RCTs (Appendix 7) and the Newcastle Ottawa Scale (NOS) for the cohort studies (Appendix 8). Two of the RCTs were rated as low risk of bias (Wilt[28] and Bill-Axelson[29]), and the cohort studies all received between 7 to 9 stars on the NOS (out of 9 possible stars), with more stars indicating a low risk of bias.

Prostatectomy

Two RCTs and six cohort studies assessed the effect of treatment with prostatectomy on prostate cancer- specific mortality.[13,28-34] All-cause mortality was assessed in three RCTs and eight observational studies.[13,14,28-36] One additional cohort study was identified, but it did not report event data and therefore was not included in the meta-analysis.[37]

For prostate cancer-specific mortality, the pooled results show a positive effect of treatment with prostatectomy (Table 7) in both RCTs (high quality evidence) and cohort studies (low quality evidence). The number needed to treat (NNT) is 20 (95% CI: 13-58) in the RCTs and 30 (95% CI: 26-37) in the cohort studies with 5% and 3% absolute risk reduction of death due to prostate cancer, for those treated compared to those who were not treated. There was no serious risk of bias, inconsistency, indirectness, or imprecision assessed in either the RCTs or the cohort studies. There were methodological differences in detection (clinically vs. screen detected), follow-up time, and cancer stage, however downgrading of the evidence was not warranted due to these factors.

Pooled RCT data show that all-cause mortality was not affected following treatment with prostatectomy (moderate quality of evidence), although it is unclear if these studies had adequate statistical power to detect such a difference. Pooling of the cohort studies demonstrates a reduction in all-cause mortality with prostatectomy (low quality of evidence). There was no serious risk of bias, inconsistency, indirectness, or imprecision in either the RCTs or the cohort studies.

One additional cohort study[37] was identified that treated patients with prostatectomy and assessed all-cause mortality. Although this study had 14.5% of participants with stage 3 prostate cancer (we excluded those with >10% T3 cancers), the study specifically states that this population was all clinically localized and therefore was included in the USPSTF review and this update. This study was not included in the meta-analysis because events rates were not reported.

Radiation therapy and hormone therapy – single and combination

Prostate cancer-specific mortality was assessed in six cohort studies[13,30,32-34,38] in prostate cancer patients treated with radiation therapy compared with controls.(Table 8) All-cause mortality was assessed in eight cohort studies.[13,14,30,32-34,36,38] One additional cohort study was identified, but it did not report event data and therefore was not included in the meta-analysis.[37] Prostate cancer-specific mortality and all-cause mortality were reduced in the studies (low quality of evidence). The NNT was 54 (95% CI: 33-352) for prostate cancer-specific mortality and 7 (95% CI: 6-10) for all-cause mortality, with

an absolute risk reduction of 2% and 14% respectively. There was no serious risk of bias, indirectness, or imprecision in these studies. In the studies that assessed prostate cancer-specific mortality, there was serious inconsistency but large effect size. No inconsistency was found in the studies that assessed all-cause mortality.

Two of the studies that reported on the benefits of radiation therapy also included combination treatment with hormone therapy.[13,32] When radiation therapy was combined with hormone therapy in these studies, the significant benefit to reduce both prostate cancer-specific mortality and all-cause mortality remained, and in fact was more beneficial in combination (Table 8). The NNT was 18 (95% CI: 12-114) for prostate cancer-specific mortality and 3 (95% CI: 3-5) for all cause mortality. In contrast, hormone therapy on its own did not have an effect on mortality. Three cohort studies assessed prostate cancer-specific mortality[13,32,39] and four cohort studies assessed all-cause mortality[13,14,32,39] after treatment with hormonal therapy (Table 9). The risk of prostate cancer-specific mortality and all-cause mortality was higher in the treated group compared to controls (low quality evidence). There was no serious risk of bias, inconsistency, indirectness, or imprecision in these studies.

Cryotherapy and high-intensity focused ultrasonography

No studies on the effect of treatment with cryotherapy or HIFU on all-cause or prostate cancer-specific mortality were identified (Table 10 and Table 11).

Key question 4: Tailoring follow-up

No studies were found that met inclusion criteria for this review about whether tailoring the method of following up abnormal screening results to patient characteristics leads to clinically important differences in benefits or harms of screening for prostate cancer with PSA (Table 12).

Key question 5: Harms of treatment for prostate cancer

Evidence Set 4 includes the GRADE evidence profiles and forest plots for studies on harms of treatment. Risk of bias for studies assessing harms of treatment for prostate cancer is reported in Appendix 9. The USPSTF review included one RCT and four cohort studies[40-44] for the harm of urinary incontinence, one RCT and five cohort studies[40-45] for erectile dysfunction, and one RCT and three cohort studies [41,43,44,46] for bowel dysfunction with treatment with prostatectomy. This updated search identified one additional RCT[28] and an update of the RCT from the USPSTF review.[40] Four uncontrolled studies assessed the post-surgical harms of prostatectomy[28,47-49] and eight assessed quality of life outcomes.[42,43,50-55] Harms of radiation therapy were reported in one RCT and six observational studies.[41-45,56,57] The same eight studies

that assessed QoL following prostatectomy also assessed radiation therapy. One additional observational studied also assessed QoL outcomes following treatment with radiation therapy.[57] Hormonal therapy harms were assessed in three observational studies[43,44,58] and QoL in four observational studies.[43,52,53,58] Hormone and radiation combination therapy harms were assessed in one study.[43] HIFU harms were reported in three observational studies[59-61] and QoL outcomes for cryotherapy reported in one observational study.[55] For the continous outcomes such as quality of life using various domains of SF-36 as harms of treatment of localized prostate cancer, the data were insufficient (most studies did not provide any measure of variance such as standard deviation or standard error) to allow a quantitative synthesis or meta-analysis. Therefore, the results were synthesized descriptively using mean difference with ranges, between treatment and control groups at post-intervention.

Prostatectomy

Pooled estimates (Table 13) indicate a significant increase in risk of urinary incontinence with treatment with prostatectomy (both RCTs [high quality evidence] and cohort studies [moderate quality evidence]), whereas the cohort studies indicated an increased risk of erectile dysfunction (low quality evidence). There was no effect of prostatectomy on risk of bowel dysfunction. Another study assessed harms of prostatectomy but did not report events data and therefore is not included in the GRADE tables and analysis. Talcott et al.[62] assessed harms of prostatectomy and radiation therapy and found increased urinary incontinence with treatment with prostatectomy at 3 months which improved slightly but remained increased at 12 and 24 months (patient reported scores increased from 4.9 to 35.0 at 3 months, and improved to 23.9 and 23.4 at 12 months and 24 months respectively). Sexual dysfunction also increased with prostatectomy.

Post-surgical complications (any) were reported in 11.4% to 21.4% of patients whereas post-surgical mortality was reported in less than 0.5% of patients (very low quality evidence) (Table 14). Details on the post-surgical harms are reported in Appendix 10.

Health related quality of life (HR-QoL) outcomes (measured using SF-36) that were found to be significantly improved with treatment included physical functioning, general health, social function, and the summary score for the physical component (low and very low quality evidence). No HR-QoL outcomes were found to be worse in the treated group compared to controls (Table 15). Disease-specific QoL (DS-QoL) scores were reported in other studies and not included in GRADE. Decreased mean scores for urinary incontinence and sexual function were reported following prostatectomy, indicating worse QoL.[63] Steenland et al.[64] also examined DS-QoL following treatment with

prostatectomy, radiation therapy, and hormonal therapy. Mean change in QoL scores indicated reduction in sexual QoL, bowel QoL, emotional bother QoL, and physical bother QoL with prostatectomy.

Radiation therapy

Radiation therapy was reported to increase the risk of erectile dysfunction in cohort studies (low quality evidence) (Table 16). The risk of urinary incontinence was higher in one RCT (moderate quality evidence) but was not found to be significantly increased in the cohort studies (very low quality evidence). Neither bowel dysfunction (very low quality evidence), nor QoL (very low quality evidence) were significantly affected by treatment with radiation therapy (Table 17). Talcott et al. also assessed harms following radiation therapy in an observational study and reported slight increase in sexual dysfunction and increase in bowel dysfunction.

Steenland et al.[64] also assessed DS-QoL and reported reduction in sexual QoL, bowel QoL, emotional bother QoL, physical bother QoL, and urinary QoL with radiation therapy. Sexual function following radiation therapy was assessed by Choo et al.[65] Mean scores for sexual function declined following treatment with radiation therapy.

Hormonal therapy

Hormonal therapy significantly increased the risk of erectile dysfunction in cohort studies (moderate quality evidence) (Table 18) and showed worse summary scores for the physical component of HR-QoL outcomes (low quality evidence) (Table 21) as compared to the control group. No studies reporting other harms of hormonal therapy were identified.

Hormone and radiation combination therapy

One study reported the harms of combination therapy with hormonal therapy and radiation therapy (Table 20).[43] The authors report an increase in risk of erectile dysfunction and bowel dysfunction with combination therapy (low quality evidence). HR-QoL physical and mental component scores were also reduced with combination therapy (low quality evidence). No effect on urinary incontinence was reported (very low quality evidence).

Cryotherapy

HR-QoL outcomes following treatment with cryotherapy were improved for physical function, physical role, social function, emotional role and mental health (very low quality evidence) (Table 21). No studies reporting other harms of cryotherapy were identified.

HIFU

Urinary incontinence was experienced by 1.5% to 14.7% of patients who received HIFU (in three uncontrolled studies), and erectile dysfunction in 23.5% and 44.7% (in two uncontrolled studies; Table 22) (very low quality evidence). Harms following HIFU were also assessed by Muto et al.[66] Data was reported as mean scores and therefore not included in the GRADE Table. No change in urinary function and bother was reported following treatment with HIFU.

Patient values and preferences

A contextual question to help inform development of recommendation was asked about patient values and preferences for PSA screening. One systematic review[67] looking at patient preferences among "older men" (mean age ≥ 60 years) and three uncontrolled observational studies[68,69,70] were identified to address this question.

The systematic review included 20 studies: 14 from the physician's perspective, five from the patient's perspective, and one that contained information from both. Physicians were more likely to order a PSA test if the patient had a family history of prostate cancer, was of African descent, had low urinary track symptoms, or an abnormal DRE. Patients were more likely to request a PSA test if they had perceived self-vulnerability to the disease or if their physician recommended it. Four studies found that a patient's knowledge and beliefs about prostate cancer screening and treatment played an important role in the decision making process. The review also found that physicians initiate screening more often than patients.

Three additional studies published after the systematic review were identified. Ferrante et al.[69] provided a qualitative analysis as to whether the decisions that patients made regarding PSA testing were based on scientific evidence. Sixty-four men aged 50 years or older were interviewed in New Jersey. None of these men reported having discussions with their physicians about the harms of PSA screening, and most men had low levels of knowledge about the screening procedure.

Allen et al.[68] investigated prostate cancer knowledge, decision self-efficacy (confidence in the ability to make an informed decision), consistency between values and screening decision, perceived risk of prostate cancer, and preference for control in decision making among 812 men aged 45 years or older. They found that men who made a decision about PSA screening (whether for or against) were older (>55 years), of white race, had higher income, had a college education, had received prior PSA screening, had family history of prostate cancer, and had previously discussed screening with their doctors. These men

were also more likely than those who were undecided about PSA testing, to have higher levels of knowledge about the test, higher levels of decision self-efficacy, and more likely to make a decision consistent with their values and preferences. Most men in this study reported a preference for screening.

Smith and Birtwhistle[70] studied the patient perceptions of PSA screening in 2012 in 57 Canadian men aged 41 to 80 years. They reported that despite the lack of effectiveness of PSA screening, the majority of men surveyed had a positive perception of PSA screening and were unaware of the potential risks associated with screening.

DISCUSSION

Screening for prostate cancer with PSA does not decrease all-cause or other-cause mortality. However, two of the six trials (Göteborg and ERSPC) included in this review reported statistically significant reductions in prostate cancer-specific mortality. These differences correspond to absolute risk reductions of 0.08% and 0.34% over the study period (11 years and 14 years respectively). The NNS was 293 (95% CI: 177-799) and 1221 (95% CI: 676-6337) men in the two studies that reported an effect of screening.[11,12] Because the Göteborg study was assessed with the lowest risk of bias, and originally began as its own study, and later added to ERSPC, its results were reported separately from the larger multi-centre ERSPC trial. Three of the trials that reported no effect on mortality had the highest risk of bias (Norrköping, Stockholm, Quebec). These trials had methodological flaws that may have overestimated the benefit of screening on mortality. Inadequate randomization and allocation concealment occurred in all three of these trials. The Stockholm trial used a high PSA threshold for biopsy (10ng/mL). Both this study and the Quebec study could not assess the contamination rate of screened men in the control group which may have underestimated the effect. In addition, the Quebec study did not follow intention-to-treat analysis.

There was methodological and clinical variation across the trials. The screening interval varied: screening occurred at two year and four year intervals in trials showing a positive effect on mortality, while those designed with one time, annual, or screens every three years did not report associations between screening and mortality. The trial with a one-time screen (Stockholm) may not be generalizable to other screened populations. One of the trials only included digital rectal exam (DRE) as the screening test for the first two screening rounds, and only added PSA for the last two rounds of screening which limits the applicability of this trial (Norrköping). DRE was also included in the other trials, with the exception of

Göteborg, albeit at different intervals and for different purposes (some as part of the initial screening and some as follow-up to PSA). DRE was initially included in some of the sites of the ERSPC trial, but was later dropped from the screening protocol and only PSA was used (Netherlands, Belgium). An analysis of the Rotterdam section of the ERSPC study showed that omitting DRE from the screening had no effect on detection of prostate cancer.[71] DRE results are correlated with PSA levels, with DRE performing better with higher PSA, but not performing well at lower PSA levels (less than 3.0 ng/mL).[72]

Another difference included the age range for screening. In the ERSPC trial, subgroup analysis by age indicated that the effect on prostate cancer mortality is only seen in men aged 65 to 69 years. Age may therefore be a consideration for screening recommendations.

Contamination of the control groups in the screening trials, which occurs when participants in the unscreened control population receive PSA testing, is a concern. This was reported to be 20% in the ERSPC trial and the Göteborg trial indicated a very low rate of contamination. Not all trials reported contamination rates or reported being unable to calculate this rate. The PLCO trial compared population -screening to usual care which could have included opportunistic screening, and therefore 52% of participants in the control group received screening. Higher rates of screening in the control group would underestimate the effect of screening.

The Cochrane review on screening for prostate cancer was published in 2013.[5] This review included the same studies as the present review, however, did not include the Göteborg study separately. The review conducted a meta-analysis on the five trials and performed a GRADE assessment and found no statistically significant differences in prostate cancer-specific mortality or all-cause mortality. The pooled RR was 1.00 (95% CI: 0.96-1.03) for all-cause mortality in four studies with moderate quality evidence and 1.00 (95% CI: 0.86-1.17) for prostate cancer-specific mortality in five studies with moderate quality evidence. The ERSPC and PLCO trials were assessed by the Cochrane authors as having an overall low risk of bias, whereas the other included trials had a high risk of bias. Including only the studies assessed at low risk of bias in the meta-analysis, the pooled RR was 0.96 (95% CI: 0.70-1.30) for prostate-cancer specific mortality. The Cochrane authors conducted a subgroup analysis based on age and found no differences based on age group (≥ 45 years; ≥ 50 years; ≥ 55 years) for prostate cancer-specific or all-cause mortality.

The same studies were also included in the USPSTF systematic review on screening. [7] Our findings are generally consistent with the USPSTF systematic review, which focused on the two highest quality

studies (ERSPC and PLCO). The American Urological Association (AUA) commissioned a systematic review to inform their recent guideline.[74] The AUA systematic review included the same six trials and also reported the Göteborg study separately.

The harms of screening included false-positives, biopsy-related harms and overdiagnosis. The false positive results were higher using a lower PSA threshold (19.82% for 3 ng/mL and 11.30% for 4 ng/mL). The number of screens can also affect the false positive rate. Croswell et al.[27] used 3 years post positive PSA screen without a diagnosis to define false-positive, whereas Kilpeläinen et al[26] used one year post-positive PSA test. The Croswell study assessed the false positive rate from the PLCO study, and therefore the rate reported is the rate for the entire period for any false positive. Kilpeläinen also found an increased risk of a false positive in subsequent screening rounds if a false positive occurred in the first screening round.

Prostate cancer overdiagnosis ranged from 40% to 54% for screening every four years (3ng/mL and 4 ng/mL PSA thresholds). This estimate suggests that up to 54% of men screened are diagnosed with prostate cancer that may not progress and do not require treatment. Unnecessarily treating these men may lead to harms such as urinary incontinence and erectile dysfunction for a disease that otherwise would have resulted in no symptoms. Lower overdiagnosis rates were reported in the other studies, but these used a single screen as opposed to multiple screens, so a lower rate would be expected. In addition, the lowest rate reported was for indolent tumors which used a different method to calculate the overdiagnosis rate, and was based on a single screen. The other studies used the method of modeling the expected number of cancers and determining how many of the actual cancers were therefore overdiagnosed, among all screen detected cases. Varying the interval for screening, the PSA threshold, and the age range for testing can all affect the overdiagnosis rate.

Harms of biopsy following a positive PSA screening test included haematuria, infection, hospitalization and death. Whereas hematuria occurred in a mean of 30.86% of patients, infection only occurred in 0.94% and hospitalization in 2.07%. Death was rare, with a mean of 0.17%.

In order to help inform the question about the effectiveness of screening for prostate cancer, the effectiveness of treatment for early prostate cancer was investigated to determine if treating cancers that may be detected by screening would be beneficial. The trials however, did not always specify whether the patients were screen-detected. None of the three treatment RCTs reported the percentage of patients that were screen detected. Of the cohort studies on benefits of treatment, four reported

percent screen-detected which ranged from 31% to 100%. If it was reported, this information is included in the study characteristics table. In addition, not all cases were early stage although we excluded studies with more than 10% of patients with later stage (T3) prostate cancer. Overall, treatment for prostate cancer with prostatectomy and radiation therapy is effective in decreasing prostate cancer-specific mortality. Of the two RCTs examining an effect of prostatectomy, one (Wilt et al)[28] found no effect of prostatectomy on prostate cancer-specific mortality, whereas the other (Bill-Axelson) did find an effect.[29] The meta-analysis weighted the Bill-Axelson trial higher and the result was a pooled effect showing a benefit of prostatectomy. The NNT for prostatectomy was 20 (95% CI: 13-58) in the RCTs and 30 (95% CI: 26-37) in the cohort studies for prostate cancer-specific mortality. Radiation therapy had a NNT of 54 (95% CI: 32-352) for prostate cancer specific mortality and 18 (95% CI 12-114) when combined with hormone therapy. Hormonal therapy alone appears to increase mortality. No studies were found on the effectiveness of cryotherapy or HIFU on prostate cancer-specific or all-cause mortality.

Active surveillance may have been included as the control in some of the treatment studies; however, this is unclear due to the limited information provided in the studies. Active surveillance is the repeat monitoring of disease progression, with PSA monitoring and biopsy if needed, with treatment dependent on changing PSA level. Watchful waiting includes treatment decisions based on symptom presentation.[75] The terms active surveillance and watchful waiting are also often used interchangeably.

Some studies included in this review based treatment decisions on symptom progression, which is considered watchful waiting, however, others use “signs of disease progression” and it is unclear if the signs could have included PSA monitoring. No study specifically discussed the use of PSA surveillance in the control population, but “active follow-up” was used in one study,[32] which may have included PSA testing as surveillance although this was not specified. One study[33] specified “active surveillance” was part of the control group, however, there was no mention of PSA testing in this group. Because of the limitations in the descriptions of the control groups, no definitive statement can be made about the effectiveness of active surveillance.

Treatment for prostate cancer was associated with harms, such as urinary incontinency (prostatectomy, radiation therapy) and erectile dysfunction (prostatectomy, radiation therapy, hormonal therapy, and HIFU). The quality of evidence for these harms ranged from high to very low. Three domains of HR-QoL were improved with treatment with prostatectomy, whereas other treatments either did not affect QoL

or resulted in decreased scores in some domains (such as a decreased score for the HR-QoL physical component after treatment with hormonal therapy).

The USPSTF review[8] on effects of treatments for prostate cancer had similar findings, with a decrease in mortality with prostatectomy and radiation therapy, with the associated harms of erectile dysfunction and urinary incontinence.

Conflicting recommendations for screening for prostate cancer have been developed by specialist organizations and the USPSTF. The USPSTF recommends against screening[79] and other organizations state that evidence is insufficient or recommend discussing screening with their patients.[80] The Canadian Urological Association[76] recommends screening starting at age 50 years for average risk men, and the European Association of Urology[77,78] recommend screening at 40 years. Guidelines developed based on the review for the AUA recommend shared decision making in men aged 55 years – 69 years.[74]

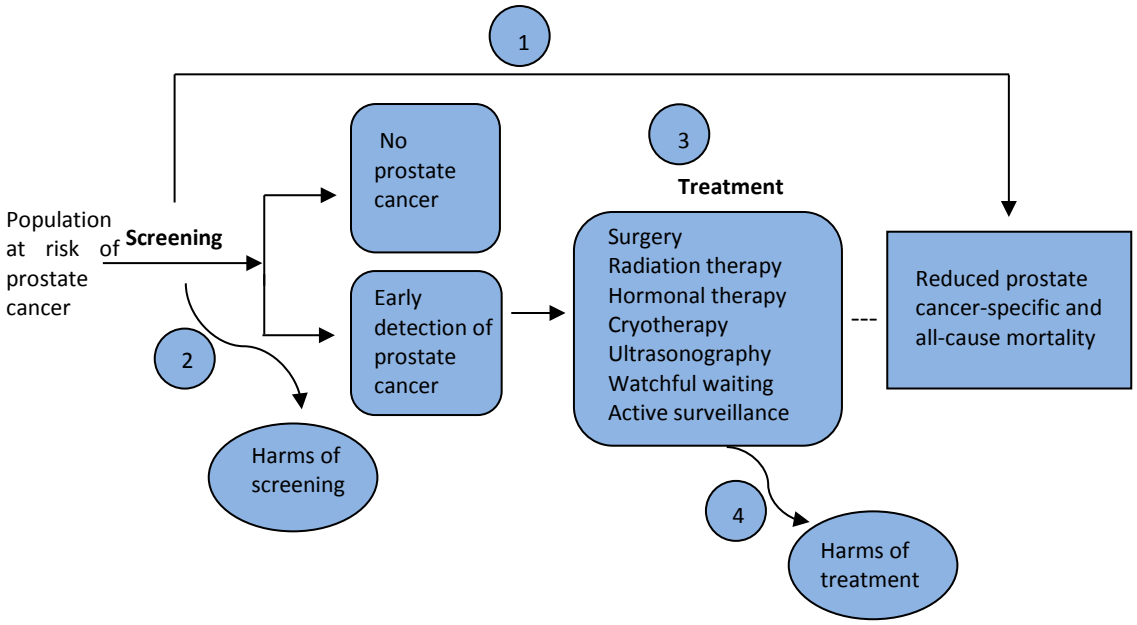
Limitations of this review include overall quality of the studies for harms of screening (very low) and lack of RCTs on the majority of the treatments (only prostatectomy assessed in RCTs). In addition, the methodological and clinical variability in the screening studies did not allow pooling of these studies and made comparison of the studies difficult. Control definitions in the treatment studies also varied and most did not identify whether patients were screen detected, although the majority had clinically localized, early stage prostate cancer.

CONCLUSIONS

To address the question of whether screening is effective and if population screening is beneficial to improve mortality, further studies or additional years of follow-up for the existing RCTs are required. Based on the current review, there is not enough evidence to say conclusively if screening with PSA will improve prostate cancer or all-cause mortality. The existing RCTs vary in their populations, PSA thresholds, intervals, and follow up, and the issue of contamination and appropriate controls adds to the inability to clearly address this question. No study demonstrated effectiveness of screening with DRE. Treatment of prostate cancer shows a benefit, however, some of these studies also have flaws and the treatments all have harms. In addition, the treatment studies were not limited to screen detected patients and therefore these results do not aid in the understanding of the benefits of screening with PSA.

