JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Prostate-Specific Antigen–Based Screening for Prostate Cancer
Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Prostate cancer is the second leading cause of cancer death among US men.

OBJECTIVE To systematically review evidence on prostate-specific antigen (PSA)–based prostate cancer screening, treatments for localized prostate cancer, and prebiopsy risk calculators to inform the US Preventive Services Task Force.

DATA SOURCES Searches of PubMed, EMBASE, Web of Science, and Cochrane Registries and Databases from July 1, 2011, through July 15, 2017, with a surveillance search on February 1, 2018.

STUDY SELECTION English-language reports of randomized clinical trials (RCTs) of screening; cohort studies reporting harms; RCTs and cohort studies of active localized cancer treatments vs conservative approaches (eg, active surveillance, watchful waiting); external validations of prebiopsy risk calculators to identify aggressive cancers.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES Prostate cancer and all-cause mortality; false-positive screening results, biopsy complications, overdiagnosis; adverse effects of active treatments. Random-effects meta-analyses were conducted for treatment harms.

RESULTS Sixty-three studies in 104 publications were included (N = 1 904 950). Randomization to PSA screening was not associated with reduced risk of prostate cancer mortality in either a US trial with substantial control group contamination (n = 76 683) or a UK trial with low adherence to a single PSA screen (n = 408 825) but was associated with significantly reduced prostate cancer mortality in a European trial (n = 162 243; relative risk [RR], 0.79 [95% CI, 0.69-0.91]; absolute risk reduction, 1.1 deaths per 10 000 person-years [95% CI, 0.5-1.8]). Of 61 604 men screened in the European trial, 17.8% received false-positive results. In 3 cohorts (n = 15 136), complications requiring hospitalization occurred in 0.5% to 1.6% of men undergoing biopsy after abnormal screening findings. Overdiagnosis was estimated to occur in 20.7% to 50.4% of screen-detected cancers. In an RCT of men with screen-detected prostate cancer (n = 1643), neither radical prostatectomy (hazard ratio [HR], 0.63 [95% CI, 0.21-1.93]) nor radiation therapy (HR, 0.51 [95% CI, 0.15-1.69]) were associated with significantly reduced prostate cancer mortality vs active monitoring, although each was associated with significantly lower risk of metastatic disease. Relative to conservative management, radical prostatectomy was associated with increased risk of urinary incontinence (pooled RR, 2.27 [95% CI, 1.82-2.84]; 3 trials; n = 1796) and erectile dysfunction (pooled RR, 1.82 [95% CI, 1.62-2.04]; 2 trials; n = 883). Relative to conservative management (8 cohort studies; n = 3066), radiation therapy was associated with increased risk of erectile dysfunction (pooled RR, 1.31 [95% CI, 1.20-1.42]).

CONCLUSIONS AND RELEVANCE PSA screening may reduce prostate cancer mortality risk but is associated with false-positive results, biopsy complications, and overdiagnosis. Compared with conservative approaches, active treatments for screen-detected prostate cancer have unclear effects on long-term survival but are associated with sexual and urinary difficulties.

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Prostate cancer is the most commonly diagnosed cancer in US men and the second leading cause of cancer death.[1] It has been estimated that in 2018, approximately 165 000 US men will be diagnosed with prostate cancer and 29 000 men will die of prostate cancer.[2] Prostate cancer incidence is 74% greater among African American than white men[1] and is also relatively greater in men with vs men without a family history of prostate cancer.[3]

US prostate cancer incidence increased sharply with the dissemination of prostate-specific antigen (PSA)–based screening beginning in the late 1980s.[4] In 2012, the US Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer, concluding that there was moderate certainty that the benefits of screening do not outweigh the harms (D recommendation). New evidence has since emerged from screening and treatment trials, and among US men prostate cancer is increasingly managed with active surveillance, in which treatment is deferred indefinitely unless evidence of progression is found during periodic physical examination, PSA–based testing, or repeat biopsy. This systematic review of screening and treatment benefits and harms and whether prebiopsy risk calculators can reliably detect higher-risk prostate cancers, along with a review of decision modeling studies,[5] was conducted to inform the USPSTF in its update of the 2012 recommendation regarding PSA-based screening for prostate cancer.

Methods

Scope of Review

This review addressed 5 key questions (KQs) (**Figure 1**) encompassing the benefits and harms of PSA screening (KQ1 and KQ2), benefits and harms of treatments for localized prostate cancer (KQ3 and KQ4), and the utility of prebiopsy risk calculators to identify men with higher-risk prostate cancers (KQ5). Results addressing primary key questions are summarized here, while results for subquestions 2a, 3a, 4a, 4b, and 5a, as well as additional methodological details regarding search strategies, study inclusion criteria, quality assessment, excluded studies, and data analyses, are publicly available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prostate-cancer-screening1.

Data Sources and Searches

MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched to locate studies informing the key questions (eMethods in the Supplement) that were published since the end of the search periods for the 2011 USPSTF reviews[7,8] (July 1, 2011, through July 15, 2017). Database searches were supplemented with expert suggestions and by reviewing reference lists from relevant systematic reviews and prior USPSTF reports. KQ5, on prebiopsy risk calculators, was new to this review; a preliminary search revealed that the earliest article in this field was published in 2006, so databases were searched from January 1, 2006, through October 6, 2016, for KQ5. Since October 2016, ongoing surveillance continued through article alerts and targeted searches of high-impact journals to identify studies published that could affect the conclusions or the related USPSTF recommendation. The last surveillance search was conducted in February 2018; during ongoing surveillance, we identified extended follow-up from a treatment trial,[9] 2 cohort studies reporting longitudinal treatment outcomes,[10,11] and 3 studies of multivariable risk calculators.[12-14] We also included a recently published large screening trial.[15]

Study Selection

For KQ1, randomized clinical trials (RCTs) of asymptomatic men undergoing PSA screening vs no screening were included that assessed cancer incidence, prostate cancer–related morbidity, prostate cancer–specific mortality, or all-cause mortality. For KQ2, RCTs and cohort studies of asymptomatic men undergoing PSA screening or prostate biopsy after abnormal screening results were included that assessed the frequency of false-positive PSA screening, physical or psychological harms of screening or biopsy, or health-related quality of life. As has been performed for breast and lung cancer screening,[16-19] extra-incidence data from trials were used to estimate the percentage of men diagnosed with cancer in the screening groups who were overdiagnosed. In the absence of overdiagnosis, the number of cases in the control group of a screening trial would be expected to eventually catch up with the number of cases diagnosed in the screening group; therefore, an excess of cases in the screening group with extended follow-up implies overdiagnosis.