Previous CTFPHC recommendations found insufficient evidence for prostate cancer screening with PSA. While RCTs have been published since the 1994 recommendation, which was based on observational data, there may now be sufficient evidence to provide a recommendation. The inconclusive results of screening benefit may not warrant a positive recommendation, in line with recommendations and reviews from other organizations, such as the USPSTF and the Cochrane Collaboration.

Figure 1. Analytical framework and key questions.



Key questions

1. What is the direct evidence that screening for prostate cancer with prostate-specific antigen (PSA), as a single-threshold test or as a function of multiple tests over time, decreases prostate cancer-specific and all-cause mortality?
   1b. Is there evidence to support differential screening based on individual risk factors for prostate cancer such as age, African descent, family history of prostate cancer or previously assessed increased PSA values – either absolute values or increased PSA measures over time?
2. What are the harms of PSA-based screening for prostate cancer?
3. What are the benefits of treatment of early-stage or screen-detected prostate cancer?
4. Is there evidence that tailoring the method of following up abnormal screening results to patient characteristics (example: active surveillance vs. treatment A vs. B) lead to clinically important differences in the harms and benefits of screening with PSA?
5. What are the harms of treatment of early-stage or screen-detected prostate cancer?

Contextual Questions

Contextual questions will be addressed in two stages, depending on whether evidence of PSA test screening performance of screening is identified.

Stage one:

Question that is necessary to assist in making a decision about the direction of the recommendation:

1. What are the patient values and preferences for PSA screening for prostate cancer?

Stage two:

If evidence of effectiveness is sufficient for the Task Force to recommend screening, the following additional questions will be added:

2. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of PSA screening for prostate cancer?
3. What is the optimal screening interval for PSA screening for prostate cancer and should this interval vary based on risk level (e.g., age, prior PSA levels, or other measures such as Gleason score)?
4. What are the most effective (accurate and reliable) risk assessment tools to identify: a) risk of prostate cancer and b) risk of poor outcomes after PSA testing and biopsy?
5. What is the cost-effectiveness of PSA screening asymptomatic adults for prostate cancer? Costs to the system and to patients will be included if found.

Evidence set 1. Benefits of screening

- Overview of screening trials
- GRADE evidence profile table
- Subgroup analysis by age < 65 years and ≥ 65 years

Table 1. Overview of randomized controlled trials on screening for prostate cancer

	Göteborg (Hugosson)[12]	ERSPC (Schroder)[11]	PLCO (Andriole)[17]	Norrköping (Sandblom)[20]	Stockholm (Kjellman)[18]	Quebec (Labrie)[19]
PCM RR	0.56 (0.39-0.82)	0.79 (0.68-0.91) 0.84* (0.71 - 0.98)	1.09 (0.87-1.36)	1.16 (0.78-1.73)	1.04 (0.76-1.45)	1.08 (0.82-1.43)
NNS	290 (209 to 709)	1209 (667 to 9670)	N/A	N/A	N/A	N/A
Age	50-64 years	50-74 years 55-69 years in core group	55-74 years	50-69 years	55-70 years	45-80 years
Test	PSA every 2 years (3.0; 2.9; 2.5 ng/mL)†	PSA every 4 years (3.0 ng/mL‡)	Annual PSA (4.0 ng/mL) & DRE every 4 years	DRE; then DRE & PSA every 3 years (4.0 ng/mL; last 2 rounds)	One time PSA (7.0ng/mL), DRE, TRUS	Annual PSA (3.0 ng/mL) and DRE
Follow-up	14 years	11 years	13 years	20 years	15 years	11 years
RoB	Low	Low	Low	High	High	High

PCM RR = Relative risk of prostate cancer-specific mortality; NNS = number needed to screen; DRE = digital rectal exam; RoB = risk of bias
*RR excluding Göteborg study results; †PSA threshold was lowered throughout the study period, beginning at 3.0ng/mL in the first year and ending with a threshold of 2.5 ng/mL; ‡most sites included in ERSPC used a threshold of 3.0 ng/mL

Table 2. Benefits of screening with PSA

Quality Assessment							Results				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rate ratio (RR)	Absolute Risk Reduction (ARR)	Quality	Importance	NNS (95% CI)*
Prostate cancer-specific mortality (Overall) (follow-up 11 to 20 years; assessed with: death registry)											
6[a]	randomised trials	serious[b]	serious[c]	no serious indirectness[d]	serious[e]	none[f,g,h,i]	2 found an effect: RR = 0.84 (95% CI; 0.71 - 0.98)[11] RR = 0.56 (95% CI; 0.39 - 0.82)[12] 4 trials found no effect: RR = 1.09 (0.87-1.36)[17] RR = 1.16 (0.78-1.73)[20] RR = 1.04 (0.76-1.45)[18] RR = 1.08 (0.82-1.43)[19]	ERSPC: 0.08%[11] Göteborg: 0.34%[12]	⊕OOO VERY LOW	CRITICAL	Göteborg: 293 (177-799) ERSPC: 1221 (676-6337)
All-cause /other-cause mortality (overall) (follow-up 11 to 20 patient-years; assessed with: death registry)											
4[j]	randomised trials	serious[k]	no serious inconsistency[l]	no serious indirectness[m]	serious[n]	none[f,g,h,i]	No effect in 4 trials; RR[o] = 0.96 (95% CI; 0.93 - 1.00)[5,17] RR[p] = 0.98 (95% CI; 0.92 - 1.05)[18] RR[q] = NR, p-value = 0.14[20] RR = 0.99 (95% CI; 0.97 - 1.01)[11]		⊕⊕OO LOW	CRITICAL	N/A

*
calculated from the Göteborg and ERSPC trial data (for ERSPC data, the Göteborg data were removed)

[a] Andriole (PLCO)[17]; Kjellman (Stockholm)[18]; Labrie (Quebec)[19]; Sandblom (Norköpping)[20]; Schroder (ERSPC)[11]; Hugosson (Göteborg)[12]

[b] Only two of the studies (Andriole, 2012; Schroder, 2012) provided a clear description of appropriate random sequence generation and only one of these (Andriole 2012) clearly described the allocation concealment processes. Given the nature of the intervention, blinding of participants and study personnel would not be possible, but would not likely affect the outcome of mortality. It was unclear in one study (Labrie, 2004) if the outcome assessment process was blinded. All but two studies (Andriole, 2012; Labrie, 2004) provided a complete and appropriate description of outcome data and attrition. The risk of bias for selective reporting was rated as high for two studies (Kjellman, 2009; Schroder, 2012) and most studies, with the exception of one (Sandblom, 2011), were judged as being at high or unclear risk for other types of bias. Given the rate of potential biases noted, particularly in the randomization and allocation concealments processes, we have downgraded the evidence for this domain.

[c] The direction of effect is not consistent across studies i.e. with different messages based on two studies showing a "protective" effect of screening (Schroder, 2012 and Hugosson, 2010) and all of the others a "null" effect.

[d] All but one study (Labrie,2004) provided useful information on cancer stage at diagnosis. Most studies included measurement of PSA as a screening test in all participants, with the exception of Kjellman, 2009, which initially used only digital rectal examination (DRE) but then used a combination of PSA and DRE. In the ERSPC the screening method differed by participating country and was mostly based on PSA Screening intervals ranged from a single screening session (Kjellman, 2009) to four years (Andriole 2012). PSA cut-offs differed among the studies ranging from 2.5 in one of the ERSPC Centres to 4.0 ng/mL (Andriole, 2012). Follow-up times varied across studies ranging from 11 to 20 years. However, downgrading the quality of evidence is not warranted.

[e] There is a large sample size but the range for effect estimate (RR) at is not precise and includes no effect value of "1 ", range = 0.56 to 1.16

f Insufficient studies to determine publication bias.

[g] Large effect not detected.

[h] Unlikely that plausible confounders would change the effect size.

[i] Dose response not relevant.

[j] Andriole[17]; Kjellman[18]; Sandblom[20]; Schroder[11]

[k] Only two of the studies (Andriole, 2012; Schroder, 2012) provided a clear description of appropriate random sequence generation and only one of these (Andriole 2012) clearly described the allocation concealment processes. Given the nature of the intervention, blinding of participants and study personnel would not be possible, but would not likely affect the outcome of mortality All but one study (Andriole, 2012) provided a

complete and appropriate description of outcome data and attrition. The risk of bias for selective reporting was rated as high for two studies (Kjellman, 2009; Schroder, 2012) and most studies, with the exception of one (Sandblom, 2011), were judged as being at high or unclear risk for other types of bias. Given the rate of potential bias noted, particularly in the randomization and allocation concealments processes, we have downgraded the evidence for this domain.

[l] The direction of effect is consistent across studies i.e. all studies showing a "null" effect.

[m] All but one study (Kjellman 2009) included measurement of PSA as a screening test in all participants. Kjellman initially used only DRE but then used a combination of PSA and DRE. In the ERSPC the screening method differed by participating country and was mostly based on PSA. Screening intervals ranged from a single screening session (Kjellman, 2009) to four years (Andriole 2012). PSA cut-offs differed among the studies ranging from 2.5 in one of the ERSPC centres to 4.0 ng/mL (Andriole, 2012). Follow-up times varied across studies ranging from 11 to 20 years. However, downgrading the quality of evidence is not warranted.

[n] There is a large sample size but the effect estimate (RR) is not precise and confidence intervals of the studies include no effect value of "1 ".

[o] Andriole et al. only included data on causes other than prostate, colorectal and lung cancers. A recent Cochrane review contacted the authors and received data with these cancers included.[5]

[p] Kjellman A et al. only provided the estimate of rate ratio for cause other than prostate cancer.

[q] Sandblom et al. included overall mortality for those diagnosed with prostate cancer only and only reported p-value for all-cause mortality rate ratio.

Table 3. Benefits of screening with PSA by age

Design	# Studies	# Participants (Events / person-yrs.)	Results Rate Ratio (95% CI)
Age < 65 yrs, prostate cancer-specific mortality			
RCT	2* (PLCO[17]) and ERSPC[11])	**Screening**: 65 / 276170; 206 / 670888 **No screening;** 54 / 274314; 289 / 806670	RR = 1.19 (0.83 to 1.72)[17] RR = 0.86 (0.72 to 1.02)[11]
Age ≥ 65 yrs, prostate cancer-specific mortality			
RCT	2 (PLCO)[17] and ERSPC[11]	**Screening**: 93 / 150807; 158 / 203757 **No screening;** 91 / 151125; 233 / 236002	RR = 1.02 (0.77 to 1.37)[17] **RR = 0.79 (0.64 to 0.96)[11]**

*The Göteborg study is not included as the data are included in the ERSPC study results and could not be separated by study site for this subgroup analysis.

Evidence set 2. Harms of screening for prostate cancer

- Grade evidence profile tables:
  - Overdiagnosis
  - False positives
  - Harms of biopsy

Table 4. Harms of screening for prostate cancer with PSA - overdiagnosis

Author, year	Study population	PSA threshold	Age (yrs.)	Lead time (yrs.)	# of screen	Overdiagnosis (% of men screened)
Wu, 2012[22]	Finland – ERSPC	≥3.0 ng/ml	55-65	5.24 yrs.	Every 4 years	40.45% (31.9% to 48.9%)¥
Pashayan, 2006[81]	Cambridge area	1.4% to 5.2% increase / year	40-89	5 to 10 yrs.	Single screen	31% (0.08% to 63.8%)*
Graif, 2007[82]	Participants in longitudinal screening study	≥2.5 or ≥ 4.0 ng/ml	Mean age 64-65	5 yrs.	Single screen	7.1% (for PSA 2.5 ng/ml)
						1.3% (for PSA 4.0 ng/ml)
Xia, 2013[83]	PIVOT	NR	50-79	7.7 yrs.	Single screen	32% (8% to 56%)*
Draisma, 2009[25]	SEER	≥4.0 ng/ml	50-84	7.8 yrs.	Every Year	42%
Pelzer, 2008[84]	Tyrol & rest of Austria	≥4.0 ng/ml	40-75	NR	Single screen	17.4%
Pashayan, 2009[85]	ProtecT	≥3.0 ng/ml	50-69	11.3 to 12.6 yrs.	Single screen	19% (10% to 31%)*
Heijnsdijk, 2009[23]	ERSPC	≥3.0 ng/ml	55-70	7 yrs.	Every 4 years	42%
Draisma, 2003[86]	Rotterdam – ERSPC	≥4.0 ng/ml	55-75	6.0 to 12.3 yrs.	Single screen	47% (27% to 56%)*
					Every Year	56% (54% to 61%)*
					Every 4 years	54% (51% to 59%)*

¥ Mean with 95% Confidence interval.

* Range across overdiagnosis data presented separately for various age subgroups.

Table 5. Harms of screening for prostate cancer with PSA - false positives

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
False-Positive PSA > 3.0 ng/mL (at least one FP for men screened at least once follow-up 1 year from screening test; assessed with: biopsy)									
1[a]	Observational	Serious[b]	No Serious Inconsistency[c]	No Serious Indirectness[d]	No Serious Imprecision[e]	None[f]	False positive rate: 19.82% (CI 95%: 11.51% - 28.13%)) total = 32,137 # FP = 7403	⊕OOO VERY LOW	CRITICAL
False-Positive PSA > 4.0 ng/mL (at least one FP for men screened at least once follow up 1 year from screening test; assessed with: biopsy)									
2[g]	Observational	Serious[b]	Serious[h]	No serious Indirectness[i]	No Serious Imprecision[e]	None[f]	False positive rate: 11.30% (9.92% - 12.67%) Total = 62,044 # FP = 6957	⊕OOO VERY LOW	CRITICAL

[a] Kilpeläinen[26]

[b] Uncontrolled observational design.

[c] A single study provided evidence for this outcome, therefore we cannot assess inconsistency.

[d] For this study and this outcome, the population (men, ages 50 to 75), intervention (PSA screening, interval range 2 to 7 years), location (Europe), and outcome (false positive) are similar to the context/criteria specified by the key questions for this review.

[e] The sample size is adequate (≥2,000). The results do not include an effect estimate or confidence interval.

[f] There was an insufficient number of studies to assess publication bias.

[g] Kilpeläinen[26]; Croswell[27]

[h] The confidence intervals for this outcome in these two studies do not overlap.

[i] Across the body of evidence for this outcome, the population (men, ages 50-75), intervention (PSA screening, interval range annual to 7 years), location (Europe, United States), and outcome (false positive) are similar to the context/criteria specified by the key questions for this review.

Table 6. Harms of screening for prostate cancer with PSA – harms of biopsy

Complication	Study Design	# of studies	Results (proportion % with 95% CI)	GRADE Rating
Hospitalization	Observation/uncontrolled	24[87-110]	2.07% (1.59% to 2.54%)	VERY LOW*
Death	Observation/uncontrolled	8[88,92,93,98,102,103,110,111]	0.17% (0.09% to 0.25%)	VERY LOW*
Hematuria (< 30 days)	Observation/uncontrolled	14[88,90,91,95,98-101,105,106,108,112-114]	30.86% (20.18% to 41.51%)	VERY LOW*
Infection (< 30 days)	Observation/uncontrolled	6[87,91,100,106,113,115]	0.94% (0.01% to 1.86%)	VERY LOW*

*uncontrolled observational studies receive an automatic GRADE rating of very low.

Evidence set 3. Benefits of treatment

- GRADE evidence profile tables
  - Benefits of prostatectomy
  - Benefits of radiotherapy
  - Benefits of hormonal therapy
  - Benefits of cryotherapy
  - Benefits of HIFU
- Forest plots
  - Benefits of prostatectomy
  - Benefits of radiotherapy
  - Benefits of hormonal therapy
  - Benefits of cryotherapy
  - Benefits of HIFU
  - Subgroup analysis by control group definition

Table 7. Benefits of treatment for prostate cancer - prostatectomy

Quality assessment							No of patients		Effect		Quality	Importance	NNT (95% CI)
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Prostat-ectomy	Control	Relative (95% CI)	Absolute			
Prostate cancer-specific mortality - RCT (follow-up 10.8 to 12.8 years; assessed with: death registry)													
2[a]	randomised trials	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[e]	none[f,g,h,i]	76/711 (10.7%)	112/715 (15.7%)	RR 0.68 (0.52 to 0.89)	50 fewer per 1000 (from 17 fewer to 75 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	20 (13 – 58)
Prostate cancer-specific mortality - Cohort (follow-up 5 to 13.6 years; assessed with: death registry)													
6[j]	observational studies	no serious risk of bias[k]	no serious inconsistency[l]	No serious indirectness[m]	no serious imprecision[n]	none[f,g,h,i]	398/17036 (2.3%)	924/16095 (5.7%)	RR 0.42 (0.33 to 0.53)	33 fewer per 1000 (from 27 fewer to 38 fewer)	⊕⊕OO LOW	CRITICAL	30 (26 – 37)
All-cause Mortality - RCT (follow-up 10.8 to 23 years; assessed with: death registry)													
3[a,o]	randomised trials	no serious risk of bias[p]	no serious inconsistency[q]	no serious indirectness[r]	serious imprecision[s]	none[f,g,h,i]	404/785 (51.5%)	447/783 (57.1%)	RR 0.92 (0.83 to 1.02)	46 fewer per 1000 (from 97 fewer to 11 more)	⊕⊕⊕⊕ MODERATE	CRITICAL	N/A
All-cause Mortality - Cohort (follow-up 5 to 13.6 years; assessed with: death registry)													
8[j,t]	observational studies	no serious risk of bias[u]	no serious inconsistency[v]	no serious indirectness[w]	no serious imprecision[x]	none[f,g,h,i]	5586/31638 (17.7%)	10427/ 29317 (35.6%)	RR 0.38 (0.32 to 0.47)	221 fewer per 1000 (from 189 fewer to 242 fewer)	⊕⊕OO LOW	CRITICAL	5 (4-5)

[a] Bill-Axelson[29]; Wilt[28]

[b] Of the two studies, one did not adequately describe random sequence generation, while the other did not describe the method of allocation concealment. In the case of the later, this would not affect the mortality outcome. As well, blinding would not be possible due to the nature of the intervention (surgery) and would not affect the outcome.

[c] The confidence intervals overlap and the level of heterogeneity is minimal (Heterogeneity: $Tau^2 = 0.00$; (P = 0.99); $I^2 = 0\%$).

[d] Prostate cancer in all RCTs was primarily clinically rather than screen detected. There was a high proportion of stage T2 cancer in one of the three studies (Bill-Axelson, 2011). In both studies, limited information was provided on specific surgical techniques evaluated. Definition of control differed and included "no immediate treatment" (Bill-Axelson, 2011), and "observation" (Wilt, 2012). Follow-up times ranged from 10 to 13 years. However, downgrading the quality of evidence is not warranted.

[e] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded. There is an adequate sample size and the estimate of effect is precise with narrow confidence intervals (RR=0.68 [0.52, 0.89]).

[f] Insufficent studies to determine publication bias.

[g] Large effect not detected.

[h] No evidence that controlling for plausible confounder would change the effect size.

[i] Dose response not relevant to intervention (surgery).

[j] Abdollah[31]; Albertsen[30]; Merglen[32]; Stattin[33]; Tewari[34]; Zhou[13]

[k] The six cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum)

[l] The confidence intervals overlap and the level of heterogeneity is moderate (Heterogeneity: $Tau^2 = 0.04$; (P = 0.04); $I^2 = 56\%$).

[m] Limited information provided on surgical techniques evaluated. One study (Tewari, 2007) only evaluated stage 3 cancers, while two studies did not provide adequate information on stage of cancer (Albertson, 2007; Zhou, 2009). Definitions of control differed among studies and included "active follow-up with treatment for disease progression" (Merglen, 2007) "observation" (Abdollah, 2011; Albertson, 2007) "combined active surveillance and watchful waiting"(Stattin, 2010), and "no definitive therapy within 6 months of diagnosis" (Zhou, 2009). One study did not report type of control (Tewari, 2007). One study only reported on a follow-up time for mortality of 5 years (Tewari, 2007), while the remaining ranged from 7 to 13.6 years of follow-up. However, downgrading the quality of

evidence is not warranted.

[n] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with narrow confidence intervals (RR=0.42 [0.33, 0.53]).

[o] Iversen[35]

[p] Of the three studies, only one adequately describes random sequence generation (Wilt, 2012), while only one described the method of allocation concealment (Bill-Axelson, 2011). In the case of the later, this would not affect the mortality outcome. As well, blinding would not be possible due to the nature of the intervention (surgery) and would not affect the outcome.

[q] The confidence intervals overlap and the level of heterogeneity is moderate (Heterogeneity: $Tau^2 = 0.00$; ($P = 0.17$); $I^2 = 44\%$).

[r] Prostate cancer in all RCTs was primarily clinically rather than screen detected. There was a high proportion of stage T2 cancer in one of the three studies (Bill-Axelson, 2011) and in one of the studies (Iversen, 1995) tumour stage was not adequately reported. In all studies, limited information was provided on specific surgical techniques evaluated. Definition of control differed and included "no immediate treatment" (Bill-Axelson, 2011), "regular monitoring and deferred treatment until time of progression" (Iversen, 1995), and "observation" (Wilt, 2012). Follow-up times ranged from 10 to 23 years. However, downgrading the quality of evidence is not warranted.

[s] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval but crosses the line of no effect (RR=0.92 [0.83, 1.02]).

[t] Schymura[14]; Wong[36]

[u] The eight cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum).

[v] The statistical heterogeneity is high ($Tau^2 = 0.07$; $Chi^2 = 205.81$, $df = 7$ ($P<0.00001$); $I^2 = 97\%$), but the confidence intervals overlap and direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.

[w] Limited information provided on surgical techniques evaluated. Definition of control varied among studies, including:" observation" (Abdollah, 2011), "active follow-up for disease progression" (Merglen, 2007), "no therapy within 6 months of diagnosis" (Schymura 2010), and "no medicare data for prostatectomy, radiation or hormonal therapy" (Wong, 2006). One study did not provide a definition of control (Tewari, 2007). One study (Tewari, 2007) only evaluated stage 3 cancers, while four studies did not provide adequate information on stage of cancer (Albertson, 2007; Zhou, 2009; Merglen, 2007; Schymura, 2010). One study reported on a follow-up time for mortality of four (Tewari, 2007) and five (Schymura, 2010) years, while the remaining studies ranged from 7 to 13.3 years of follow-up. However, downgrading the quality of evidence is not warranted.

[x] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval (RR=0.38 [0.32, 0.47]).

Table 8. Benefits of treatment for prostate cancer - radiation therapy and hormone therapy (single and combination)

Quality assessment							No of patients		Effect		Quality	Importance	NNT (95% CI)
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Control	Relative (95% CI)	Absolute			
Radiation therapy (brachytherapy or EBRT) prostate cancer-specific mortality - Cohort (follow-up 5 to 13.6 years; assessed with: death registry)													
6[a]	observational studies	no serious risk of bias[b]	Serious[c]	no serious indirectness[d]	no serious imprecision[e]	Upgraded for large effect size[f,g,h,i]	1332/24784 (5.4%)	1805/ 25412 (7.1%)	RR 0.74 (0.57 to 0.96)	18 fewer per 1000 (from 3 fewer to 31 fewer)	⊕OOO LOW	CRITICAL	54 (33-352)
Radiation therapy (brachytherapy or EBRT) all-cause mortality - Cohort (follow-up 5 to 13.6 years; assessed with: death registry)													
8[a,j]	observational studies	no serious risk of bias[k]	no serious inconsistency[l]	no serious indirectness[m]	no serious imprecision[n]	none[f,g,h,i]	15288/44070 (34.7%)	17033/ 38634 (44.1%)	RR 0.69 (0.62 to 0.77)	137 fewer per 1000 (from 101 fewer to 168 fewer)	⊕⊕OO LOW	CRITICAL	7 (6-10)
Combination radiation and hormone therapy prostate-specific mortality (follow-up 7 - 10 years)													
2[o]	observational studies	No serious risk of bias[p]	no serious inconsistency[q]	No serious indirectness[r]	no serious imprecision[s]	None[t]	126/2095 (6%)	246/ 2094 (11.7%)	RR 0.5206 (0.2929 to 0.9251)	56 fewer per 1000 (from 9 fewer to 83 fewer)	⊕⊕OO LOW	CRITICAL	18 (12-114)
Combination radiation and hormone therapy all-cause mortality (follow-up 7 - 10 years)													
2[o]	observational studies	no serious risk of bias[p]	no serious inconsistency[u]	No serious indirectness[r]	no serious imprecision[v]	None[t]	512/2095 (24.4%)	1075/ 2094 (51.3%)	RR 0.4367 (0.3236 to 0.5892)	289 fewer per 1000 (from 211 fewer to 347 fewer)	⊕⊕OO LOW	CRITICAL	3 (3-5)

[a] Abdollah[38]; Albertsen[30]; Merglen[32]; Stattin[33]; Tewari[34]; Zhou[13]

[b] The six cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum).

[c] The confidence intervals do not overlap and high statistical heterogeneity was observed across studies [Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 25.71$, df = 5 (P=0.0001); $I^2 = 81\%$].

[d] Limited information provided on specific radiation therapy techniques used. Definition of control varied among studies, including: observation (Abdollah, 2012; Albertson, 2007), and combined active surveillance and watchful waiting (Stattin, 2012). One study did not provide a definition of control (Tewari, 2007). One study (Tewari, 2007) only evaluated stage 3 cancers, while three studies did not provide adequate information on stage of cancer (Albertson, 2007; Zhou, 2009; Merglen, 2007). One study reported on a follow-up time for mortality of 5 (Tewari, 2007) years, while the remaining ranged from 7 to 13.6 years of follow-up. However, downgrading the quality of evidence is not warranted.

[e] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval (RR=0.74 [0.57, 0.96]).

[f] Insufficient studies to determine publication bias.

[g] Large effect not detected.

[h] No evidence that controlling for plausible confounder would change the effect size.

[i] Information on dose-response gradient not provided.

[j] Schymura[14]; Wong[36]

[k] The eight cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum).

[l] The statistical heterogeneity is high ($Tau^2 = 0.02$; $Chi^2 = 138$, df = 7 ($P<0.00001$); $I^2 = 95\%$), but the confidence intervals overlap and the direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.

[m] Limited information provided on radiation techniques evaluated. Definition of control varied among studies, including:" observation" (Abdollah, 2012), "active follow-up for disease progression" (Merglen, 2007), "no therapy within 6 months of diagnosis" (Schymura 2010), and "no medicare data for prostatectomy, radiation or hormonal therapy" (Wong, 2006). One study did not provide a definition of control (Tewari, 2007). One study (Tewari, 2007) only evaluated stage 3 cancers, while four studies did not provide adequate information on stage of cancer (Albertson, 2007; Zhou, 2009; Merglen, 2007; Schymura, 2010). One study reported on a follow-up time for mortality of four (Tewari, 2007) and five (Schymura, 2010) years, while the remaining studies ranged from 7 to 13.3 years of follow up. However, downgrading the quality of evidence is not warranted.

[n] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval (RR=0.69 [0.62, 0.77]).

[o] Merglen et al.[32]; Zhou et al.[13]

[p] Both cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9.

[q] Although the statistical heterogeneity is high [Chi2=9.41, df=2 (p=0.009); I2=79%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[r] Two cohort studies provided data for this outcome. One study (Merglen, 2007) included men with age 65 years or older while the other study (Zhou,2009) included patient with age ranged from 44 to 97 years. The combination therapy in one study (Merglen, 2007) was hormonal treatment (ADT or surgical castration) plus external radiotherapy (EBRT), while in the other study (Zhou,2009) two types of combination therapies were used i.e. ADT plus Brachytherapy and ADT plus external radiotherapy. The watchful waiting group in one study was defined as active follow-up with invasive treatment on disease progression for first 6 months after diagnosis; while in the other study it was defined as no treatment in the first 6 months after diagnosis. One study was conducted in US, and one was conducted in Switzerland. One study was published in 2007 and the other study was published in 2009. The length of follow-up was 7 years in one study and 10 years in the other study. There were concerns regarding indirectness for this body of evidence however the concerns were not sufficient to downgrade.

[s] The sample size is adequate (2095 intervention arm, 2094 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.5206 (0.2929, 0.9251)]. This body of evidence was not downgraded for imprecision

[t] There were too few studies (n<10) to assess publication bias

[u]Although the statistical heterogeneity is high [Chi2=13.29, df=2 (p=0.001); I2=85%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[v] The sample size is adequate (2095 intervention arm, 2094 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.4367 (0.3236, 0.5892)]. This body of evidence was not downgraded for imprecision

Table 9. Benefits of treatment for prostate cancer – hormonal therapy

Quality assessment							No of patients		Effect		Quality	Importance	NNT (95% CI)
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hormonal therapy	Control	Relative (95% CI)	Absolute			
Prostate cancer-Specific Mortality - Cohort (follow-up mean 7 years; assessed with: death registry)													
3[a]	observational studies	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[e]	none[f,g,h,i]	1139/9988 (11.4%)	938/ 13498 (6.9%)	RR 1.62 (1.16 to 2.26)	43 more per 1000 (from 11 more to 88 more)	⊕⊕OO LOW	CRITICAL	N/A
All-cause Mortality - Cohort (follow-up 5 to 7 years; assessed with: death registry)													
4[a,j]	observational studies	no serious risk of bias[k]	no serious inconsistency[l]	no serious indirectness[m]	no serious imprecision[n]	none[f,g,h,i]	5866/10327 (56.8%)	7541/ 14112 (53.4%)	RR 1.13 (1 to 1.27)	69 more per 1000 (from 0 more to 144 more)	⊕⊕OO LOW	CRITICAL	N/A

[a] Merglen[32];Zhou[13]; Lu-Yao[39]

[b] The three cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum).

[c] The statistical heterogeneity is high ($Tau^2 = 0.08$; $Chi^2 = 19.07$, df = 2 ($P<0.0001$); $I^2 = 90\%$), but the confidence intervals overlap and the direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.

[d] Limited information provided on specific hormonal therapy regimens evaluated. Two studies did not provide adequate information on stage of cancer (Zhou, 2009; Merglen, 2007). One study's population was slightly older (Lu-Yao, 2008). The follow-up times were similar across studies (mean 7 years and median 7 years). However, downgrading the quality of evidence is not warranted.

[e] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval (RR=1.62 [1.16, 2.26]).

[f] Insufficient studies to determine publication bias.

g Large effect not detected.

[h] No evidence that controlling for plausible confounder would change the effect size.

[i] Information on dose-response gradient not provided.

[j] Schymura[14]

[k] The four cohort studies were rated high on the Newcastle-Ottawa scale, with assessed stars ranging from 7 to 9 (9 is maximum).

[l] The statistical heterogeneity is high ($Tau^2 = 0.01$; $Chi^2 = 25.61$, df = 3 ($P<0.0001$); $I^2 = 88\%$), but the confidence intervals overlap and the direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.

[m] Limited information provided on specific hormonal therapy regimens evaluated. Two studies did not provide adequate information on stage of cancer (Zhou, 2009; Merglen, 2007). One study's population was slightly older (Lu-Yao, 2008). The follow-up time was 5 years in one study (Schymura, 2010) and was similar across the other three studies (mean 7 years and median 7 years). However, downgrading the quality of evidence is not warranted.

[n] The number of events is adequate (>300, a threshold rule of thumb value for dichotomous outcomes). There is an adequate sample size and the estimate of effect is precise with a narrow confidence interval (RR=1.13 [1.00, 1.27])

Table 10. Benefits of treatment for prostate cancer - cryotherapy

Quality assessment							Results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prostate Specific Mortality									
0[a]	N/A[b]	N/A[c]	N/A[d]	N/A[e]	N/A[f]	N/A[g]	0[h]	N/A[i]	Critical
All-cause Mortality									
0[a]	N/A[b]	N/A[c]	N/A[d]	N/A[e]	N/A[f]	N/A[g]	0[h]	N/A[i]	Critical

[a]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[b]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[c]Risk of bias cannot be assessed
[d]Inconsistency cannot be assessed
[e]Indirectness cannot be assessed
[f]Imprecision cannot be assessed
[g]Other considerations cannot be assessed
[h]There are no studies to provide data on the effect of this treatment for these outcomes
[i]Since there no studies the overall quality of the evidence cannot be determined

Table 11. Benefits of treatment for prostate cancer – high-intensity focused ultrasonography

Quality assessment							Results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prostate Specific Mortality									
0[a]	N/A[b]	N/A[c]	N/A[d]	N/A[e]	N/A[f]	N/A[g]	0[h]	N/A[i]	Critical
All-cause Mortality									
0[a]	N/A[b]	N/A[c]	N/A[d]	N/A[e]	N/A[f]	N/A[g]	0[h]	N/A[i]	Critical

[a]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[b]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[c]Risk of bias cannot be assessed
[d]Inconsistency cannot be assessed
[e]Indirectness cannot be assessed
[f]Imprecision cannot be assessed
[g]Other considerations cannot be assessed
[h]There are no studies to provide data on the effect of this treatment for these outcomes
[i]Since there no studies the overall quality of the evidence cannot be determined

Table 12. Tailoring method of follow-up

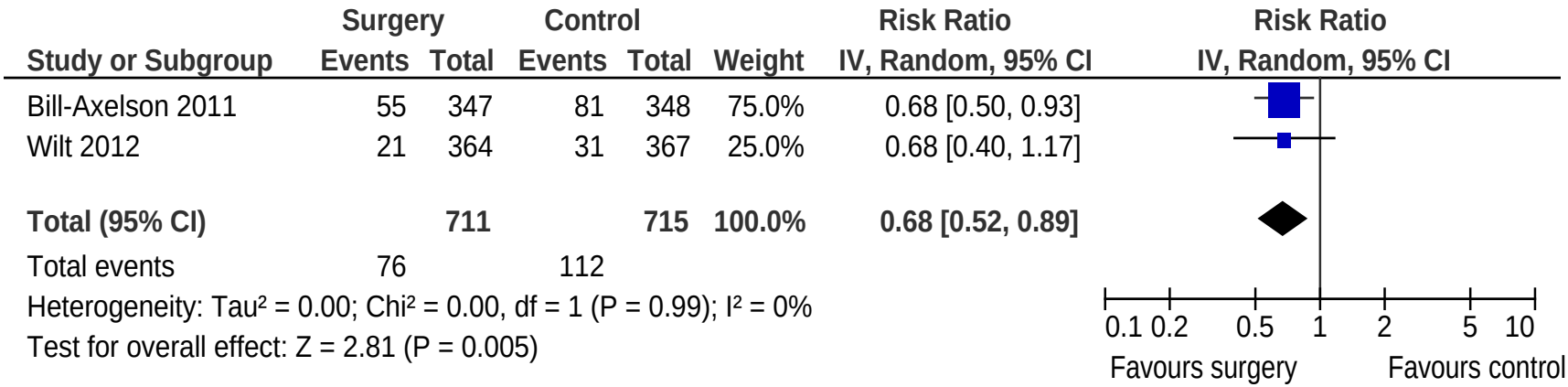
Quality assessment							Results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
0[a]	N/A[b]	N/A[c]	N/A[d]	N/A[e]	N/A[f]	N/A[g]	0[h]	N/A[i]	Critical

[a]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[b]No studies were found that met the inclusion criteria of this review for this treatment or outcomes
[c]Risk of bias cannot be assessed
[d]Inconsistency cannot be assessed
[e]Indirectness cannot be assessed
[f]Imprecision cannot be assessed
[g]Other considerations cannot be assessed
[h]There are no studies to provide data on the effect of this treatment for these outcomes
[i]Since there no studies the overall quality of the evidence cannot be determined

Figure 2. Forest plots for benefits of treatments for prostate cancer

Forest Plots: prostatectomy vs control

Prostate-cancer specific mortality - RCTs

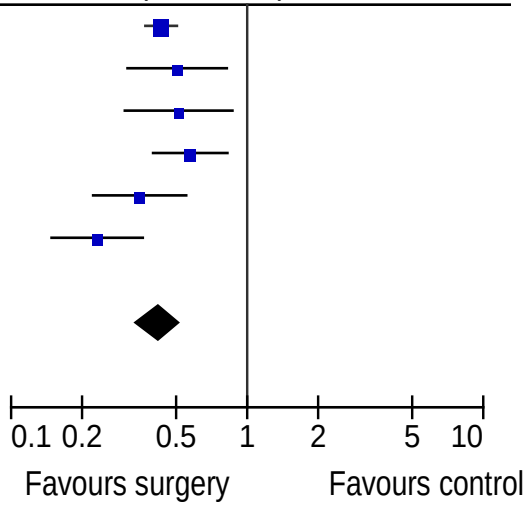


Prostate-cancer specific mortality - cohort

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Abdollah 2011	224	11669	518	11669	28.0%	0.43 [0.37, 0.50]
Albertsen 2007	64	802	18	114	13.3%	0.51 [0.31, 0.82]
Merglen 2007	15	158	70	378	12.0%	0.51 [0.30, 0.87]
Stattin 2010	56	3399	58	2021	17.9%	0.57 [0.40, 0.83]
Tewari 2007	18	119	85	197	14.3%	0.35 [0.22, 0.55]
Zhou 2009	21	889	175	1716	14.6%	0.23 [0.15, 0.36]
Total (95% CI)		**17036**		**16095**	**100.0%**	**0.42 [0.33, 0.53]**
Total events	398		924			

Heterogeneity: Tau² = 0.04; Chi² = 11.48, df = 5 (P = 0.04); I² = 56%

Test for overall effect: Z = 7.38 (P < 0.00001)

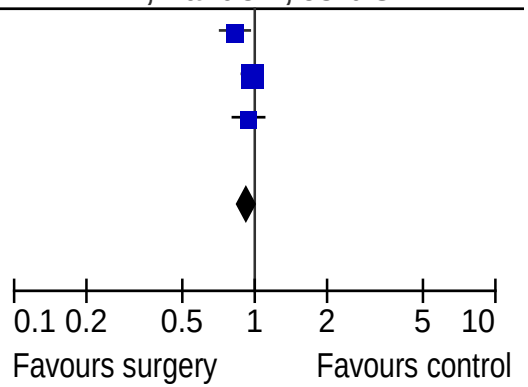


All-cause mortality - RCTs

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Bill-Axelson 2011	166	347	201	348	29.5%	0.83 [0.72, 0.95]
Iversen 1995	67	74	63	68	42.8%	0.98 [0.88, 1.08]
Wilt 2012	171	364	183	367	27.6%	0.94 [0.81, 1.09]
Total (95% CI)		**785**		**783**	**100.0%**	**0.92 [0.83, 1.02]**
Total events	404		447			

Heterogeneity: Tau² = 0.00; Chi² = 3.54, df = 2 (P = 0.17); I² = 44%

Test for overall effect: Z = 1.63 (P = 0.10)

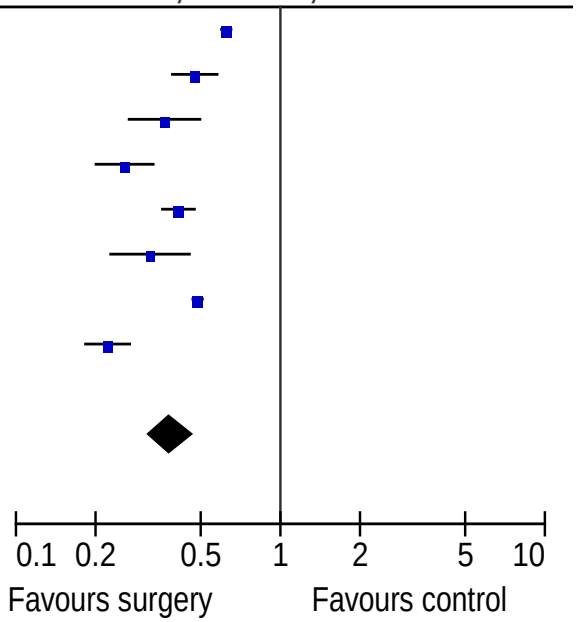


All-cause mortality - cohort

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Abdollah 2011	2448	11669	3922	11669	14.3%	0.62 [0.60, 0.65]
Albertsen 2007	217	802	65	114	12.7%	0.47 [0.39, 0.58]
Merglen 2007	34	158	223	378	10.7%	0.36 [0.27, 0.50]
Schymura 2010	83	1310	151	614	11.7%	0.26 [0.20, 0.33]
Stattin 2010	286	3399	413	2021	13.5%	0.41 [0.36, 0.47]
Tewari 2007	27	119	139	197	10.1%	0.32 [0.23, 0.45]
Wong 2006	2393	13292	4663	12608	14.3%	0.49 [0.47, 0.51]
Zhou 2009	98	889	851	1716	12.7%	0.22 [0.18, 0.27]
Total (95% CI)		**31638**		**29317**	**100.0%**	**0.38 [0.32, 0.47]**
Total events	5586		10427			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 205.81$, df = 7 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 9.48 ($P < 0.00001$)



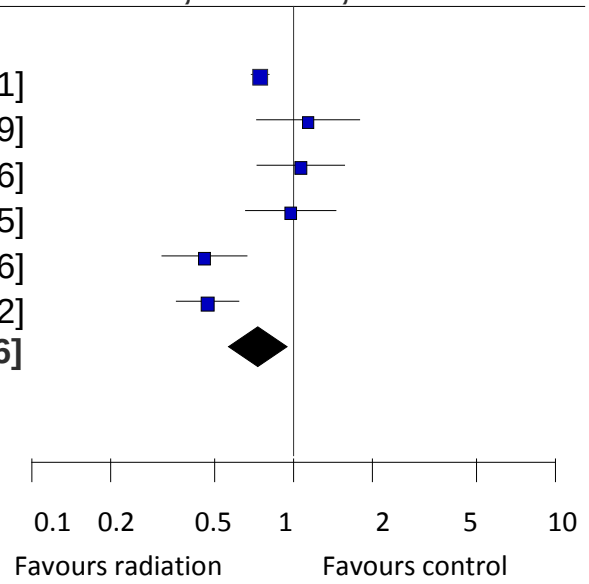
Forest plots: radiation therapy vs control

Prostate-cancer specific mortality

Study or Subgroup	Radiation Events	Radiation Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Cohort						
Abdollah 2012	1043	20986	1399	20986	22.3%	0.75 [0.69, 0.81]
Albertsen 2007	126	702	18	114	13.6%	1.14 [0.72, 1.79]
Merglen 2007	30	152	70	378	15.3%	1.07 [0.73, 1.56]
Stattin 2010	40	1429	58	2021	15.0%	0.98 [0.66, 1.45]
Tewari 2007	27	137	85	197	15.6%	0.46 [0.31, 0.66]
Zhou 2009	66	1378	175	1716	18.2%	0.47 [0.36, 0.62]
Total (95% CI)		**24784**		**25412**	**100.0%**	**0.74 [0.57, 0.96]**
Total events	1332		1805			

Heterogeneity: Tau² = 0.08; Chi² = 25.71, df = 5 (P = 0.0001); I² = 81%

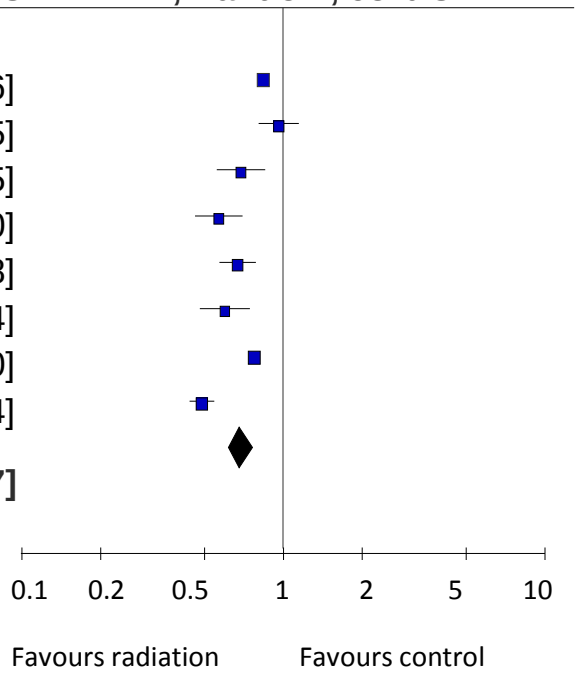
Test for overall effect: Z = 2.25 (P = 0.02)



All-cause mortality

Study or Subgroup	Radiation Events	Radiation Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Cohort						
Abdollah 2012	8860	20986	10528	20986	15.9%	0.84 [0.82, 0.86]
Albertsen 2007	386	702	65	114	11.5%	0.96 [0.81, 1.15]
Merglen 2007	62	152	223	378	10.2%	0.69 [0.56, 0.85]
Schymura 2010	145	1037	151	614	10.3%	0.57 [0.46, 0.70]
Stattin 2010	196	1429	413	2021	12.2%	0.67 [0.57, 0.78]
Tewari 2007	58	137	139	197	10.0%	0.60 [0.48, 0.74]
Wong 2006	5246	18249	4663	12608	15.8%	0.78 [0.75, 0.80]
Zhou 2009	335	1378	851	1716	14.0%	0.49 [0.44, 0.54]
Total (95% CI)		**44070**		**38634**	**100.0%**	**0.69 [0.62, 0.77]**
Total events	15288		17033			

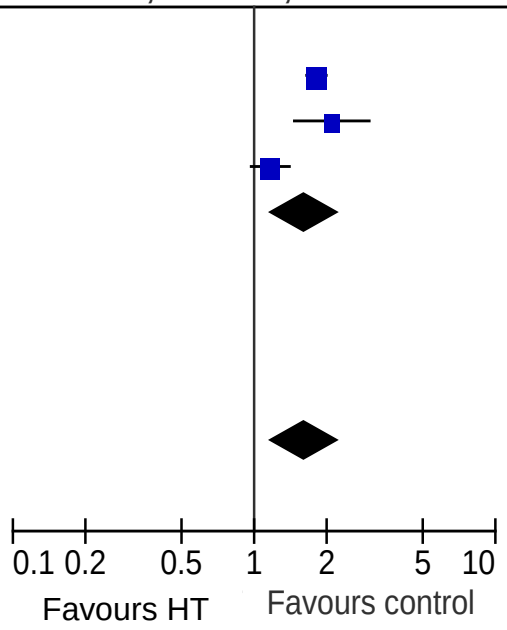
Heterogeneity: Tau² = 0.02; Chi² = 138.00, df = 7 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.50 (P < 0.00001)



Forest plots: hormonal therapy vs control

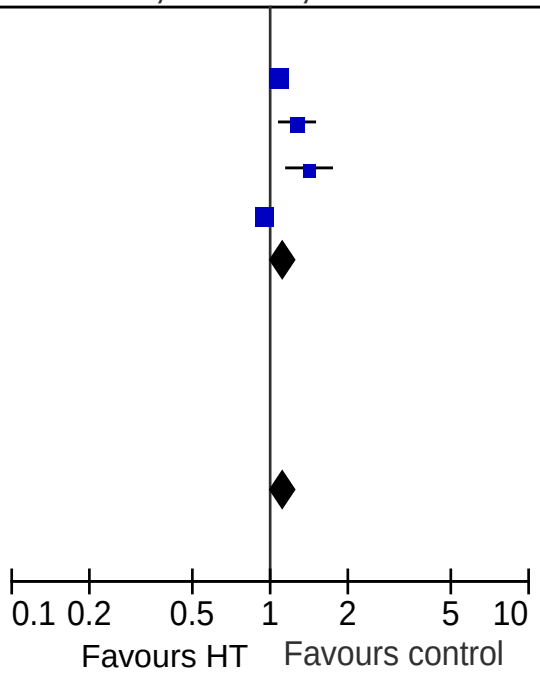
Prostate cancer-specific mortality

Study or Subgroup	HT Events	HT Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Cohort						
Lu-Yao 2008	867	7867	693	11404	37.9%	1.81 [1.65, 2.00]
Merglen 2007	28	72	70	378	27.1%	2.10 [1.47, 3.01]
Zhou 2009	244	2049	175	1716	35.0%	1.17 [0.97, 1.40]
Subtotal (95% CI)		**9988**		**13498**	**100.0%**	**1.62 [1.16, 2.26]**
Total events	1139		938			
Heterogeneity: Tau² = 0.08; Chi² = 19.07, df = 2 (P < 0.0001); I² = 90%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Total (95% CI)		**9988**		**13498**	**100.0%**	**1.62 [1.16, 2.26]**
Total events	1139		938			
Heterogeneity: Tau² = 0.08; Chi² = 19.07, df = 2 (P < 0.0001); I² = 90%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Not applicable						



All-cause mortality

Study or Subgroup	HT Events	HT Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Cohort						
Lu-Yao 2008	4729	7867	6316	11404	32.3%	1.09 [1.06, 1.11]
Merglen 2007	54	72	223	378	20.9%	1.27 [1.09, 1.49]
Schymura 2010	118	339	151	614	17.0%	1.42 [1.16, 1.73]
Zhou 2009	965	2049	851	1716	29.8%	0.95 [0.89, 1.01]
Subtotal (95% CI)		**10327**		**14112**	**100.0%**	**1.13 [1.00, 1.27]**
Total events	5866		7541			
Heterogeneity: Tau² = 0.01; Chi² = 25.61, df = 3 (P < 0.0001); I² = 88%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**10327**		**14112**	**100.0%**	**1.13 [1.00, 1.27]**
Total events	5866		7541			
Heterogeneity: Tau² = 0.01; Chi² = 25.61, df = 3 (P < 0.0001); I² = 88%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Not applicable						



Evidence set 4. Harms of treatment

- GRADE evidence profile tables
  - Harms of prostatectomy
    - Erectile dysfunction, urinary incontinence, bowel dysfunction
    - Post-surgical harms
    - QoL
  - Harms of radiotherapy
    - Erectile dysfunction, urinary incontinence, bowel dysfunction
    - QoL
  - Harms of hormonal therapy
    - Erectile dysfunction, urinary incontinence, bowel dysfunction
    - QoL
  - Harms of cryotherapy
    - QoL
  - Harms of HIFU
    - Erectile dysfunction, urinary incontinence, bowel dysfunction
- Forest plots
  - Harms of prostatectomy
  - Harms of radiotherapy
  - Harms of hormonal therapy
  - Harms of cryotherapy
  - Harms of HIFU

Table 13. Harms of treatment for prostate cancer - prostatectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prostatectomy	Control	Relative (95% CI)	Absolute		
Prostatectomy and urinary incontinence - RCT (follow-up 10 to 12 years; assessed with: number of events)												
2[a]	Randomised trials	No serious risk of bias[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[e]	None[f,g,h,i]	120/460 (26.1%)	36/448 (8%)	RR 3.22 (2.27 to 4.56)	178 more per 1000 (from 102 more to 286 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Prostatectomy and urinary incontinence - Cohort (follow-up 1 to 3 years; assessed with: number of events)												
4[j]	Observational studies	No serious risk of bias[k]	No serious inconsistency[l]	No serious indirectness[m]	No serious imprecision[n]	upgraded for large effect size[f,g,h,i]	630/2488 (25.3%)	32/515 (6.2%)	RR 3.68 (2.37 to 5.72)	167 more per 1000 (from 85 more to 293 more)	⊕⊕OO MODERATE	CRITICAL
Prostatectomy and erectile dysfunction - RCT (follow-up 2 to 9 years; assessed with: number of events)												
2[a]	Randomised trials	No serious risk of bias[b]	Serious[o]	No serious indirectness[d]	Serious[p]	None[f,g,h,i]	377/458 (82.3%)	246/ 434 (56.7%)	RR 1.39 (0.77 to 2.53)	221 more per 1000 (from 130 fewer to 867 more)	⊕⊕OO LOW	CRITICAL
Prostatectomy and erectile dysfunction - Cohort (follow-up 6 months to 4.5 years; assessed with: number of events)												
5[j,q]	Observational studies	No serious risk of bias[r]	No serious inconsistency[s]	No serious indirectness[t]	No serious imprecision[u]	None[f,g,h,i]	1914/2881 (66.4%)	242/ 579 (41.8%)	RR 1.56 (1.33 to 1.83)	234 more per 1000 (from 138 more to 347 more)	⊕⊕OO LOW	CRITICAL
Prostatectomy and bowel dysfunction - RCT (follow-up 2 to 8 years; assessed with: number of events)												
2[v]	Randomised trials	No serious risk of bias[w]	Serious[x]	No serious indirectness[y]	Serious[z]	None[f,g,h,i]	36/448 (8%)	41/439 (9.3%)	RR 0.42 (0.04 to 4.14)	54 fewer per 1000 (from 90 fewer to 293 more)	⊕⊕OO LOW	CRITICAL
Prostatectomy and bowel dysfunction - Cohort (follow-up 6 months to 3 years; assessed with: number of events)												
3[aa]	Observational studies	No serious risk of bias[bb]	No serious inconsistency[cc]	No serious indirectness[dd]	Serious[ee]	None[f,g,h,i]	56/2451 (2.3%)	23/490 (4.7%)	RR 0.69 (0.43 to 1.11)	15 fewer per 1000 (from 27 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL

[a] Johansson[40]; Wilt[28]

[b] Random sequence generation was reported in one of the RCTs (Wilt, 2012) and it was unclear in the other (Johansson, 2011). Neither of the studies reported on allocation concealment nor blinding, primarily because of the nature of the intervention (surgery). This would not likely have an effect on the outcome. Both RCTs reported on loss-to-follow-up and reporting bias. Johansson, 2011 was judged as high risk for other bias given that baseline data was not reported.

[c] Based on pooled analyses, minimal statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.00$; ($P = 0.36$); $I^2 = 0\%$).

[d] Limited information provided on specific surgical technique evaluated. Prostate cancer in the RCTs was most likely primarily clinically diagnosed rather than screen detected. One of the studies (Johansson, 2011) used patients for whom QOL and symptoms were evaluated with a cross-sectional design. Unfortunately no information about QOL and symptoms was available on the patients' general health or physical function before diagnosis and treatment. Conversely, side effects are compared within a randomized population, which will strengthen the results. With this limitation of lack of baseline values, we cannot be sure how much the RP affected the outcome. However, downgrading the quality of evidence is not warranted.

[e] Adequate sample size (overall 460 for intervention and 448 for control) and number of events (overall 120 for intervention and 36 for control). The point estimate was also precise,

with a narrow confidence interval 3.22 (2.27, 4.56)
[f] Insufficient studies to determine publication bias.
[g] No large effect found across studies.
[h] Unlikely that plausible confounders would change the effect size.
[i] Dose response not applicable to the type of intervention examined (surgery).
[j] Hoffman[44]; Litwin[41]; Schapira[42]; Smith[43]
[k] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. Three of the four studies (Hoffman, 2003; Schapira, 2001; Smith, 2009) rated 6 and above out of 9.
[l] Based on pooled analyses, minimal statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.05$; ($P = 0.28$); $I^2 = 22\%$).
[m] Limited information provided on specific surgical techniques. Outcome definition for urinary incontinence differed across studies (urinary leakage [Hoffman, 2003; Litwin,1995], and urinary incontinence [Schapira, 2001; Smith 2009]). Tumour stage was not reported in two (Hoffman, 2003; Litwin,1995) of the four cohort studies. However, downgrading the quality of evidence is not warranted.
[n] There was an overall adequate sample size (overall 2488 for intervention and 515 for control) and number of events (overall 630 for intervention and 32 for control. One study had a wider confidence interval (Schapira, 2001 - RR=11.11 [1.57, 78.47]), but the overall effect on point estimate is minimal and the point estimate was also precise, with a narrow confidence interval (RR=3.68 [2.37, 5.72]).
[o] Based on pooled analyses, statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.18$; ($P < 0.00001$); $I^2 = 98\%$) with confidence intervals in one of the studies crossing over the null.
[p] There was an adequate sample size (overall 458 for intervention and 434 for control) and number of events (overall 377 for intervention and 246 for control). However, the pooled estimate is not precise, showing both benefits and harms of the treatment (RR=1.39 [0.77, 2.53]).
[q] Siegel[45]
[r] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. Three of the five studies (Litwin, 1995; Schapira, 2001; Smith, 2009) rated 6 and above out of 9.
[s] Based on pooled analyses, statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.02$; ($P = 0.03$); $I^2 = 63\%$) but the confidence intervals overlap and the direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.
[t] Limited information provided on specific surgical techniques. Outcome definition for erectile dysfunction different across studies (poor to very poor sexual function [Litwin, 1995], impotence [Schapira, 2001; Siegel, 2001; Smith, 2009], and erectile dysfunction [Hoffman, 2003]). Tumour stage was not reported in three of the five cohort studies (Hoffman, 2003; Litwin, 1995; Seigel 2001). However, downgrading the quality of evidence is not warranted.
[u] There was an adequate sample size (overall 2881 for intervention and 579 for control) and number of events (overall 1914 for intervention and 292 for control). The point estimate was also precise, with a narrow confidence interval (RR=1.56 [1.33, 1.83]).
[v] Johansson[46]; Wilt[28]
[w] Random sequence generation was reported in one of the RCTs (Wilt, 2012) and it was unclear in the other as to randomization technique (Johansson, 2009). Neither of the studies reported on allocation concealment nor blinding, primarily because of the nature of the intervention (surgery). This would not have an effect on the outcome. Both RCTs reported on loss-to-follow-up.
[x] Based on pooled analyses, statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 2.23$; ($P <0.03$); $I^2 = 80\%$).
[y] Limited information provided on specific surgical technique evaluated. Prostate cancer in the RCTs was most likely clinically diagnosed rather than screen detected. One of the studies (Johansson) used patients for whom QOL and symptoms were evaluated with a cross-sectional design. Unfortunately no information about QOL and symptoms was available on the patients' general health or physical function before diagnosis and treatment. Conversely, side effects are compared within a randomized population, which will strengthen the results. With this limitation of lack of baseline values, we cannot really be sure how much the RP affected the outcome. However, downgrading the quality of evidence is not warranted.
[z] The pooled estimate is not precise with the confidence interval including no effect value of 1 (RR: 0.42 [0.04, 4.14]).
[aa] Hoffman[44]; Litwin[41];Smith[43]
[bb] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. All but one of the three studies (Litwin, 1995) rated 6 and above out of 9.
[cc] Based on pooled analyses, statistical heterogeneity was not observed across studies (Heterogeneity: $Tau^2 = 0.00$; ($P <0.57$); $I^2 = 0\%$).
[dd] Limited information provided on specific surgical techniques. Outcome definition for bowel dysfunction different across studies (bowel urgency all most every day (Hoffman, 2003); rectal urgency more than once a day (Litwin 1995b); moderate or severe bowel problems (Smith, 2009). Tumour stage was not reported in two (Hoffman, 2003; Litwin 1995b) of the three cohort studies.
[ee] There was an overall adequate sample size (overall 2452 for intervention and 490 for control) and number of events (overall 56 for intervention and 23 for control. One study had a wider confidence interval (Hoffman, 2003 - RR=1.84 [0.24, 1420]), and the pooled estimate is not precise, showing both benefits and harms of the treatment (RR=0.69 [0.43, 1.11]).

Table 14. Harms of treatment for prostate cancer – prostatectomy and post-surgical harms (<30d; uncontrolled studies)

Quality Assessment							Results Proportion % (CI 95%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Post-surgical (Prostatectomy) outcomes, ANY <30 days									
4[a]	Observational	Serious[b]	No Serious[c]	No serious[d]	No serious[e]	None[f]	2246/11010 20 (19.7-21.2)[47] 247/1243 20 (17.8-22.2)[48] 395/3458 11.4 (10.4-12.5)[49] 60/280 21.4 (17.0-26.8)[28]	⊕OOO VERY LOW	Critical
Post-surgical Outcomes (Prostatectomy), Mortality <30days									
2[g]	Observational	Serious[b]	No serious[c]	No serious[d]	No Serious[e]	None[f]	53/11010 0.48 (0.36-0.63)[47] 1/280 0.36 (0.02-2.3)[28]	⊕OOO VERY LOW	Critical

[a] Alibhai[47]; Augustin[48]; Rabbani[49]; Wilt[28]
[b] Uncontrolled observational study
[c] The proportion of men across the studies who reported this outcome was approximately 20% in three of the studies and 11% in the fourth.
[d] Across the body of evidence for this outcome, the population (men, ages 50-75), intervention (PSA screening, interval range annual to 7 years), location (Europe, United States), and outcome (surgical harms) are similar to the context/criteria specified by the key questions for this review.
[e] The sample was >2000, sufficient for optimal information size. The results do not include an effect estimate or confidence interval.
[f] There are an insufficient number of studies to assess publication bias
[g] Alibhai[47]; Wilt[28]
See Appendix 10 for specific harms

Table 15. Harms of treatment for prostate cancer – prostatectomy and QoL SF-36 outcomes

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prostatectomy	Control	Median MD at post-intervention with range		
QoL_Physical function (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
6[a]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[c]	No Serious Indirectness[d]	No Serious Imprecision[e]	None[f]	2218	355	MD 8.5 higher (2.0 to 16.8 higher)	⊕⊕OO LOW	CRITICAL
QoL_Physical role function (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
6[a]	Observational Studies	No serious RoB[b]	Serious[g]	No Serious Indirectness[d]	Serious[h]	None[f]	2218	355	MD 3.2 higher (10 lower to 9.5 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Bodily pain (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
6[a]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[j]	No Serious Indirectness[d]	Serious[j]	None[f]	2218	355	MD 3.8 higher (5 lower to 10.2 higher)	⊕OOO VERY LOW	CRITICAL
QoL_General health (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
6[a]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[c]	No Serious Indirectness[d]	No Serious Imprecision[k]	None[f]	2218	355	MD 4.5 higher (2.2 to 20.8 higher)	⊕⊕OO LOW	CRITICAL
QoL_Vitality (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
7[a,l]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[m]	No Serious Indirectness[d]	Serious[n]	None[f]	2500	421	MD 3.0 higher (2.0 lower to 13.8 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Emotional role function (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
7[a,l]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[j]	No Serious Indirectness[d]	Serious[o]	None[f]	2500	421	MD 8.0 higher (5.0 lower to 12.8 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Mental Health (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
7[a,l]	Observational Studies	No serious RoB[b]	Serious[g]	No Serious Indirectness[d]	Serious[p]	None[f]	2500	421	MD 1.0 lower (4.2 lower to 10.1 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Social function (follow-up 3 months to 6 years; measured with: SF-36; Better indicated by higher values)											
6[a,l]	Observational Studies	No serious RoB[b]	No Serious Inconsistency[j]	No Serious Indirectness[d]	Serious[q]	None[f]	2441	391	MD 3.5 higher (2.0 lower to 11.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Physical component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)+66											
2[r]	Observational Studies	No serious RoB[s]	No Serious Inconsistency[c]	No Serious Indirectness[d]	No Serious imprecision[t]	None[f]	1391	231	MD 3.0 higher (1.8 to 3.2 higher)	⊕⊕OO LOW	CRITICAL
QoL_Mental component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)											

2[r]	Observational Studies	No serious RoB[s]	No Serious Inconsistency[c]	No Serious Indirectness[d]	Serious[u]	None[f]	1391	231	MD 0.2 higher (0 to 0.6 higher)	⊕OOO VERY LOW	CRITICAL

[a] Litwin[50]; Lubeck[52]; Bacon[53]; Galbraith[54]; Schapira[42]; Smith DS[55]
[b] These observational studies were assessed with the Newcastle-Ottawa scale. For this outcome only one of the included studies was assessed below a 5/9 therefore we did not downgrade for risk of bias
[c] The direction of effect is consistent across studies
[d]The studies are mostly conducted in the US and the outcome of interest was measured with a valid and reliable instrument. Not all the studies provided details on the techniques of surgery used however we did not downgrade. Across the studies length of follow-up ranged from 3 months to 6 years.
[e] The sample size is adequate (≥ 300) and the range for effect estimate (MD) at post-intervention is precise, range = 2.0 to 16.8.
[f] Insufficient studies to determine publication bias
[g] The direction of effect is not consistent across studies i.e. Mean difference (MD) across studies at post-intervention showing both benefit and harm of treatment.
[h] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -10 to 9.5
[i] The direction of effect is consistent across studies except one study.
[j] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -5.0 to 10.2
[k] The sample size is adequate (≥ 300) and the range for effect estimate (MD) at post-intervention is precise, range = 2.2 to 20.8.
[l] Litwin[51]
[m] The direction of effect is consistent across studies except two studies.
[n] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -2.0 to 13.8
[o] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -5.0 to 12.8
[p] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -4.2 to 10.1
[q] The sample size is adequate (≥ 300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -2.0 to 11.0
[r] Bacon[53]; Smith DP[43]
[s] These observational studies were assessed with the Newcastle-Ottawa scale. For this outcome none of the included studies was assessed below a 5/9 therefore we did not downgrade for risk of bias
[t] The sample size is adequate (≥ 300) in intervention group and < 300 in control group but the range for effect estimate (MD) at post-intervention is precise, range = 1.8 to 3.2.
[u] The sample size is adequate (≥ 300) in intervention group and < 300 in control group and the range for effect estimate (MD) at post-intervention is not precise and includes no effect value of 0, range = 0 to 0.6.

Table 16. Harms of treatment for prostate cancer – radiation therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiation therapy	Control	Relative (95% CI)	Absolute		
Radiation Therapy and urinary incontinence - RCT (follow-up 30.4 to 40.6 months; assessed with: number of events)												
1[a]	randomised trials	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	serious[e]	None [f,g,h,i]	10/59 (16.9%)	1/49 (2%)	RR 8.31 (1.1 to 62.63)	149 more per 1000 (from 2 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Radiation therapy and urinary incontinence - Cohort (follow-up 1 to 3 years; assessed with: number of events)												
4[j]	observational studies	no serious risk of bias[k]	no serious inconsistency[l]	no serious indirectness[m]	serious[n]	none [f,g,h,i]	87/905 (9.6%)	32/515 (6.2%)	RR 1.35 (0.9 to 2.02)	22 more per 1000 (from 6 fewer to 63 more)	⊕OOO VERY LOW	CRITICAL
Radiation Therapy and erectile dysfunction - Cohort (follow-up 1 to 10 years; assessed with: number of events)												
6[j,o]	observational studies	no serious risk of bias[p]	no serious inconsistency[q]	no serious indirectness[r]	no serious imprecision[s]	none [f,g,h,i]	732/1288 (56.8%)	270/639 (42.3%)	RR 1.30 (1.17 to 1.43)	127 more per 1000 (from 72 more to 182 more)	⊕⊕OO LOW	CRITICAL
Radiation therapy and bowel dysfunction - Cohort (follow-up 2 to 6 years; assessed with: number of events)												
3[t]	observational studies	no serious risk of bias[u]	no serious inconsistency[v]	no serious indirectness[w]	serious[x]	none [f,g,h,i]	51/865 (5.9%)	23/490 (4.7%)	RR 1.65 (0.84 to 3.25)	31 more per 1000 (from 8 fewer to 106 more)	⊕OOO VERY LOW	CRITICAL

[a] Fransson[56]

[b] The one RCT assessing RT and UI did not provided a clear description of random sequence generation. Allocation concealment and blinding were not adequately described, but, given the nature of the therapy, it would be impossible to conceal or blind participants to treatment. This would not likely affect the outcome of UI. Loss-to-follow-up was also not reported

[c] Given that only one RCT assessed RT and UI, we cannot assess heterogeneity among studies

[d] Limited information provided on specific radiation technique evaluated. Prostate cancer in the RCT was most likely primarily clinically diagnosed rather than screen detected. However, downgrading the quality of evidence is not warranted.

[e] The risk of urinary incontinence was increased after radiation therapy, but with a very imprecise estimate (RR, 8.3 [CI; 1.1 TO 63)]

[f] Insufficient studies to determine publication bias.

[g] No large effect detected.

[h] Unlikely that plausible confounders would change the effect size.

[i] A dose response gradient for radiation therapy was not examined in the RCT.

[j] Hoffman[44]; Litwin[41]; Schapira[42]; Smith DP[43]

[k] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. Three of the four studies (Hoffman, 2003; Schapira, 2001; Smith, 2009) rated 6 and above out of 9.

[l] Based on pooled analyses, minimal statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.00$; ($P = 0.73$); $I^2 = 0\%$)

[m] Limited information provided on specific surgical techniques. Outcome definition for urinary incontinence different across studies (urinary leakage [Hoffman, 2003; Litwin,1995], and urinary incontinence [Schapira, 2001; Smith 2009]). Tumour stage was not reported in two (Hoffman, 2003; Litwin,1995) of the four cohort studies. However, downgrading the quality of evidence is not warranted.

[n] Overall adequate sample size (overall 905 for intervention and 515 for control) and number of events (overall 87 for intervention and 32 for control). However, the pooled estimate is

not precise, showing both benefits and harm of the treatment (RR 1.35 [CI0.90,2.02])

[o] Thong[57]; Siegel[45]

[p] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. Four of the six studies rated 6 and above out of 9 (Hoffman 2003; Schapira, 2001; Smith, 2009; Thong 2009).

[q] Based on pooled analyses, minimal statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.00$; ($P = 0.43$); $I^2 = 0\%$).

[r] Limited information provided on specific radiation therapy techniques. Outcome definition for erectile dysfunction different across studies (poor to very poor sexual function [Litwin, 1995], impotence [Schapira, 2001; Siegel, 2001; Smith, 2009], erectile dysfunction [Hoffman, 2003]), and problems with getting or maintaining an erection [Thong, 2009]. Tumour stage was not reported in three of the six cohort studies (Hoffman, 2003; Litwin, 1995; Seigel 2001). However, downgrading the quality of evidence is not warranted.

[s] There was an overall adequate sample size (overall 1288 for intervention and 639 for control) and number of events (overall 732 for intervention and 270 for control. The overall effect on point estimate is minimal and the point estimate was also precise, with a narrow confidence interval (RR=1.30 [1.17, 1.43])

[t] Hoffman[44]; Litwin[41]; Smith DP[43]

[u] The number of assessed stars for risk of bias on the Newcastle-Ottawa Scale ranged from 3 to 8 (fair to good) on a scale of 9. All but one (Litwin, 1995) of the three studies rated 6 and above out of 9.

[v] Based on pooled analyses, minimal statistical heterogeneity was observed across studies (Heterogeneity: $Tau^2 = 0.13$; ($P = 0.21$); $I^2 = 36\%$).

[w] Limited information provided on specific surgical techniques. Outcome definition for bowel dysfunction different across studies (bowel urgency all most every day (Hoffman, 2003); rectal urgency more than once a day (Litwin 1995b); moderate or severe bowel problems (Smith, 2009). Tumour stage was not reported in two (Hoffman, 2003; Litwin 1995b) of the three cohort studies. However, downgrading the quality of evidence is not warranted.

[x] Though the sample size is okay, the point estimate is imprecise with the confidence interval on both sides of the null (HR: 1.65 [0.84, 3.25]).

Table 17. Harms of treatment for prostate cancer – radiation therapy and QoL SF-36 outcomes

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiation Therapy	Control	Median MD at post-intervention with range		
QoL_Physical function (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
7[a]	Observational studies	No serious RoB[b]	Serious[c]	No serious indirectness[d]	Serious[e]	None[f]	821	426	MD 5.0 lower (10.0 lower to 11.00 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Physical role function (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
7[a]	Observational studies	No serious RoB[b]	No serious inconsistency[g]	No serious indirectness[d]	Serious[h]	None[f]	821	426	MD 6.7 lower (22.0 lower to 15.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Bodily pain (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
7[a]	Observational studies	No serious RoB[b]	No serious inconsistency[j]	No serious indirectnes[d]	Serious[j]	None[f]	821	426	MD 4.5 lower (11.0 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
QoL_General health (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
7[a]	Observational studies	No serious RoB[b]	No serious inconsistency[g]	No serious indirectness[d]	Serious[k]	None[f]	821	426	MD 2.0 higher (9.2 lower to 7.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Vitality (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
8[a, l]	observational studies	No serious RoB[b]	No serious inconsistency[j]	No serious indirectness[d]	Serious[m]	None[f]	925	492	MD 3.5 lower (5.0 lower to 1.4 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Social function (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
7[a.l]	observational studies	No serious RoB[b]	Serious[c]	No serious indirectness[d]	Serious[n]	None[f]	829	462	MD 0.5 lower (27.10 lower to 5.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Emotional role function (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											
8[a,l]	observational studies	No serious RoB[b]	Serious[c]	No serious indirectness[d]	Serious[o]	None[f]	925	492	MD 4.0 lower (8.0 lower to 20.00 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Mental Health (follow-up 3 months to 10 years; measured with: SF-36; Better indicated by higher values)											

8[a,l]	observational studies	No serious RoB[b]	Serious[c]	No serious indirectness[d]	Serious[p]	None[f]	925	492	MD 0.0 higher (6.00 lower to 3.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Physical component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)											
3[q]	observational studies	No serious RoB[r]	Serious[c]	No serious indirectness[d]	Serious[s]	None[f]	589	302	MD 0.8 higher (3.0 lower to 2.1 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Mental component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)											
3[q]	observational studies	No serious RoB[r]	No serious inconsistency[g]	No serious indirectness[d]	Serious[t]	None[f]	589	302	MD 0.6 lower (2.0 lower to 1.0 higher)	⊕OOO VERY LOW	CRITICAL

[a] Litwin[50]; Lubeck[52]; Bacon[53]; Galbraith[54]; Schapira[42]; Smith DS[55]; Thong[57]
[b] These observational studies were assessed with the Newcastle-Ottawa scale. For this outcome only one of the included studies was assessed below a 5/9 therefore we did not downgrade for risk of bias.
[c] The direction of effect is not consistent across studies i.e. Mean difference (MD) across studies at post-intervention showing both benefit and harm of treatment.
[d]The studies are mostly conducted in the US and the outcome of interest was measured with a valid and reliable instrument. Radiation modalities were not consistent between studies however we did not downgrade. Across the studies length of follow-up ranged from 3 months to 10 years.
[f] Insufficient included studies to determine publication bias.
[e]The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -10.0 to 11.0
[g] The direction of effect is consistent across studies except two studies.
[h] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -22.0 to 15.0
[i] The direction of effect is consistent across studies except one study.
[j] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -11.0 to 0.5
[k] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -9.2 to 7.0
[l] Litwin[51]
[m] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -5.0 to 1.4
[n] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -27.1 to 5.0
[o] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -8.0 to 20.0
[p] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -6.0 to 3.0
[q] Smith DP[43]; Bacon[53]; Thong[57]
[r] These observational studies were assessed with the Newcastle-Ottawa scale. For this outcome none of the included studies was assessed below a 5/9 therefore we did not downgrade for risk of bias.
[s] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -3.0 to 2.1
[t] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -2.0 to 1.0

Table 18. Harms of treatment for prostate cancer – hormonal therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hormonal Therapy	Control	Relative (95% CI)	Absolute		
HT and urinary incontinence - Cohort (follow-up 2 to 3 years; assessed with: number of events)												
2[a]	Observational studies	No serious risk of bias[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None [f,g,h,i]	22/240 (9.2%)	25/430 (5.8%)	RR 1.32 (0.75 to 2.3)	19 more per 1000 (from 15 fewer to 76 more)	⊕OOO VERY LOW	CRITICAL
HT and erectile dysfunction - cohort (follow-up 1 to 3 years; assessed with: number of events)												
3[j]	Observational studies	No serious risk of bias[k]	No serious inconsistency[l]	No serious indirectness[m]	No serious imprecision[n]	Upgraded for large effect size [f,g,h,i]	248/328 (75.6%)	214/653 (32.8%)	RR 2.35 (1.53 to 3.59)	442 more per 1000 (from 174 more to 849 more)	⊕⊕OO MODERATE	CRITICAL
HT and bowel dysfunction (follow-up 2 to 3 years; assessed with: number of events)												
2[a]	Observational studies	No serious risk of bias[b]	Serious[o]	No serious indirectness[d]	Serious[p]	None [f,g,h,i]	10/240 (4.2%)	12/430 (2.8%)	RR 2.44 (0.24 to 24.4)	40 more per 1000 (from 21 fewer to 653 more)	⊕OOO VERY LOW	CRITICAL

[a] Hoffman[44]; Smith DP[43]

[b] Studies received six (Hoffman, 2003) and eight (Smith, 2009) stars on the Newcastle-Ottawa scale.

[c] Confidence intervals do overlap, but one of the studies (Smith, 2009) has a very wide confidence interval and both studies fall on both sides of the null. (Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 32\%$). However, there is minimal statistical heterogeneity across studies.

[d] Moderate to limited information on specific HT regimens evaluated. One study did not provide information on tumour stage (Hoffman, 2003). Definitions of control were divergent with one study describing it as "no active treatment" (Hoffman, 2003) and the other study describing it as "active surveillance" (Smith, 2009). Follow-up times were slightly different (2 and 3 years). However, downgrading the quality of evidence is not warranted.

[e] Sample sizes were adequate but the pooled estimate is not precise, showing both benefits and harm of the treatment (RR 1.32 [CI 0.75,2.30])

[f] Insufficient studies to determine publication bias.

[g] Large effect not detected.

[h] No evidence that controlling for plausible confounder would change the effect size.

[i] Dose response not examined.

[j] Potosky[58]; Hoffman[44]; Smith DP[43]

[k] Studies received six (Hoffman, 2003) and eight (Potosky, 2002; Smith, 2009) stars on the Newcastle-Ottawa scale.

[l] The level of heterogeneity is high (Heterogeneity: $Tau^2 = 0.13$; (P < 0.0001); $I^2 = 90\%$). However, the confidence intervals overlap and the direction of effect is consistent across studies. The variability is most likely due to small and large treatment effects observed across studies.

[m] Moderate (limited information on specific HT regimens evaluated). One study did not provide information on Tumour stage (Hoffman, 2003). Definitions of control were different between studies, with studies describing it as "no active treatment" (Hoffman, 2003) no therapy (Potosky, 2002) and active surveillance (Smith, 2009). Follow-up times ranged from 2 to 3 years. However, downgrading the quality of evidence is not warranted.

[n] Sample size was adequate and the estimate of effect was precise with narrow confidence intervals (RR: 2.35 [1.53, 3.59]).

[o] Based on pooled analysis, statistical heterogeneity was observed between studies, with one study (Hoffman, 2003) showing an effect and the other (Smith, 2009) showing no effect. ($Tau^2 = 2.04$; [P = 0.06]; $I^2 = 73\%$)

[p] The estimate of effect was imprecise with a moderately wide confidence interval for one of the studies on either side of the null (RR: 2.44 [0.24, 24.40]).

Table 19. Harms of treatment for prostate cancer – hormonal therapy and QoL SF-36 outcomes

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hormonal therapy	Control	Median MD at post-intervention with range		
QoL_Physical function (follow-up 11 months to 5 years; measured with: SF-36; Better indicated by higher values)											
3[a]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[g]	None[h]	279	238	MD 3.0 lower (13.0 lower to 1.8 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Physical role function (follow-up 6 months to 5 years; measured with: SF-36; Better indicated by higher values)											
4[b]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[i]	None[h]	524	654	MD 11.1 lower (23.0 lower to 13.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Bodily pain (follow-up 6 months to 5 years; measured with: SF-36; Better indicated by higher values)											
4[b]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[j]	None[h]	524	654	MD 3.7 lower (8.0 lower to 2.9 higher)	⊕OOO VERY LOW	CRITICAL
QoL_General health (follow-up 11 months to 5 years; measured with: SF-36; Better indicated by higher values)											
3[a]	Observational studies	No serious RoB[d]	Serious[k]	No serious indirectness[f]	Serious[l]	None[h]	279	238	MD 2.0 lower (5.0 lower to 10.4 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Vitality (follow-up 6 months to 5 years; measured with: SF-36; Better indicated by higher values)											
4[b]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[m]	None[h]	524	654	MD 7.0 lower (7.3 lower to 1.2 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Social function (follow-up 11 months to 5 years; measured with: SF-36; Better indicated by higher values)											
3[a]	Observational studies	No serious RoB[d]	Serious[k]	No serious indirectness[f]	Serious[n]	None[h]	279	238	MD 4.0 lower (10.0 lower to 6.0 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Emotional role function (follow-up 6 months to 5 years; measured with: SF-36; Better indicated by higher values)											
4[b]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[o]	None[h]	524	654	MD 9.1 lower (16.0 lower to 10.9 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Mental Health (follow-up 6 months to 5 years; measured with: SF-36; Better indicated by higher values)											
4[b]	Observational studies	No serious RoB[d]	No serious inconsistency[e]	No serious indirectness[f]	Serious[p]	None[h]	524	654	MD 2.3 lower (6.0 lower to 4.4 higher)	⊕OOO VERY LOW	CRITICAL
QoL_Physical component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)											
2[c]	Observational studies	No serious RoB[d]	No serious inconsistency[q]	No serious indirectness[f]	No serious imprecision[r]	None[h]	94	231	MD 5.6 lower (8.1 to 3.0 lower)	⊕⊕OO LOW	CRITICAL
QoL_Mental component (summary scores) (follow-up 3 to 5 years; measured with: SF-36; Better indicated by higher values)											
2[c]	Observational	No	Serious[k]	No serious	Serious[s]	None[h]	94	231	MD 1.5 lower (3.0 lower	⊕OOO	CRITICAL

	studies	serious RoB[d]		indirectness[f]					to 0.1 higher)	VERY LOW	

[a] Lubeck[52];Bacon[53]; Smith DS[55];
[b] Lubeck[52];Bacon[53]; Potosky[58]; Smith DS[55]
[c] Bacon[53]; Smith DP[43],
[d] These observational studies were assessed with the Newcastle-Ottawa scale. For this outcome none of the included studies was assessed below a 5/9 therefore we did not downgrade for risk of bias.
[e] The direction of effect is consistent across studies except one study.
[f]The studies are mostly conducted in the US and the outcome of interest was measured with a valid and reliable instrument. Not all the studies provided details on various regimens/dose of HT/hormonal therapy used however we did not downgrade. Across the studies length of follow-up ranged from 6 months to 5 years.
[g] The sample size is not adequate (<300) and the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -13.0 to 1.0
[h] Insufficient studies to determine publication bias.
[i] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -23.0 to 13.0
[j] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -8.0 to 2.9
[k] The direction of effect is not consistent across studies i.e. Mean difference (MD) across studies at post-intervention showing both benefit and harm of treatment.
[l] The sample size is not adequate (<300) and the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -5.0 to 10.4
[m] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -7.3 to 1.2
[n] The sample size is not adequate (<300) and the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -10.0 to 6.0
[o] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -16.0 to 10.9
[p] The sample size is adequate (≥300) but the range of effect estimate (MD) at post-intervention includes the no effect value of 0. Range = -6.0 to 4.4
[q] The direction of effect is consistent across studies.
[r] The sample size is not adequate (<300) but the range of effect estimate (MD) at post-intervention is precise. Range = -8.1 to -3.0
[s] The sample size is not adequate (<300) but the range of effect estimate (MD) at post-intervention is precise. Range = -3.0 to 0.1

Table 20. Harms of treatment for prostate cancer – hormone and radiation combination therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Harms of Combined therapy	Control	Relative (95% CI)	Absolute		
Urinary incontinence (follow-up mean 3 years)												
1	observational studies[a]	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	Serious[e]	None[f]	6/166 (3.6%)	6/200 (3%)	RR 1.2048 (0.3960 to 3.6658)	6144 more per 1,000,000 (from 18120 fewer to 79974 more)	⊕OOO VERY LOW	CRITICAL
Bowel dysfunction (follow-up mean 3 years)												
1	observational studies[a]	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[g]	None[f]	19/166 (11.4%)	11/200 (5.5%)	RR 2.0811 (1.0196 to 4.2476)	59460 more per 1,000,000 (from 1078 more to 178618 more)	⊕⊕OO LOW	CRITICAL
Erectile dysfunction (follow-up mean 3 years)												
1	observational studies[a]	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[h]	None[f]	121/166 (72.9%)	94/200 (47%)	RR 1.55 (1.3 to 1.85)	258500 more per 1,000,000 (from 141000 more to 399500 more)	⊕⊕OO LOW	CRITICAL
Physical component score (SF-36) (follow-up mean 3 years; measured with: SF-12 (Based of SF-36); Better indicated by higher values)												
1	observational studies[a]	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[i]	None[f]	166	200	-	MD 1.8000 lower (3.4705 to 0.1295 lower)	⊕⊕OO LOW	CRITICAL
Mental component score (SF-36) (follow-up mean 3 years; measured with: SF-12 (Based of SF-36); Better indicated by higher values)												
1	observational studies[a]	no serious risk of bias[b]	no serious inconsistency[c]	no serious indirectness[d]	no serious imprecision[j]	None[f]	166	200	-	MD 2.4000 lower (3.7543 to 1.0457 lower)	⊕⊕OO LOW	CRITICAL

[a] Smith et al.[43]
[b] The study was rated high on the Newcastle-Ottawa scale, with assessed stars 8 out of 9.
[c] The consistency could not be assessed as only one study reported data for this outcome.
[d] One cohort study provided data for this outcome. It included men with ages between 37 to 69 years. The combination therapy used in the study was hormonal treatment (ADT) plus external radiotherapy (EBRT). The control group in the study was defined as active surveillance in the first 6 months after diagnosis. The study was conducted in Australia. The study was published in 2009. The length of follow-up was 3 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[e] The sample size is inadequate (<300 per arm) and the effect estimate is imprecise with 95% CI including the no effect value of 1 (RR = 1.2048 (95% CI, 0.3960 to 3.6658). This body of evidence was downgraded for serious concerns regarding imprecision.
[f] Too few studies (n<10) to assess publication bias.
[g] The sample size inadequate i.e. less than 300 per arm, but effect estimate is precise with narrow confidence intervals (RR = 2.0811 (95% CI, 1.0196 to 4.2476). The body of evidence was not downgraded for imprecision.
[h] The sample size inadequate i.e. less than 300 per arm, but effect estimate is precise with narrow confidence intervals (RR = 1.5509 (95% CI, 1.3032 to 1.8456). The body of evidence was not downgraded for imprecision.
[9] The sample size inadequate i.e. less than 300 per arm, but effect estimate is precise with narrow confidence intervals (MD = -1.8000 (95% CI, -3.4705 to -0.1295). The body of evidence was not downgraded for imprecision.
[j] The sample size inadequate i.e. less than 300 per arm, but effect estimate is precise with narrow confidence intervals (MD = -2.4000 (95% CI, -3.7543 to -1.0457). The body of evidence was not downgraded for imprecision.

Table 21. Harms of treatment for prostate cancer – cryotherapy QoL SF-36 outcomes

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cryotherapy	control	MD at post-intervention		
QoL_Physical function (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 2.0 higher	⊕OOO VERY LOW	CRITICAL
QoL_Physical role function (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 4 higher	⊕OOO VERY LOW	CRITICAL
QoL_Bodily pain (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 0 higher	⊕OOO VERY LOW	CRITICAL
QoL_General health (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 1.0 higher	⊕OOO VERY LOW	CRITICAL
QoL_Vitality (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 0 higher	⊕OOO VERY LOW	CRITICAL
QoL_Social function (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 3.0 higher	⊕OOO VERY LOW	CRITICAL
QoL_Emotional role function (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 6.0 higher	⊕OOO VERY LOW	CRITICAL
QoL_Mental Health (follow-up 6 years) (measured with: SF-36; Better indicated by higher values)											
1[a]	Observational studies	No serious RoB[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious[e]	None[f]	28	120	MD 4.0 higher	⊕OOO VERY LOW	CRITICAL

[a]Smith, DS [55]
[b]We assessed this study with the Newcastle-Ottawa scale. It scored a 7/9.
[c]A single study provided evidence for this outcome, therefore we cannot assess inconsistency.
[d] The sample is men in the United States who had screen detected prostate cancer. The length of follow-up for this outcome is up to 6 years. These factors are consistent for the context/outcome of interest for the key questions of this review.
[e] The sample size is not adequate (<300) and the precision of effect estimate could not be assessed due to no confidence intervals provided and only one study for the outcome.
[f] There was an insufficient number of studies to assess publication bias.

Table 22. Harms of treatment for prostate cancer – HIFU

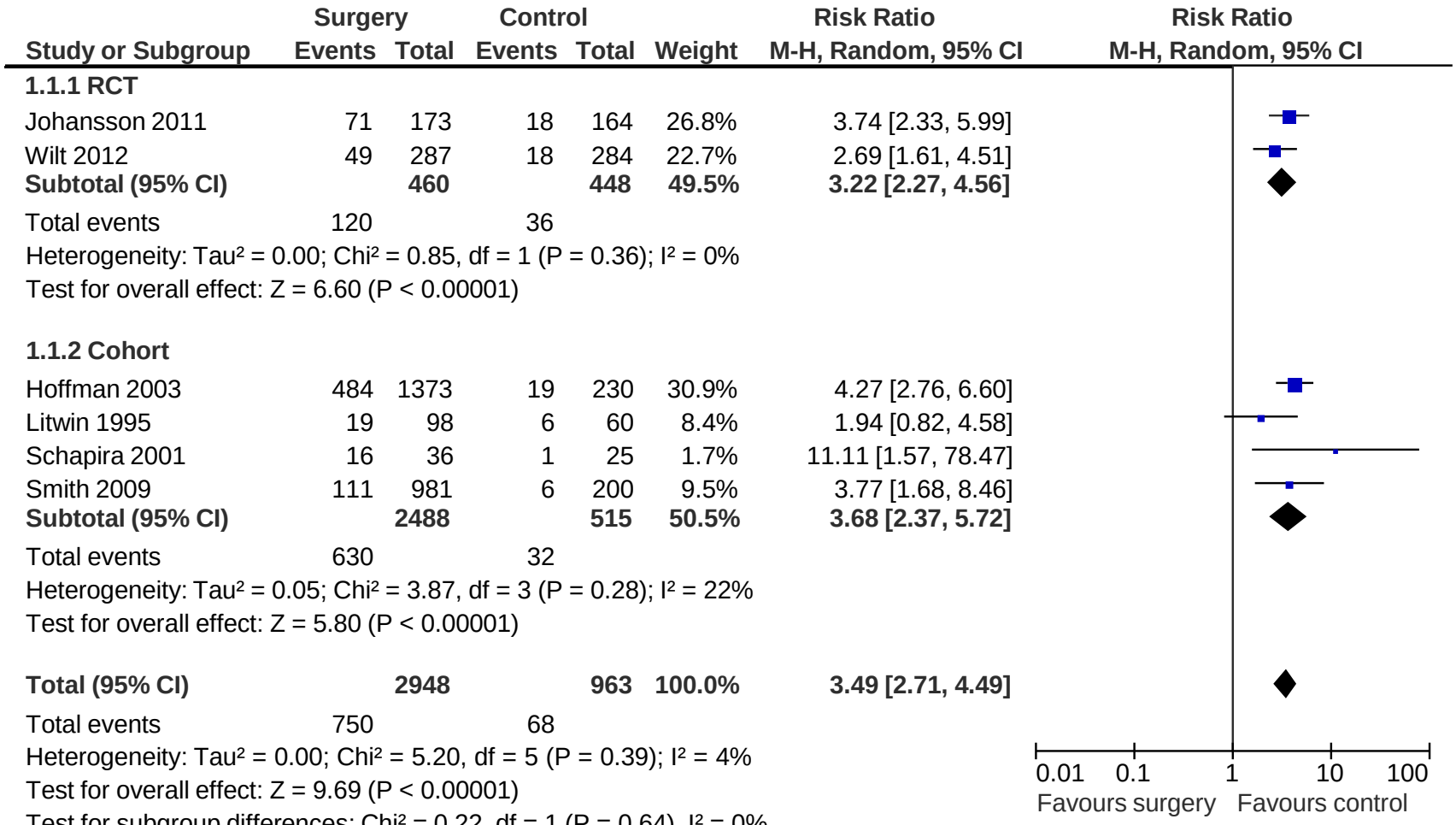
Quality Assessment							Results Proportion % (CI 95%)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Post-surgical (HIFU) outcomes, Any Urinary Incontinence									
3[a]	Observational	Serious[b]	Serious[c]	No serious[d]	Serious[e]	None[f]	13/163 8% (4.5-13.5)[59] 59/402 14.7% (11.4-18.6)[60] 1/63 1.5% (0.1-9.7)[61]	⊕OOO VERY LOW	Critical
Post-surgical Outcomes (HIFU), Erectile Dysfunction									
2[g]	Observational	Serious[b]	Serious[c]	No serious[d]	Serious[e]	None[f]	34/76 44.7% (33.5-56.5)[59] 8/34 23.5% (11.4-41.6)[61]	⊕OOO VERY LOW	Critical

[a] Blana[59]; Thuroff[60]; Uchida[61]
[b] Uncontrolled observational study
[c] The confidence intervals did minimally overlap.
[d] Across the body of evidence for this outcome, the population (men, ages 45-87), intervention, location (Europe, Japan), and outcome (surgical harms) are similar to the context/criteria specified by the key questions for this review
[e] The confidence intervals were wide and the sample was not sufficient for optimal information size.
[f] There are an insufficient number of studies to assess publication bias
[g] Blana[59]; Uchida[61]

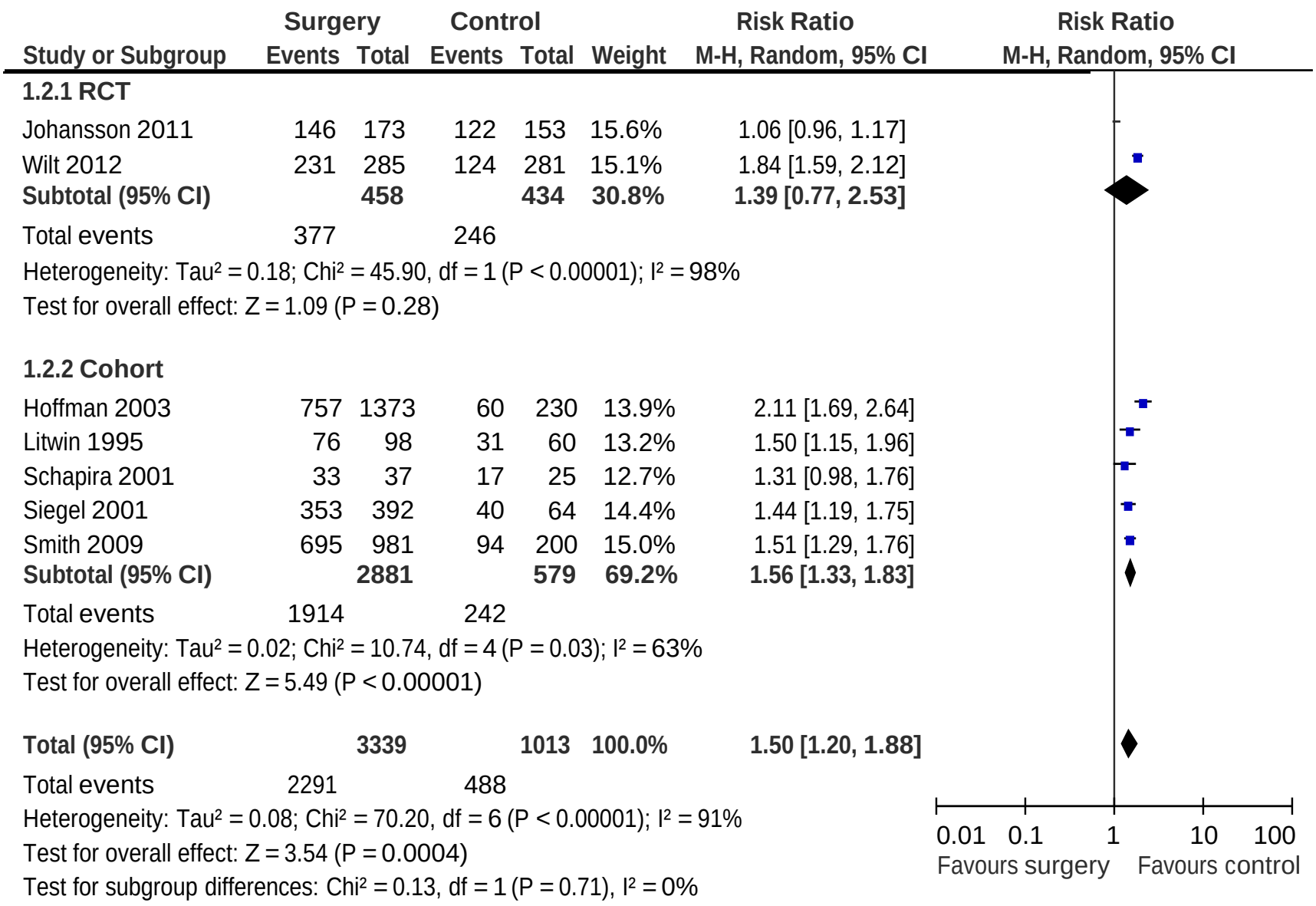
Figure 3. Forest plots of harms of treatment

Forest plots: prostatectomy vs control

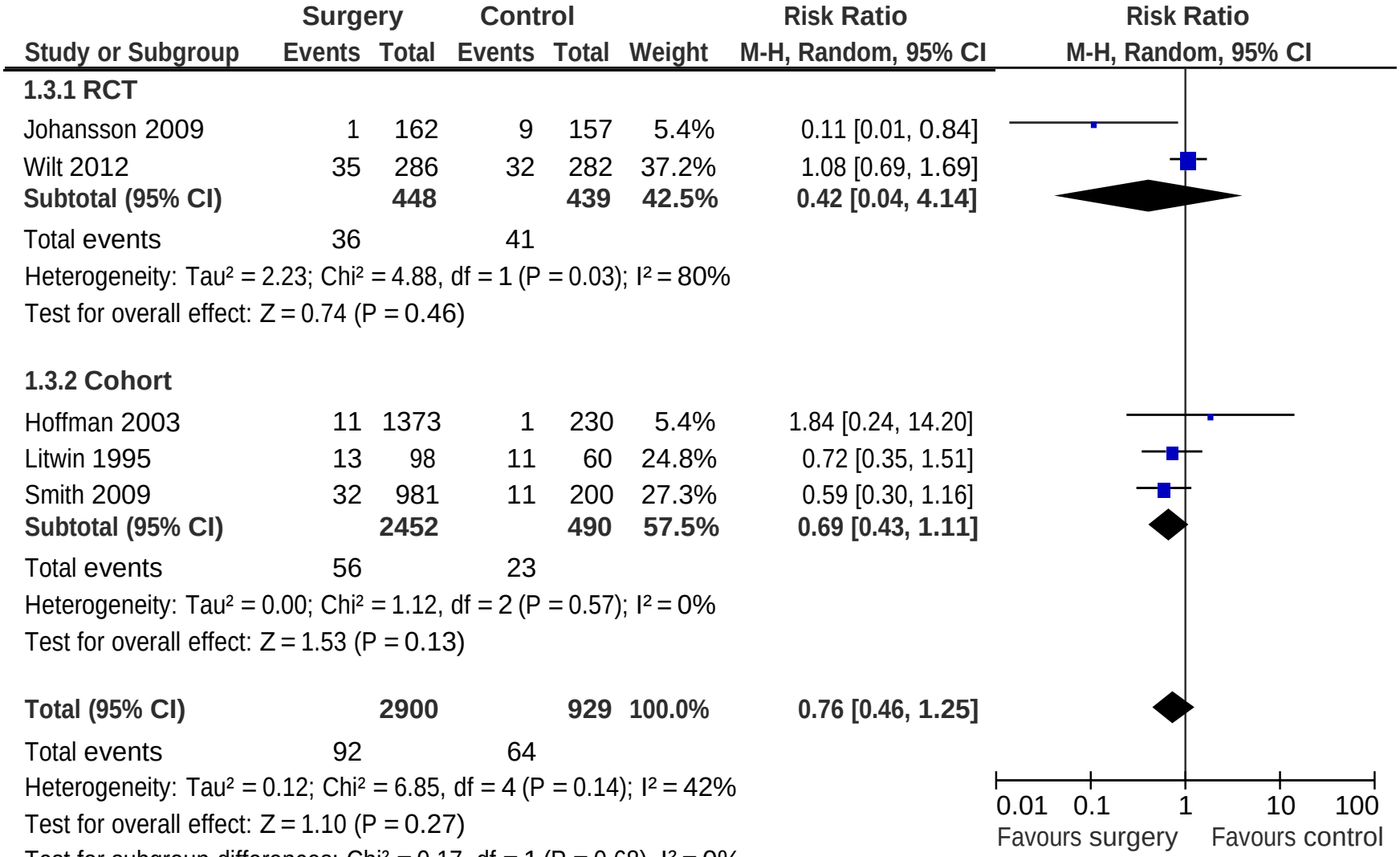
Urinary incontinence



Erectile dysfunction

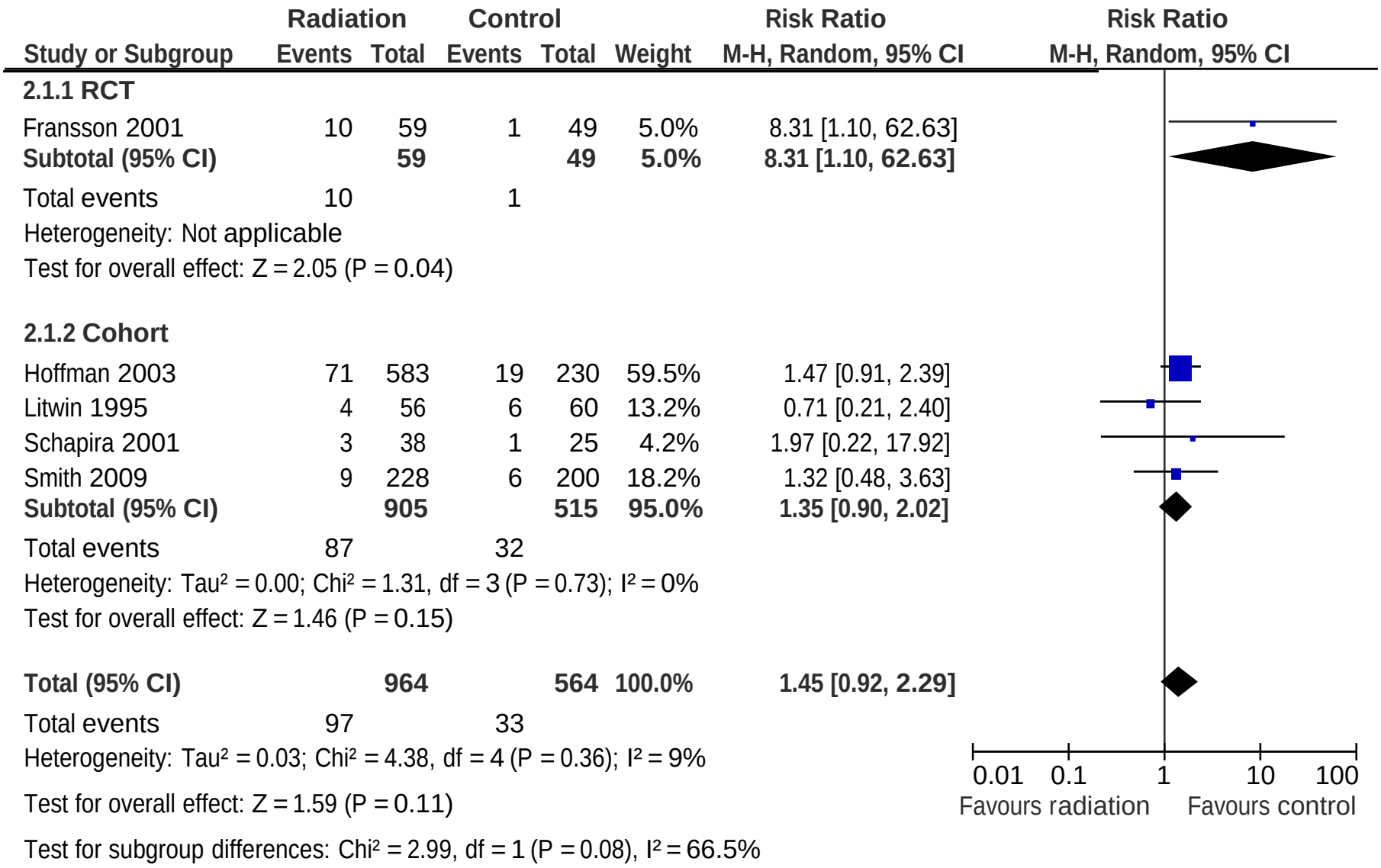


Bowel dysfunction



Forest plots: radiation therapy vs control

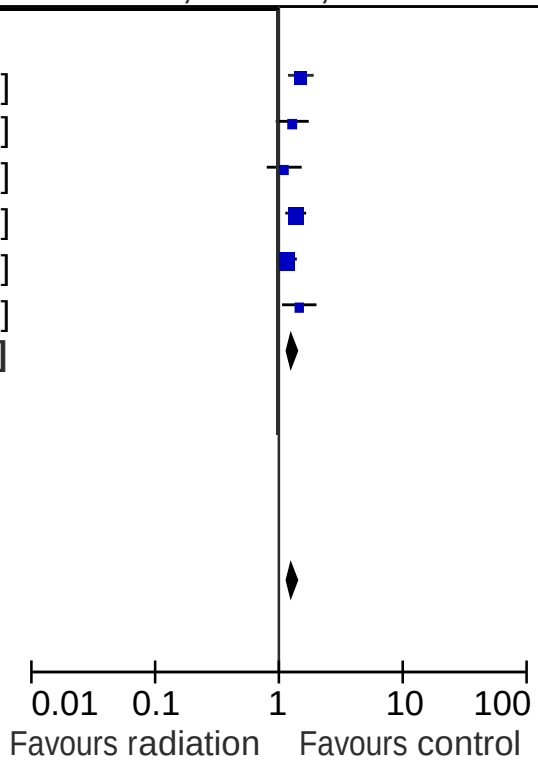
Urinary incontinence



Erectile dysfunction

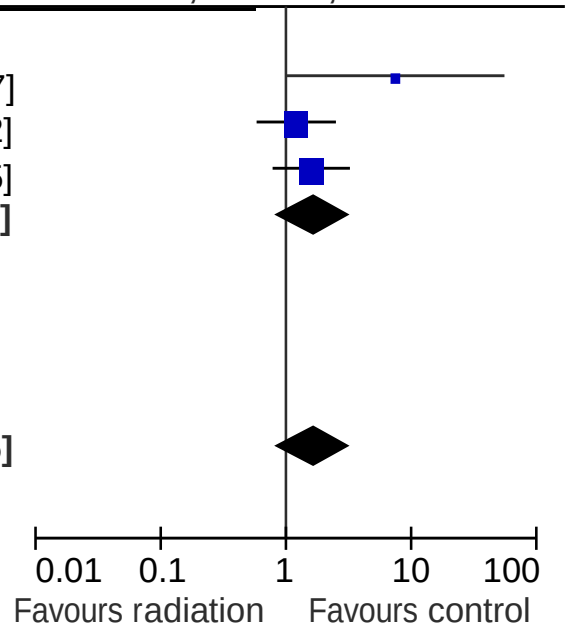
Study or Subgroup	Radiation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.2 Cohort						
Hoffman 2003	228	583	60	230	17.1%	1.50 [1.18, 1.91]
Litwin 1995	39	59	31	60	10.6%	1.28 [0.94, 1.74]
Schapira 2001	30	40	17	25	9.4%	1.10 [0.80, 1.52]
Siegel 2001	269	315	40	64	25.9%	1.37 [1.12, 1.66]
Smith 2009	123	228	94	200	27.3%	1.15 [0.95, 1.39]
Thong 2009	43	63	28	60	9.7%	1.46 [1.06, 2.01]
Subtotal (95% CI)		**1288**		**639**	**100.0%**	**1.30 [1.17, 1.43]**
Total events	732		270			
Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 5 (P = 0.43); I² = 0%						
Test for overall effect: Z = 5.13 (P < 0.00001)						
Total (95% CI)		**1288**		**639**	**100.0%**	**1.30 [1.17, 1.43]**
Total events	732		270			
Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 5 (P = 0.43); I² = 0%						
Test for overall effect: Z = 5.13 (P < 0.00001)						

Test for subgroup differences: Not applicable



Bowel dysfunction

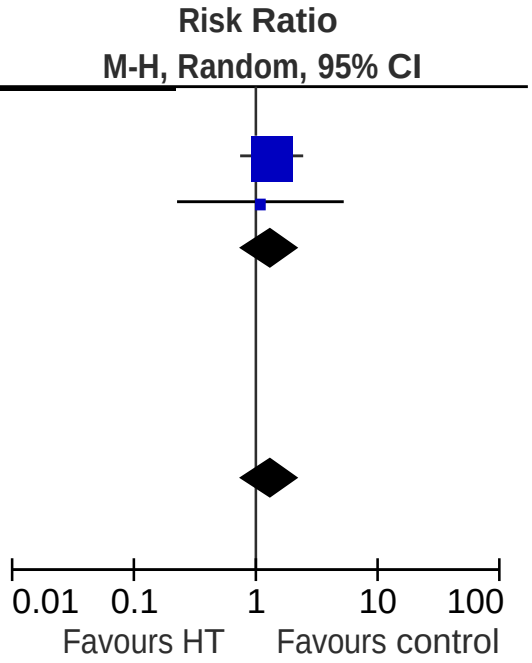
Study or Subgroup	Radiation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Cohort						
Hoffman 2003	19	583	1	230	10.1%	7.50 [1.01, 55.67]
Litwin 1995	12	54	11	60	44.3%	1.21 [0.58, 2.52]
Smith 2009	20	228	11	200	45.6%	1.59 [0.78, 3.25]
Subtotal (95% CI)		**865**		**490**	**100.0%**	**1.65 [0.84, 3.25]**
Total events	51		23			
Heterogeneity: Tau² = 0.13; Chi² = 3.14, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**865**		**490**	**100.0%**	**1.65 [0.84, 3.25]**
Total events	51		23			
Heterogeneity: Tau² = 0.13; Chi² = 3.14, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Not applicable						



Forest plots: hormonal therapy vs control

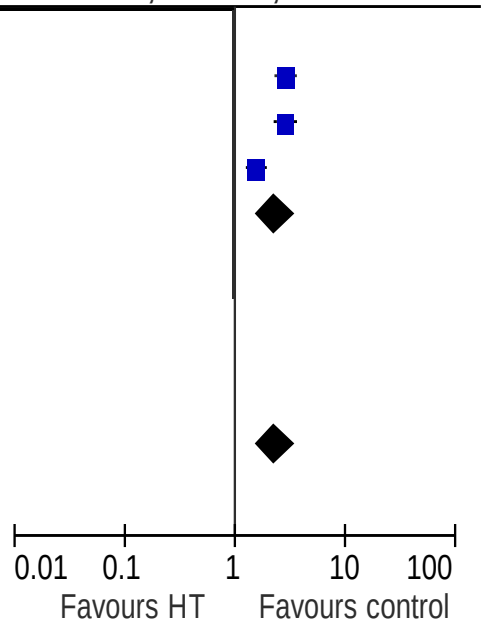
Urinary incontinence

Study or Subgroup	ADT Events	ADT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Cohort						
Hoffman 2003	20	179	19	230	87.4%	1.35 [0.74, 2.46]
Smith 2009	2	61	6	200	12.6%	1.09 [0.23, 5.28]
Subtotal (95% CI)		**240**		**430**	**100.0%**	**1.32 [0.75, 2.30]**
Total events	22		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**240**		**430**	**100.0%**	**1.32 [0.75, 2.30]**
Total events	22		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						



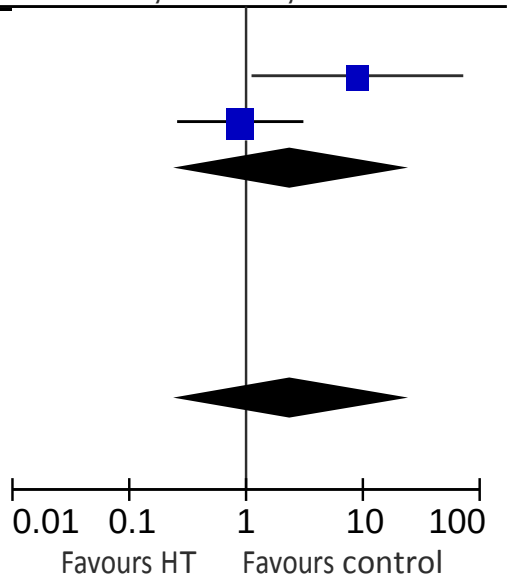
Erectile dysfunction

Study or Subgroup	ADT Events	ADT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Cohort						
Hoffman 2003	135	179	60	230	33.2%	2.89 [2.29, 3.65]
Potosky 2002	68	88	60	223	32.9%	2.87 [2.25, 3.67]
Smith 2009	45	61	94	200	33.9%	1.57 [1.27, 1.94]
Subtotal (95% CI)		**328**		**653**	**100.0%**	**2.35 [1.53, 3.59]**
Total events	248		214			
Heterogeneity: Tau² = 0.13; Chi² = 20.73, df = 2 (P < 0.0001); I² = 90%						
Test for overall effect: Z = 3.93 (P < 0.0001)						
Total (95% CI)		**328**		**653**	**100.0%**	**2.35 [1.53, 3.59]**
Total events	248		214			
Heterogeneity: Tau² = 0.13; Chi² = 20.73, df = 2 (P < 0.0001); I² = 90%						
Test for overall effect: Z = 3.93 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Bowel dysfunction

Study or Subgroup	ADT Events	ADT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Cohort						
Hoffman 2003	7	179	1	230	43.5%	8.99 [1.12, 72.44]
Smith 2009	3	61	11	200	56.5%	0.89 [0.26, 3.10]
Subtotal (95% CI)		**240**		**430**	**100.0%**	**2.44 [0.24, 24.40]**
Total events	10		12			
Heterogeneity: Tau² = 2.04; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**240**		**430**	**100.0%**	**2.44 [0.24, 24.40]**
Total events	10		12			
Heterogeneity: Tau² = 2.04; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						



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APPENDICES

Appendix 1 Search strategy

Medline-OVID

Last Updated November 25 2013

1. Prostate-Specific Antigen/
2. (prostate-specific antigen or prostate specific antigen or gamma seminoprotein or gamma-seminoprotein or kallikrein hk3 or semenogelase or psa).tw.
3. 1 or 2
4. Mass Screening/
5. (screen* or test*).tw.
6. 4 or 5
7. Prostatic Neoplasms/
8. (prostat* adj (neoplasm* or cancer* or tumour* or tumor*)).tw.
9. 7 or 8
10. 3 and 6 and 9
11. ((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
12. (safe* or side effect*).tw.
13. (ae or to or co or mo or de).fs.
14. (toxicity or complication* or noxious or tolerability).tw.
15. (overdiagnosis or over diagnosis or over-diagnosis or over detection or overdetection or over-detection or overtreatment or over treatment or over-treatment).tw.
16. Diagnostic Errors/
17. (false negative or false positive).tw.
18. or/11-17
19. 10 and 18
20. limit 19 to (english or french)
21. limit 20 to yr="2003 - 2013"
22. limit 21 to (case reports or comment or editorial or letter or newspaper article)
23. 21 not 22
24. Prostatic Neoplasms/
25. (prostat* adj (neoplasm* or cancer* or tumour* or tumor*)).tw.
26. 24 or 25
27. biops*.tw.
28. exp biopsy/
29. 27 or 28
30. (safe* or side effect*).tw.
31. ((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
32. (ae or co or mo).fs.
33. (false negative or false positive).tw.
34. Diagnostic Errors/
35. or/30-34
36. 26 and 29 and 35
37. limit 36 to (english or french)
38. limit 37 to yr="2003 - 2013"

39. limit 38 to (case reports or comment or editorial or letter or newspaper article)
40. 38 not 39
41. 23 or 40
42. (ae or co or de or mo).fs.
43. (adverse and (effect* or event*)).mp.
44. (safe* or harm* or side effect*).mp.
45. or/42-44
46. Quality of Life/
47. Anxiety/
48. Depression/
49. px.fs.
50. or/46-49
51. (overdiagnosis or over diagnosis or over detection or overdetection).tw.
52. False Positive Reactions/
53. false positive.tw.
54. Prostate-Specific Antigen test*.ti.
55. *Prostate-Specific Antigen/
56. *Prostatic Neoplasms/di [Diagnosis]
57. (psa or prostate specific antigen).tw.
58. 56 and 57
59. 45 or 50 or 51 or 52 or 53
60. 54 or 55 or 58
61. 59 and 60
62. clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
63. random*.ti,ab.
64. ((singl* or doubl* or treb* or tripl*) adj3 (blind* or mask*)).tw.
65. 62 or 63 or 64
66. 60 and 65
67. limit 66 to (english or french)
68. limit 67 to ed=20120712-20131121
69. 41 or 68

Cochrane Central-OVID

Last Updated: November 25 2013
1. Prostate-Specific Antigen/
2. (prostate-specific antigen or prostate specific antigen or gamma seminoprotein or gamma-seminoprotein or kallikrein hk3 or semenogelase or psa).tw.
3. 1 or 2
4. Mass Screening/
5. (screen* or test*).tw.
6. 4 or 5
7. Prostatic Neoplasms/
8. (prostat* adj (neoplasm* or cancer* or tumour* or tumor*)).tw.

9. 7 or 8
10. 3 and 6 and 9
11. ((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
12. (safe* or side effect*).tw.
13. (ae or to or co or mo or de).fs.
14. (toxicity or complication* or noxious or tolerability).tw.
15. (overdiagnosis or over diagnosis or over-diagnosis or over detection or overdetection or over-detection or overtreatment or over treatment or over-treatment).tw.
16. Diagnostic Errors/
17. (false negative or false positive).tw.
18. or/11-17
19. 10 and 18
20. limit 19 to yr="2003 - 2013"
21. Prostatic Neoplasms/
22. (prostat* adj (neoplasm* or cancer* or tumour* or tumor*)).tw.
23. 21 or 22
24. biops*.tw.
25. exp biopsy/
26. 24 or 25
27. (safe* or side effect*).tw.
28. ((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
29. (ae or co or mo).fs.
30. (false negative or false positive).tw.
31. Diagnostic Errors/
32. or/27-31
33. 23 and 26 and 32
34. limit 33 to yr="2003 - 2013"
35. 20 or 34
36. (ae or co or de or mo).fs.
37. (adverse and (effect* or event*)).mp.
38. (safe* or harm* or side effect*).mp.
39. 36 or 37 or 38
40. Quality of Life/
41. Anxiety/
42. Depression/
43. px.fs.
44. 40 or 41 or 42 or 43
45. (overdiagnosis or over diagnosis or over detection or overdetection).tw.
46. False Positive Reactions/
47. false positive.tw.
48. Prostate-Specific Antigen test*.ti.
49. *Prostate-Specific Antigen/
50. *Prostatic Neoplasms/di [Diagnosis]
51. (psa or prostate specific antigen).tw.

52. 50 and 51
53. 39 or 44 or 45 or 46 or 47
54. 48 or 49 or 52
55. 53 and 54
56. limit 55 to yr="2012 - 2013"
57. 35 or 56

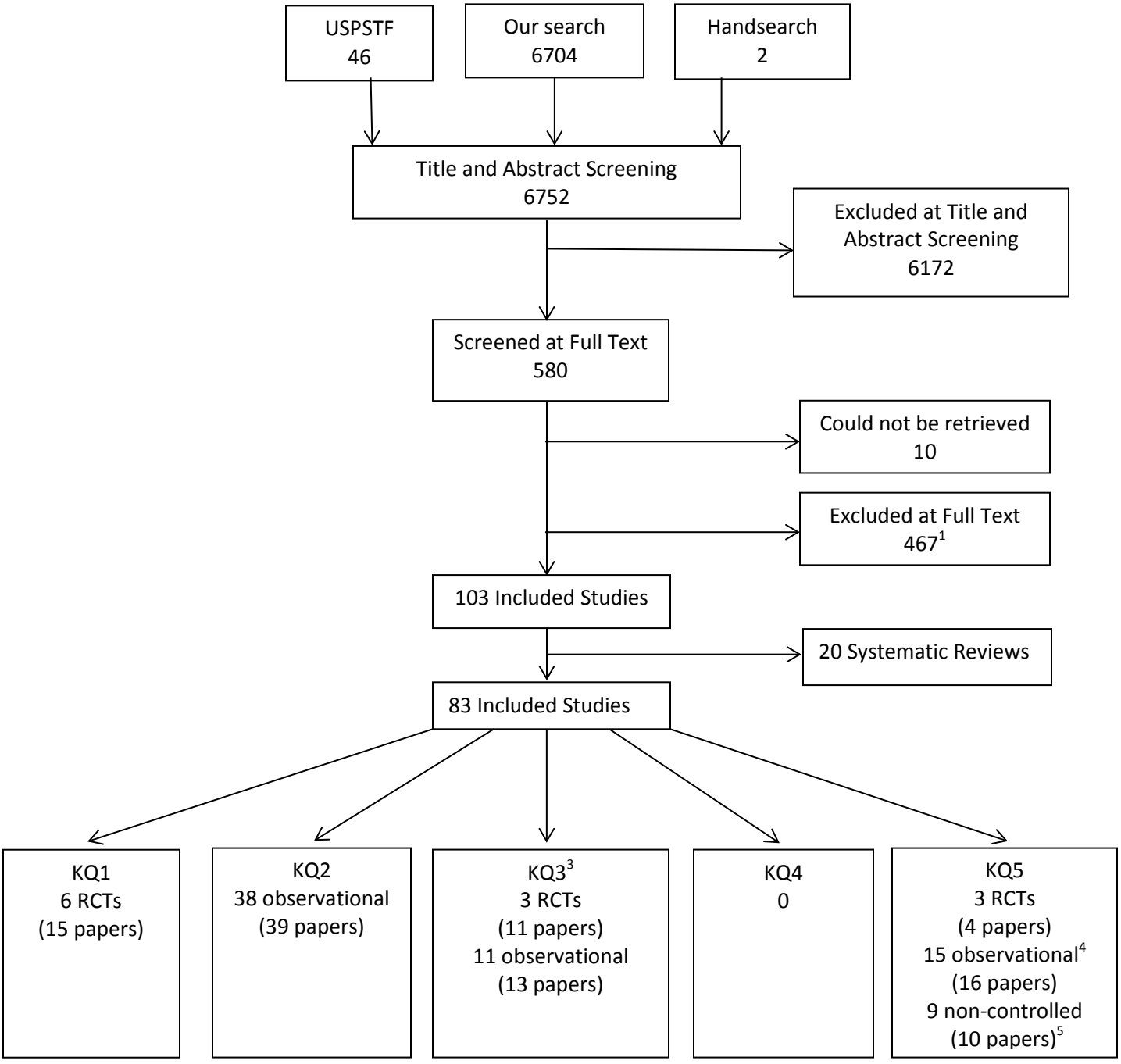
EMBASE-OVID

Last Updated: November 25 2013
1. Prostate-Specific Antigen test*.ti.
2. *Prostate-Specific Antigen/
3. *Prostatic Neoplasms/di
4. cancer screening/
5. (psa or prostate specific antigen test*).tw.
6. 3 or 4 or 5
7. 2 and 6
8. 1 or 7
9. 4 and 5
10. 8 or 9
11. (safe* or harm* or side effect*).mp.
12. false positive.tw.
13. false positive result/ or diagnostic error/
14. (overdiagnosis or over diagnosis or over detection or overdetection or overtreatment or over-treatment).tw.
15. 11 or 12 or 13 or 14
16. 10 and 15
17. limit 10 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
18. random*.ti,ab.
19. ((singl* or doubl* or treb* or tripl*) adj3 (blind* or mask*)).tw.
20. 18 or 19
21. 10 and 20
22. 17 or 21
23. limit 22 to em=201225-201347
24. limit 16 to yr="2003 -Current"
25. 23 or 24
26. prostate biopsy/
27. 15 and 26
28. limit 27 to yr="2003 -Current"
29. 25 or 28
30. limit 29 to (english or french)

Treatment Searches (Update of USPSTF using same strategy)

Medline and Cochrane Central
November 19, 2012
1. Prostatic Neoplasms/dh, dt, rt, su, th, us
2. prostate cancer.mp. or Prostatic Neoplasms/
3. Treatment Outcome/
4. 2 and 3
5. 1 or 4
6. (ae or co or de or mo).fs.
7. (adverse and (effect$ or event$)).mp.
8. (safe$ or harm$ or side effect$).mp.
9. or/6-8
10. Quality of Life/
11. Anxiety/
12. Depression/
13. px.fs.
14. or/10-13
15. 5 and (9 or 14)
16. limit 15 to ed=20110701-20121119
17. 16 not (case reports or comment or editorial or letter).pt.
18. limit 17 to (english or french)

Appendix 2 Flow diagram of included studies



[1]Three USPSTF studies were excluded: 2 studies did not report tumour stage and one study reported up to 47% of their population having tumors in stages 3 and 4
[2]Data was not extracted from 1 of these papers
[3]Wilt et al. and Schymura et al. were common to KQ3 and KQ5
[4]Data was not extracted from 2 of these papers
[5]Data was not extracted from 3 of these papers

Appendix 3 Study characteristics of RCTs of benefits of screening for prostate cancer

First author **Country**	Andriole[17] United States (PLCO)
Name of study	Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up
Objective	To provide updated analysis of primary and secondary outcomes of the PLCO trial, prostate component, through 13 years of follow-up.
Methods	**Design:** randomized controlled trial. **Selection:** recruitment occurred at 10 screening centres in the U.S., between 1993 and 2001. Block randomization with stratification by centre and age.
Participants	**Sample:** 76,685 men (intervention n=38,340, control n=38,345). **Characteristics:** aged 55-74 years that met the following: no history of prostate, lung or colorectal cancer; not undergoing treatment for cancer except non-melanoma skin cancer; no previous removal of entire prostate, one lung or entire colon; no participation in another cancer screening or prevention study; no use of finasteride in past 6 months; and (from 1995) no history of 1+ PSA test in previous 3 years). **Follow-up:** median follow-up = 11.5 years; maximum follow-up = 14.8 years.
Intervention	**Type of test:** prostate-specific antigen (PSA), annually for 6 years and digital rectal examination (DRE), annually for 4 years. **PSA cut-off for positive prostate cancer:** 4.0 ng/mL
Outcomes	**Reported by study authors:** primary outcome was prostate-specific mortality (92% at 10 yr; 57% at 13 yr). Secondary outcome was prostate cancer-specific incidence rate. Additional outcomes reported included: Gleason score, all-cause mortality (excluding death from lung and colorectal cancers), Charlson score, pretrial PSA testing and clinical stage. There was no difference in the prostate-specific mortality rate in the intervention arm compared to the control arm (RR=1.09, 95% CI=0.87 to 1.36).
	Reported in this review:
Comments	Contamination (control subject who had PSA test within the past year) ranged from 40% in the 1st year to 52% in the 6th year.
First author	Hugosson[12]

Country	Sweden (Göteborg; ERSPC sub-study)
Name of study	Mortality Results from the Göteborg Randomised Population-Based Prostate-Cancer Screening Trial
Objective	To describe the effect of screening for prostate cancer using PSA test on the prostate-cancer mortality.
Methods	**Design:** randomized controlled trial. **Selection:** men from the Swedish population register randomized 1:1 via computer randomization to intervention or control before informed consent, prospectively from 1995.
Participants	**Sample:** 20,000 (of n_t=32,298) randomized (intervention n=7,578, 75.8% response rate; control=9952). **Characteristics:** aged 50-64 years. Men were excluded if they had a previous prostate cancer diagnosis. **Follow-up:** 78% of participants reached the maximum follow-up time of 14 years.
Intervention	**Type of test:** PSA every 2 years. **PSA cut-off for further investigation:** 3.4 ng/mL (1995-1998); 2.9 ng/mL (1999-2004); 2.5 ng/mL (2005-present).
Outcomes	**Reported by study authors:** primary outcomes were absolute and relative-risk reduction in cumulative prostate-cancer mortality. Secondary outcomes included: prostate-cancer incidence and proportion of screening attendees. Additional measures included: number needed to screen, number needed to treat, tumour grouping (advanced disease, high, moderate, low risk), treatment received. There was a significantly reduced risk of death from prostate cancer in the intervention group, compared to the control group (RR=0.56, 95% CI 0.39 to 0.82).
	Reported in this review:
Comments	PSA cut-offs reported were calibrated to the WHO 96/670 calibrator. Non-calibrated cut-offs were: 3.0 ng/mL (1995-1998) and 2.5 ng/mL (1999-2004).
First author **Country**	Kjellman[18] Sweden (Stockholm)
Name of study	15-Year Follow-up of a Population Based Prostate Cancer Screening Study
Objective	To compare survival between attendees and non-attendees of a one-time prostate cancer screening intervention.
Methods	**Design:** randomized controlled trial.

	Selection: in 1988 men from the Swedish census with current addresses within the catchment area of Stockholm South Hospital. A subset (n=2,374) was randomly selected for screening intervention, of which n=1,769 were screened.
Participants	**Sample:** 27,146 (intervention n=2,374; control n=24,772). **Characteristics:** aged 55-70 years. Men were excluded if they had a previous prostate cancer diagnosis. **Follow-up:** median follow-up = 12.9 years; maximum = 15.7.
Intervention	**Type of test:** one-time PSA, DRE and transrectal ultrasound. **PSA cut-off for further investigation:** 7.0 ng/mL = repeat transrectal ultrasound; 10 ng/mL = randomized quadrant biopsies.
Outcomes	**Reported by the study authors:** prostate cancer mortality, all-cause mortality, survival. There was no difference in incidence of death due to prostate cancer in the intervention group compared to the source population (IRR=1.04, 95% CI 0.76 to 1.45).
	Reported in this review:
Comments	
First author **Country**	Labrie[19] Canada
Name of study	Screening Decreases Prostate Cancer Mortality: 11-Year Follow-Up of the 1988 Quebec Prospective Randomized Controlled Trial
Objective	To determine the effect of prostate cancer screening on prostate cancer mortality.
Methods	**Design:** randomized controlled trial. **Selection:** 46,486 men were randomized 2:1 to intervention and control arms, stratified by age and residential area from November 1988 (participation rate of 23.6% among men invited for screening). Men with previous prostate cancer diagnosis and/or previous screening were excluded.
Participants	**Sample:** 46,486 (intervention n=31,133; control n=15,353). **Characteristics:** aged 45-80 years. **Follow-up:** median follow-up = 7.9 years; maximum = 11 years.
Intervention	**Type of test:** PSA and DRE. **PSA cut-off for further examination: >**3.0 ng/mL (or increase of >20% from measurement 1 year earlier, if PSA was above 3.0 at a previous visit or increase of

	>20% if predicted PSA was calculated at previous visit).
Outcomes	**Reported by the study authors:** primary outcome was prostate-cancer mortality. Secondary outcomes included: survival, clinical stage, and treatment. There was no difference in risk of death from prostate cancer among men invited for screening compared to uninvited men (RR=1.08, 95% CI 0.82-1.43).
	Reported in this review:
Comments	Level of contamination on control group could not be assessed (above the n=1,122 men that had documentation of screening during the study period).
First author **Country**	Sandblom[20] Sweden (Norrköping)
Name of study	Randomised Prostate Cancer Screening Trial: 20 Year Follow-up
Objective	To assess whether screening for prostate cancer reduces prostate cancer mortality.
Methods	**Design:** randomized controlled trial. **Selection:** in 1987, all men aged 50-69 years identified in Norrköping, Sweden's population registry were randomized 1:6 to the intervention and control arms, via list of dates of birth. Men with previous prostate cancer diagnosis were excluded.
Participants	**Sample:** 9,026 (intervention n=1,494; control n=7,532). **Characteristics:** aged 50-69 years. **Follow-up:** median follow-up time = 6.3 years. Study duration = 20 years.
Intervention	**Type of test:** DRE-only (1987 and 1990); DRE and PSA (1993 and 1996). **PSA cut-off:** >4.0 ng/mL
Outcomes	**Reported by study authors:** prostate cancer mortality, all-cause mortality, survival, tumour stage, grade, treatment. There was no difference in risk of death from prostate cancer between the intervention and control groups (Risk ratio=1.16, 95% CI 0.78-1.73).
	Reported in this review:
Comments	Level of contamination in control group not assessed. Analysis includes men diagnosed with prostate cancer up to 31 December 2008.
First author **Country**	Schroder[11] Europe (ERSPC)

Name of study	Prostate-Cancer Mortality at 11 Years of Follow-up
Objective	To report mortality results from the multi-centre, European, prostate cancer screening trial after 11 years of follow-up.
Methods	**Design:** randomized controlled, multi-centre (n=8), trial. Mortality results from France were not presented in the current study as that country joined later and participants have short follow-up time (median 4.6 years). **Selection:** varied by centre. Finland/Sweden/Italy: selection through population registry with randomization via random number generators before informed consent. The Netherlands/Belgium/Switzerland/Spain: selection through population registry with randomization via random number generators after informed consent. Randomization occurred in a 1:1 ratio in all countries except Finland, where subjects were randomized 1:1.5 to the intervention, because the entire birth cohort underwent randomization to populate a fixed-size intervention group. Men with previously diagnosed prostate cancer were excluded.
Participants	**Sample:** total: 182,000 (intervention n=82,816; control n=99,184). Core age group: 162,243 (intervention n=72,891; control n=89,352). **Characteristics:** ages 50-74 years, with men aged 55-69 years forming the predefined "core age group" (*i.e.* this age group was consistent across all study centres). **Follow-up:** median follow-up = 11 years.
Intervention	**Type of test:** PSA every 4 years (every 2 years in Sweden). **PSA cut-off for positive test result:** varied by centre, but was 3.0 ng/mL unless otherwise noted below. Finland: 4.0 ng/mL, with results of 3.0-3.9 leading to DRE (to 1998) and free PSA/total PSA (1999 onwards). Italy: 4.0 ng/mL, with results of 2.5-3.9 leading to DRE and TRUS. The Netherlands: DRE, TRUS and PSA (4.0 ng/mL) until February 1997. PSA-only from 1997 onwards. Belgium: DRE, TRUS and PSA until February 1997. PSA-only from 1997 onwards. Initial cut-off for PSA was 10 ng/mL (pilot study from 1991-1994). Interval between 1st and 2nd screen was 7 years due to interruption in funding.
Outcomes	**Reported by the study authors:** primary outcome was prostate cancer mortality. Secondary outcomes included: all-cause mortality, number needed to invite to prevent one death from prostate cancer, number of prostate cancers needed to be detected to prevent one death, prostate cancer incidence, Gleason scores,

	tumour stage and treatment type. There was a significantly reduced risk of death due to prostate cancer among men in the intervention arm, compared to the control arm (RR=0.79, 95% CI 0.68-0.91).
	Reported in this review:
Comments	160 men died before randomization (145 from core age group).

Appendix 4 Risk of Bias of studies assessing benefits of PSA-based screening for prostate cancer

Appendix 5 Risk of Bias (ROB) details of included studies

Bias	Authors' judgement	Support for judgement
PLCO (Andriole)		
Random sequence generation (selection bias)	Low risk	Individual randomization was performed within blocks stratified according to center, age, and sex.
Allocation concealment (selection bias)	Low risk	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 of participants and personnel (performance bias)	Low risk	No mention of blinding but blinding of participants would not be possible due to nature of intervention but unlikely to have an effect on outcome
Blinding of outcome assessment (detection bias)	Low risk	The trial used a special end-point adjudication process to assign the cause of death in a uniform and unbiased manner. Reviewers of these deaths were unaware of study-group assignments for deceased subjects.
Incomplete outcome data (attrition bias)	Low risk	Used intent-to-screen analysis to account for missing data.
Selective reporting (reporting bias)	Low risk	The outcomes of interest appear both in methods and results section.
Other bias	High risk	The authors reported 52% PSA contamination (extent of opportunistic PSA screening) in control group. The authors also report that Approximately 57% of the study participants were followed to 13 years. 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.
Göteborg (Hugosson)		
Random sequence generation (selection bias)	Low risk	By computer randomization (ratio 1:1) 20,000 of these men were identified and allocated to either the intervention arm (screening group) or to a control group.
Allocation concealment (selection bias)	Low risk	The randomization procedure was done at the Department of Statistics at the University of Göteborg. 10-digit personal identifiers were the only available personal data for those doing the computer randomization.
Blinding of participants and personnel (performance bias)	Low risk	No mention of blinding, but blinding of participants would not be possible due to nature of intervention but unlikely to have an effect on outcome.
Blinding of outcome assessment (detection bias)	Low risk	Masking of the group assignment was done for the cause of death committee. The committee did a blinded review of all cases diagnosed with prostate cancer, including all medical records, pathology reports, and autopsy protocols, according to a standard algorithm used in the ERSPC.
Incomplete outcome data (attrition bias)	Low risk	The study used intent-to-screen analysis to account for missing data.
Selective reporting (reporting bias)	Low risk	The primary outcome of interest of the study was Prostate-specific mortality and it appears both in methods and results section of the paper.

Other bias	Low risk	A pre-study power calculation (two-sided test; p<0·05 and 80% power) was done with the assumption of a 70% participation rate. A 40% mortality difference between the study arms was calculated to become significant 15 years after the study began. Authors also mention a very low PSA contamination rate in the control group and a very low rate (3%) of PSA testing before the start of the study. The follow-up for this particular study is much longer than other ERSPC centers i.e. 14 years vs. 11 years. One limitation recognized by authors is that the PSA threshold for biopsy was lower than other ERSPC branches (2.5 ng/ml vs. 3.0 ng/ml) and DRE was never used as a screening tool in this study.
Stockholm (Kjellman)		
Random sequence generation (selection bias)	Unclear risk	No description of method used for randomization
Allocation concealment (selection bias)	Unclear risk	No description of method used for randomization
Blinding of participants and personnel (performance bias)	Low risk	No mention of blinding, but blinding of patients would not be possible due to nature of intervention but unlikely to have an effect on outcome.
Blinding of outcome assessment (detection bias)	Low risk	From the Cause of Death register the authors collected the information on date of death and the underlying cause of death. In an earlier study 3 senior urologists independently reviewed the medical records and assigned the cause of death
Incomplete outcome data (attrition bias)	Low risk	The authors used intent-to-treat principle to handle missing data.
Selective reporting (reporting bias)	High risk	In the method section, the author report on evaluating prostate-specific mortality and all-cause mortality, but in results section they report IRR on prostate-specific mortality and other-cause (excluding prostate cancer) mortality.
Other bias	High risk	The study has both internal and external validity concerns. Firstly, out of 26,602 participants, only 2374 were invited for screening (of whom 1,767 actually had screening). 2nd, PSA level testing was not used as the primary method for screening instead combined DRE, TRUS and PSA was performed as single intervention and a very high threshold of PSA > 10 ng/ml was used to permit biopsy. Third, authors mentioned that the original data for 24,772 participants could not be retrieved due to change of record holders and a reconstruction of cohort with help of Statistics Sweden was performed. Finally, the authors mentioned no method of assessing rate of contamination in control group = 24,202 (91%) of total participants in study.
Quebec (Labrie)		
Random sequence generation (selection bias)	Unclear risk	No description on method used for randomization. The age and residential area were used for stratification to balance possible differences in socio-demographic factors between groups.
Allocation concealment (selection bias)	Unclear risk	No description on allocation concealment

Blinding of participants and personnel (performance bias)	Low risk	No mention of blinding but blinding of patients would not be possible due to nature of intervention but unlikely to have an effect on outcome
Blinding of outcome assessment (detection bias)	Unclear risk	The information on cause-specific death was obtained from the Death Registry of the Health Department of the Province of Quebec.
Incomplete outcome data (attrition bias)	High risk	The study did not primarily used intent-to-treat principle to account for missing data.
Selective reporting (reporting bias)	Low risk	The outcome of interest (prostate-specific mortality) appears in both methods and results section of the paper.
Other bias	High risk	No baseline socio-demographic comparison of the screening and control groups. From a total of 31,133 participants randomized to screening arm, only 7348 (24%) actually accepted the invitation and got screened. Similarly 15353 men randomized to the control group (no screening group), 1122 (7.3 %) got screening done. The authors also mention that the level of contamination by screening in the control group could not be assessed.
Norköpping (Sandblom)		
Random sequence generation (selection bias)	High risk	Inadequate randomization. 1494 men were randomly allocated to be screened by including every sixth man from a list of dates of birth.
Allocation concealment (selection bias)	High risk	Though allocation concealment is not clearly mentioned but inadequate technique for randomization (predictable group assignment) possibly lead to inadequate concealment of allocation.
Blinding of participants and personnel (performance bias)	Low risk	No mentioning of blinding but blinding of patients would not be possible due to nature of intervention but unlikely to have an effect on outcome.
Blinding of outcome assessment (detection bias)	Low risk	Date and cause of death were recorded in South-East Region Prostate Cancer Register. The Central Death Register was checked for deaths not registered in the South-East Region Prostate Cancer Register. In September 2009 cause of death was registered in a blinded review of the patients' records for all men who died.
Incomplete outcome data (attrition bias)	Low risk	All analyses were performed based on intention to screen comparisons.
Selective reporting (reporting bias)	Low risk	The outcome of interest (prostate-specific mortality) appears in both methods and results section of the paper.
Other bias	Low risk	The study was designed to detect a plausible reduction of prostate cancer specific mortality within 20 years from the start of the study from 1.5% to 1.0% in the screening group. A total of 1050 patients in the screening group would be required to detect this difference (80% power, two sided 5% significance level). To allow for non-compliance in the screening group and contamination in the control group, 1400 men were included in the screening group. One main limitation of the trial was that men were invited to be screened every third year from 1987 to 1996 but on the first two occasions screening was done by digital rectal examination only and PSA-based testing was not used. From 1993, this was combined with prostate specific antigen testing, with 4 ng/mL as cut-off. On the fourth occasion (1996), only men aged 69 or under at

		the time of the investigation were invited.
ERSPC (Schroder)		
Random sequence generation (selection bias)	Low risk	Within each country, men were assigned to either the screening group or the control group, without the use of blocks of numbers or stratification on the basis of random number generators.
Allocation concealment (selection bias)	Unclear risk	No description on method for allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	No mention of blinding but blinding of patients would not be possible due to nature of intervention but unlikely to have an effect on outcome
Blinding of outcome assessment (detection bias)	Low risk	Causes of death, which were obtained from registries and individual chart review, were assigned according to definitions and procedures developed for the trial. Causes of death were evaluated in a blinded fashion, and a committee that analyzed causes of death was formed at each center.
Incomplete outcome data (attrition bias)	Low risk	The statistical analysis was based on the intention to- screen principle. Data from the Portugal study center 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.
Selective reporting (reporting bias)	High risk	The methods reported prostate-specific mortality and HRQL as outcomes. Mortality is reported in results section but HRQL is not reported in this publication.
Other bias	Unclear risk	The paper mentioned the sample size calculation that would be required to show a reduction of 25% in mortality ($P<0.05$) among men who actually underwent screening, with a power of 80% at 10 years of follow-up. some concerns are as follows: First, the main data analysis was restricted to the core age group (55-69 years) but there are differing age groups across the 8 reported sites (i.e. in Sweden, study investigators included men between the ages of 50 and 54 years, and investigators in the Netherlands, Italy, Belgium, and Spain included men up to the age of 74 years at entry) “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 randomization”. Finally, it has been estimated that in the control group, approximately 20% of men per year underwent PSA screening during the early follow-up period (PSA contamination).

Appendix 6 Study characteristics of RCTs and cohort studies on benefits of treatments for prostate cancer

RCTs	
Author, Yr	Bill-Axelson et al., 2011[1] Other publications:Johansson et al., 2009; Bill-Axelson et al., 2008; Holmberg et al., 2006; Bill-Axelson et al., 2005; Steineck et al., 2002; Holmberg et al., 2002 **(SPCG-4)**
Outcomes	PCM; ACM; Surgical complications
Intervention	RP (n=347); control (n=348) [in the control group, 52 received treatment: 29 RP; 13 RT;8 BT; 2 operated but no curative treatment]
Definition of control group	Watchful Waiting: No immediate treatment, further treatment (curative or palliative) was based on signs of local progression or metastases
Control group trigger for treatment	Signs of obstructed voiding disorders were treated with transurethral resection; metastases detected by bone scan were managed with hormonal therapy
Age; **Duration of follow-up**	Mean age: 65 yrs Median follow-up : 12.8 yrs (3 wks-20.2 yrs)
Stage at diagnosis; **% screen detected**	12% (83/695) T1b; 12% (81/695) T1c; 76% (529/695) T2; <1% (2/695) unknown % screen detected NR
Adjusted variables in analysis	NA(RCT)
Author, Yr	Iversen et al., 1995 Other publications: Byar et al., 1981; Graversen et al., 1990
Outcomes	ACM
Intervention	RP (n=74)

	control (n=68)
Definition of control group	Deferred therapy: No initial treatment and only oral placebo, further treatment (curative or palliative) was based on signs of local progression or metastases)
Control group trigger for treatment;	Curative or palliative treatment was based on signs of local progression or metastases
Age; **Duration of follow-up**	Mean age: 64 yrs Median follow-up : 23 yrs (19-27 yrs)
Stage at diagnosis; **% screen detected**	54% (76/142) WHO Stage I 46% (66/142) WHO Stage II % screened detected NR
Adjusted variables in analysis	NA(RCT)
Author, Yr	Wilt et al, 2012 **(PIVOT)**
Outcomes	PCM; ACM; UI; ED; BD; adverse surgical events 30 days
Intervention	RP (n=364); control (n=367) Of control group, 75 received treatment: 36 RP, 1 attempted RP but incomplete, 29 EBRT, 8 brachytherapy, 1 cryotherapy
Definition of control group	Watchful waiting: Offered palliative (non-curative) therapies (e.g. transurethral obstruction, androgen deprivation and/or targeted radiation therapy for evidence of distant spread. Interventions for asymptomatic progression (e.g. changes in PSA value) were discouraged
Control group trigger for treatment treatment	Offered palliative therapy or chemotherapy for symptomatic or metastatic progression
Age/Duration/ Follow-up	Mean age: 67 yrs Median follow-up :10 yrs

Stage at diagnosis **% Screen detected**	50% T1c % screen detected NR
Adjusted variables in analysis	NA(RCT)

Cohorts **Author, Yr**	Abdollah et al, 2012 **(SEER)**
Outcomes	PCM; OCM
Intervention	RT (n=46,521); control (n=22,276)
Definition of control group	Observation: No therapy during the first 6 months after diagnosis, further treatment (curative or palliative) was based on symptomatic progression
Control group trigger for treatment;	not reported
Age; **Duration of follow-up**	Mean age: NR 65-69 yrs: RT 24.1%, control 21.8% 70-74 yrs: RT 41.4%, control 34% 75-80 yrs: RT 34.5%, control 44.2% Mean follow-up: 10 yrs
Stage at diagnosis; **% screen detected**	control 51.8%, RT 40.7% T1; control 41.4%, RT 47.6% T2a/b; control 6.8%, RT 11.7% T2c % screen detected NR
Adjusted variables in analysis	Age at diagnosis, race, marital status, annual median income quartiles, percentage of 4-year college education quartiles, CCI, population density, clinical stage, tumor grade, year of diagnosis, and SEER registry
Author, Yr	Abdollah et al, 2011 (**SEER)** Other publications: Abdollah et al, 2011; Abdollah et al, 2012
Outcomes	PCM, OCM
Intervention	RP (n=22,244); control (n=22,450)
Definition of control group	Observation: No therapy during the first 6 months after diagnosis, further treatment (curative or palliative) was based on symptomatic progression
Control group trigger for treatment	NR
Age;	Mean age: RP 69.8 yrs, control 73.5 yrs

Duration of follow-up	Mean follow-up: 10 yrs
Stage at diagnosis; **% screen detected**	RP 34%, WW 52% T1; RP 51% control 41% T2a/b; RP 16% control 7% T3 % screen detected NR
Adjusted variables in analysis	Age at diagnosis, race, marital status, annual median income quartiles, percentage of 4-year college education quartiles, CCI, population density, clinical stage, tumor grade, year of diagnosis, and SEER registry
Author, Yr	Albertsen et al., 2007
Outcomes	PCM
Intervention	Surgery (n=802); RT (n=702); control (n=114)
Definition of control group	Observation: No initial therapy, further treatment (curative or palliative) was based on signs of local progression or metastases
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Median age: control 70 yrs, surgery 65 yrs, RT 71 yrs Median follow-up: 13.1 to 13.6 yrs (Varied according to treatment group)
Stage at diagnosis; **% screen detected**	4% Gleason score 2-4; 6% Gleason score 5; 47% Gleason score 6 26% Gleason score 7 17% Gleason score 8-10 % screen detected NR ***We could not confirm these numbers in the paper.**
Adjusted variables in analysis	Gleason score, PSA, clinical stage, age at diagnosis, and Charlson comorbidity score
Author, Yr	Ladjevardi et al., 2010
Outcomes	ACM
Intervention	Palliative treatment, including androgen deprivation, [n=3,210]; RP (n=12,950); RT (n=6,308; EBRT n=4,443, and brachytherapy n=1,865); control [n=9,435]
Definition of control group	Conservative management: watchful waiting with palliative (non- curative) treatments
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Mean age: 65.2 ±6.3 yrs Median follow-up: 4 yrs (0-12 yrs)
Stage at diagnosis;	<1% T0; 49% T1; 35% T2; 15% T3; <1% TX

% screen detected	33% screen detected
Adjusted variables in analysis	Age, Gleason score, PSA
Author, Yr	**Lu-Yao et al., 2008**
Outcomes	PCM; ACM
Intervention	ADT (n=7,867); control (n=11,404)
Definition of control group	Conservative management: No definitive treatment in first 180 days of diagnosis, further treatment (curative or palliative excluding ADT) was based on symptomatic progression i.e. based on disease signs or symptoms
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Mean age: 78 yrs Median follow-up: 7 yrs
Stage at diagnosis; **% screen detected**	58% T1; 42% T2 % screen detected NR
Adjusted variables in analysis	Instrumental variable analysis (covariates in analysis included age, race, comorbidity status, cancer stage, cancer grade, income status, urban resident, marital status, and year of diagnosis)
Author, Yr	Merglen et al., 2007
Outcomes	PCM; ACM
Intervention	RP (n=158); any EBRT (n=205; EBRT alone [n=152] or EBRT + ADT [n=53]) ADT (n=72); other treatment (n=31; not described); control (n=378)
Definition of control group	Watchful waiting: no immediate treatment with active follow-up of the patient and invasive treatment with disease progression
Control group trigger for treatment	disease progression
Age; **Duration of follow-up**	Mean age: NR <60 yrs: 8% 60-69 yrs: 37% 70-79 yrs: 37% ≥80 yrs: 18% Mean follow-up: 7 yrs
Stage at diagnosis; **% screen detected**	29% Stage 1; 40% Stage 2; 31% Stage 3; PSA <10 22%; PSA 11-29 28%; PSA >30 23% PSA unknown 27% 31% screen detected

Adjusted variables in analysis	Age, period of diagnosis, method of detection, lymph node status, clinical tumor stage, differentiation, and PSA level
Author, Yr	Schymura et al., 2010
Outcomes	ACM
Intervention	RP (n=1310); RT (EBRT or BT; n=1037); ADT (n=339); control (n=614)
Definition of control group	Watchful waiting: No record of any therapy within the first six months following diagnosis, further conservative (non-curative) treatment was based on signs of local progression or metastases
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Median age: 68.9 yrs Mean follow-up: 12 mos
Stage at diagnosis; **% screen detected**	57% PSA <10; 18% PSA 10-20; 11% PSA >20; 13% PSA unknown 63% screen detected
Adjusted variables in analysis	Age at diagnosis, race/ethnicity, marital status, state, PSA value, Gleason score, comorbidity score, time since diagnosis
Author, Yr	Stattin et al., 2010
Outcomes	PCM; ACM
Intervention	RP (n=3399); RT (n=1429); control (n=2021)
Definition of control group	Surveillance: Both active surveillance and watchful waiting, i.e. deferred curative or palliative treatment until the perceived disease progression), active surveillance (delivering curative treatment when progression occurred) and watchful waiting (administering hormonal treatment when symptomatic progression occurred)
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Mean age at diagnosis: RP 61.2 (5.3) yrs; RT 63.4 (4.9) yrs; control 64.7 (4.6) yrs Median follow-up: 8.2 yrs
Stage at diagnosis; **% screen detected**	59% T1; 41% T2 100% screen detected
Adjusted variables in analysis	Prostate cancer risk category, Charlson comorbidity index, socioeconomic status
Author, Yr	Tewari et al., 2007
Outcomes	PCM; ACM
Intervention	RT (n=137); RP (n=119); control (n=197)

Definition of control group	Conservative treatment or watchful waiting: early hormonal therapy or administering hormonal treatment when symptomatic progression occurred
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Mean age: 60.09 ±45.6 yrs Median follow-up: 5 yrs
Stage at diagnosis; **% screen detected**	100% Stage 3 % screen detected NR
Adjusted variables in analysis	Propensity analysis (propensity score based on age at diagnosis, race, socioeconomic status, Charlson comorbidity index, and year of diagnosis)
Author, Yr	Wong et al., 2006
Outcomes	ACM
Intervention	Treatment (n=32,022; includes RP [n=13.292], and EBRT or BT [n=18,249], alone or in combination); control (n=12,608)
Definition of control group	Observation: No therapy during the first 6 months after diagnosis, further treatment (curative or palliative excluding hormonal therapy) was based on symptomatic progression
Control group trigger for treatment	NR
Age; **Duration of follow-up**	Median age at diagnosis: Treatment 71.0 yrs; control 72.9 yrs Median follow-up: 12 yrs
Stage at diagnosis; **% screen detected**	treatment 38%, control 55% Stage ≤T2a; treatment 62%, control 45% Stage T2b-T2c % screen detected NR
Adjusted variables in analysis	Propensity-adjusted (propensity score based on age at diagnosis, SEER site, year of diagnosis, tumor size, tumor Grade, marital status, residence in urban setting, race, income, educational achievement, and comorbidities)
Author, Yr	Zhou et al., 2009
Outcomes	PCM
Intervention	Monotherapy: RP (n=889); EBRT (n=783); BT (n=595); ADT (n=2049) Combination therapy: RP + EBRT, ADT or both (n=181); EBRT + ADT (n=1286); BT + EBRT or ADT (n=756) control (n=1716)
Definition of control group	No treatment: No definitive therapy within 6 months of diagnosis, further treatment (curative or palliative) was based on symptomatic progression

Control group trigger for treatment	**Control group trigger for treatment** NR
Age; **Duration of follow-up**	Mean age: NR 65-69 yrs: 21.5% 70-74 yrs: 32% ≥75 yrs: 46.5% Median follow-up: 7 yrs
Stage at diagnosis; **% screen detected**	66% Gleason score <7 % screen detected NR
Adjusted variables in analysis	Age, race, tumor stage, Gleason score, pre-treatment comorbidity

NR = not reported; ADT = androgen deprivation therapy; RP = radical prostatectomy; RT = radiation therapy; EBRT = external beam radiation therapy; PCM = prostate cancer-specific mortality; ACM = all-cause mortality; OCM = other cause mortality; BT = brachytherapy; NA = not applicable; UI – urinary incontinence; ED = erectile dysfunction; BD = bowel dysfunction; PSA = prostate specific antigen; CCI = Charlson comorbidity index

Appendix 7 Risk of Bias of RCTs assessing benefits of treatment for prostate cancer

Appendix 8 Assessment of risk of bias of cohort studies – Newcastle Ottawa Quality Assessment Scale (NOS)

	Selection				Comparability	Outcome			
	Representativeness of cohort	Selection of non-exposed	Ascertainment of exposure	Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total Stars
Benefits									
Abdollah,2012	(B*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(D)	8
Abdollah,2011	(A*)	(A*)	(A*)	(A*)	(A,B**)	(D)	(A*)	(D)	7
Albertsen,2007	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(D)	8
Ladjevardi,2010	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(A*)	9
Lu-Yao,2008	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(D)	8
Merglen,2007	(A*)	(A*)	(A*)	(A*)	(A,B**)	(B*)	(A*)	(A*)	9
Schymura,2010	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(B*)	9
Stattin,2010	(A*)	(A*)	(A*)	(A*)	(A,B**)	(B*)	(A*)	(D)	8
Tewari,2007	(A*)	(A*)	(A*)	(A*)	(A,B**)	(B*)	(A*)	(D)	8
Wong,2006)	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(D)	8
Zhou,2009	(A*)	(A*)	(D)	(A*)	(A,B**)	(A*)	(A*)	(D)	7
Harms									
Bacon,2001	(C)	(A*)	(A*)	(A*)	(A,B**)	(C)	(A*)	(D)	6
Choo,2010	(B*)	(A*)	(D)	(A*)	(C)	(C)	(A*)	(B*)	5
Galbraith,2001	(B*)	(A*)	(C)	(B)	(A,B**)	(C)	(A*)	(A*)	6
Hoffman,2003	(A*)	(A*)	(A*)	(B)	(A,B**)	(C)	(A*)	(D)	6
Litwin,1995	(B*)	(B*)	(D)	(B)	(C)	(C)	(A*)	(D)	3
Litwin,2002	(A*)	(A*)	(D)	(B)	(A,B**)	(C)	(A*)	(D)	5
Lubeck,1999	(B*)	(A*)	(A*)	(B)	(C)	(C)	(A*)	(B*)	5
Potosky,2002	(A*)	(A*)	(A*)	(A*)	(A,B**)	(C)	(A*)	(A*)	8
Schapira,2001	(B*)	(A*)	(D)	(A*)	(A,B**)	(C)	(A*)	(A*)	7
Schymura,2010	(A*)	(A*)	(A*)	(A*)	(A,B**)	(A*)	(A*)	(B*)	9
Siegel,2001	(D)	(C)	(A*)	(A*)	(C)	(C)	(A*)	(A*)	4
Smith,2000	(A*)	(A*)	(A*)	(B)	(A,B**)	(C)	(A*)	(B*)	7
Smith,2009	(A*)	(A*)	(A*)	(A*)	(A,B**)	(C)	(A*)	(A*)	8
Steenland,2011	(A*)	(A*)	(B*)	(A*)	(A,B**)	(C)	(A*)	(D)	7
Talcott,2003	(B*)	(A*)	(A*)	(A*)	(A,B**)	(C)	(A*)	(B*)	8
Thong,2009	(A*)	(A*)	(A*)	(A*)	(A,B**)	(C)	(A*)	(A*)	8

Selection

Q1. Representativeness of the exposed cohort.

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of men from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented men are likely to be representative of users while they are not representative of all men.

(A*) Truly representative of the average in the community*

(B*) Somewhat representative of the average in the community*

(C) Selected group of users eg. physicians, volunteers

(D) No description of the derivation of the cohort

Q2. Selection of the non-exposed cohort

(A*)Drawn from the same community as the exposed cohort*

(B*) Drawn from a different source

(C) No description of the derivation of the non-exposed cohort

Q3. Ascertainment of exposure

(A*) Secure records (eg. surgical records, medical records)*

(B*) Structured interview*

(C) Written self-report

(D) No description

Q4. Demonstration that outcome of interest was not present at start of study

In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

(A*) Yes*

(B) No

Comparability

Q1. Comparability of cohorts on the basis of the design or analysis

A maximum of 2 stars can be allotted in this category

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

(A*) study controls for age at diagnosis and tumor grade (the most important factors)*

(B*) Study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

(C) No relevant adjustments for confounding

Outcome

Q1. Assessment of outcome

For some outcomes (e.g. surgical complications), reference to the medical record is sufficient to satisfy the requirement for confirmation.

(A*) independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (death records, medical records, etc.)*

(B*) record linkage (e.g. identified through ICD codes on database records)*

(C) self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)

(D) No description

Q2. Was follow up long enough for outcomes to occur

30 days for perioperative complications and > 12 months for other harms.

If the follow-up period is reported with a mean and a range, and the mean is longer than the required minimum, rate it as 'yes.'

(A*) Yes (select an adequate follow up period for outcome of interest)*

(B) No

Q3. Adequacy of follow up of cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

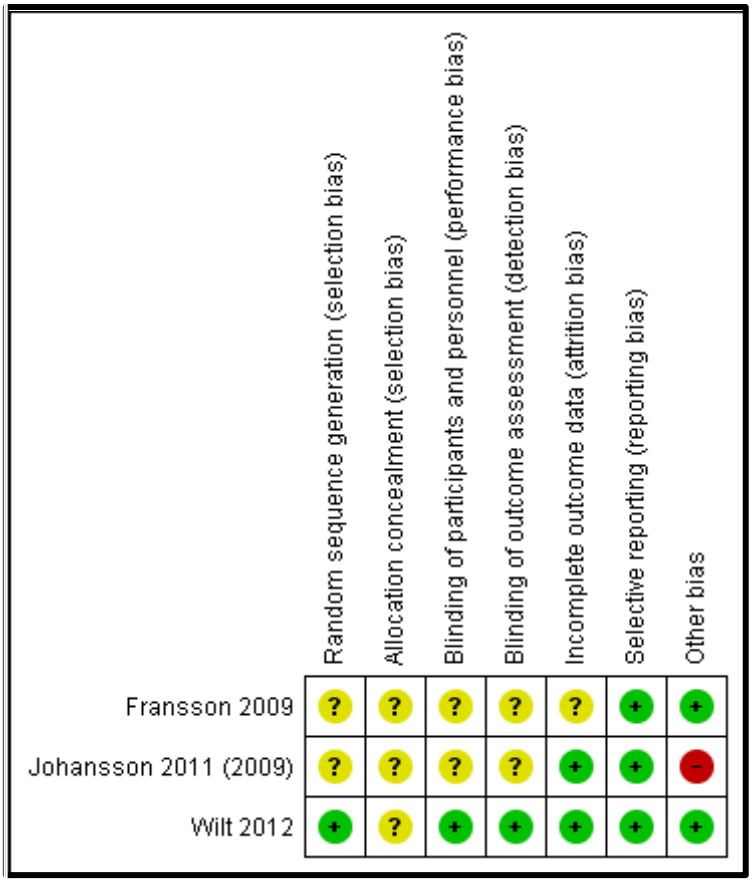
(A*) complete follow-up, all subjects accounted for, or dropout rates ≤10%*

(B*) subjects lost to follow-up are unlikely to introduce bias – small number lost

(C) There is a loss-to-follow-up and there is no description of those lost AND/OR if reasons are connected to the outcome OR there is an imbalance in the rates/reasons between groups

(D) no description or unclear

Appendix 9 Risk of bias for harms of treatment



Appendix 10 Post-surgical harms

Author	Minor Harms N (%)	Major Harms N (%)	Not Specified N(%)
Alihbai, 2005 **N=10110 (RP)**		Mortality 53 (0.48) monotonic increase in crude 30-day mortality with age, from 0.19% (95% confidence interval [CI] =0.02% to 0.30%) for men under age 60 to 0.66% (95% CI = 0.2% to 1.1%) for men aged 70 to 79 years the absolute risk of 30-day mortality remained relatively low; for a 75-year-old man with no comorbidities, the predicted 30-day mortality was 0.74%	Any 2246 (20.40) Cardiac 309 (2.81) Respiratory 293 (2.66) Vascular 215 (1.95) Wound 555 (5.04) Genitourinary 829 (7.53) Miscellaneous medical 427 (3.88) Miscellaneous surgical 576 (5.23)
Augustin, **N=1243 (RP)** **60 major complications reported from 50 patients** **233 minor complications in 197 patients**	Most commonly reported 2nd surgery 15 (1.2) Blood transfusion (29.1) UTF 19 (1.5) Urine Retention 21 (1.7) Wound dehiscence 17 (1.4)	Intraoperative 9 (0.7) Postoperative (most commonly reported) Cardiovascular 4 (0.6) Thromboembolic 15 (1.2) ICU 9 (0.7) Rehospitalization 8 (0.6) 2nd surgery 17 (104)	

Rabbini, 2010 **n- 3458 (RP)**	Overall 395 (11.4) Urologic 182 (5.3) Lymphovascular 71(2.1) Infectious 6 (0.2) Gastrointestinal 6 (0.2) Neurologic 21 (0.6) Musculoskeletal 0 (0) Wound complications 109 (3.2)	Overall 170 (4.9) Urologic 76 (2.2) Lymphovascular 47 (1.4) Infectious 13 (0.4) Gastrointestinal 23 (0.7) Neurologic 1 (0.03) Musculoskeletal 0 (0) Wound complications 10 (0.3)	
Wilt, 2012 **n=280 (RP)** **60 complications reported in 50 patients**		Death 1 (0.4)	Any 60 (21.4) Pneumonia 2 (0.7) Wound infection 12 (4.3) Urinary tract infection 7 (2.5) Sepsis 3 (1.1) Deep-vein thrombosis 2 (0.7) Stroke 1 (0.4) Pulmonary embolism 2 (0.7) Myocardial infarction 3 (1.1) Renal failure or dialysis 1 (0.4) Bowel injury requiring surgical repair 3 (1.1) Additional surgical repair 7 (2.5) Bleeding requiring transfusion 6 (2.1) Urinary catheter present >30 days after surgery 6 (2.1) Other 28 (10.0)

Appendix 11 List of excluded studies

No adequate control group

1. Hurtes X, Roupret M, Vaessen C, Pereira H, Faivre d'Arcier B, Cormier L, and Bruyere F. Anterior suspension combined with posterior reconstruction during robot-assisted laparoscopic prostatectomy improves early return of urinary continence: a prospective randomized multicentre trial. BJU international. 2012; 110(6):875-83. PM:22260307.

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Population included >10% of patients with stage T3 tumour or higher

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