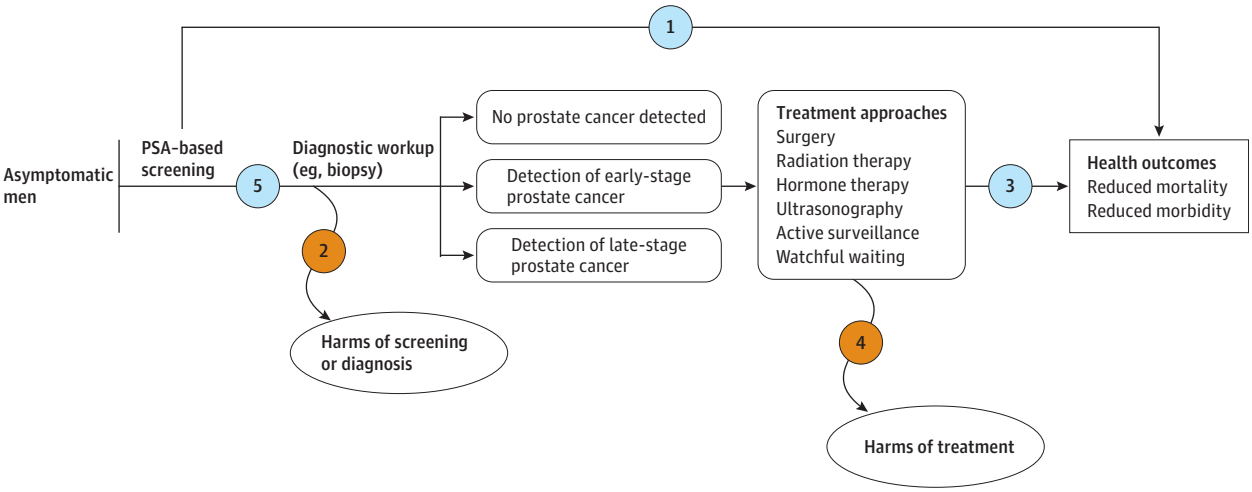
For KQ3 and KQ4, RCTs and comparative cohort studies of men with localized prostate cancer (stages T1-T2) were included that reported prostate cancer–specific morbidity or mortality, all-cause mortality (KQ3), or physical or psychological harms of treatment, including adverse quality-of-life effects (KQ4). Studies were required to compare outcomes among men receiving active treatments (including radical prostatectomy, radiation therapy, androgen deprivation therapy, cryotherapy, or high-intensity focused ultrasound) and men receiving conservative management (ie, watchful waiting, active surveillance, observation, or no treatment). Because few studies were found for treatments other than radical prostatectomy and radiation therapy, only findings for radical prostatectomy and radiation therapy are summarized in this article; evidence on other treatment modalities is reviewed in the full evidence report. For KQ4 (treatment harms), uncontrolled observational studies with sample sizes of at least 100 men were also included.

For KQ5, external validation studies of multivariable risk calculators were included if they predicted the presence of "significant" prostate cancer using PSA testing in addition to patient variables routinely available before prostate biopsy (eg, patient characteristics, rectal examination results, PSA level). Significant prostate cancers were defined as either high grade (Gleason score $\geq$7) or clinical stage T2b or higher. Studies of novel serum biomarkers or imaging studies were excluded because results from these studies would not be routinely available before biopsy in most urology practices.

Data Extraction and Quality Assessment

Two reviewers independently appraised the quality of included articles using predefined criteria,[6,20-23] with disagreements resolved by consensus or consultation with a third investigator. One reviewer extracted study-level data into standardized evidence tables; a second checked data accuracy. Included studies

Figure 1. Analytic Framework



Key questions

1 Is there direct evidence that prostate cancer–specific antigen (PSA)–based screening for prostate cancer reduces short- or long-term prostate cancer morbidity and mortality and all-cause mortality?

a. Does the effectiveness of PSA-based screening vary by subpopulation or risk factor (eg, age, race/ethnicity, family history, or clinical risk assessment)?

2 What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up?

a. Do the harms of PSA-based screening for prostate cancer and diagnostic follow-up vary by subpopulation or risk factor (eg, age, race/ethnicity, family history, or clinical risk assessment)?

3 Is there evidence that various treatment approaches for early-stage or screen-detected prostate cancer reduce morbidity and mortality?

a. Does the effectiveness of these treatment approaches vary by subpopulation or risk factor (eg, age, race/ethnicity, baseline PSA value, family history, comorbid conditions, or clinical risk assessment)?

4 What are the harms of the various treatment approaches for early-stage or screen-detected prostate cancer?

a. Do the harms of these treatment approaches vary by subpopulation or risk factor (eg, age, race/ethnicity, baseline PSA value, family history, comorbid conditions, or clinical risk assessment)?

b. Do the harms differ by treatment approach?

5 Is there evidence that use of a prebiopsy prostate cancer risk calculator, in combination with PSA-based screening, accurately identifies men with clinically significant prostate cancer (ie, cancer that is more likely to cause symptoms or lead to advanced disease), compared with PSA-based screening alone?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for further details.[6]

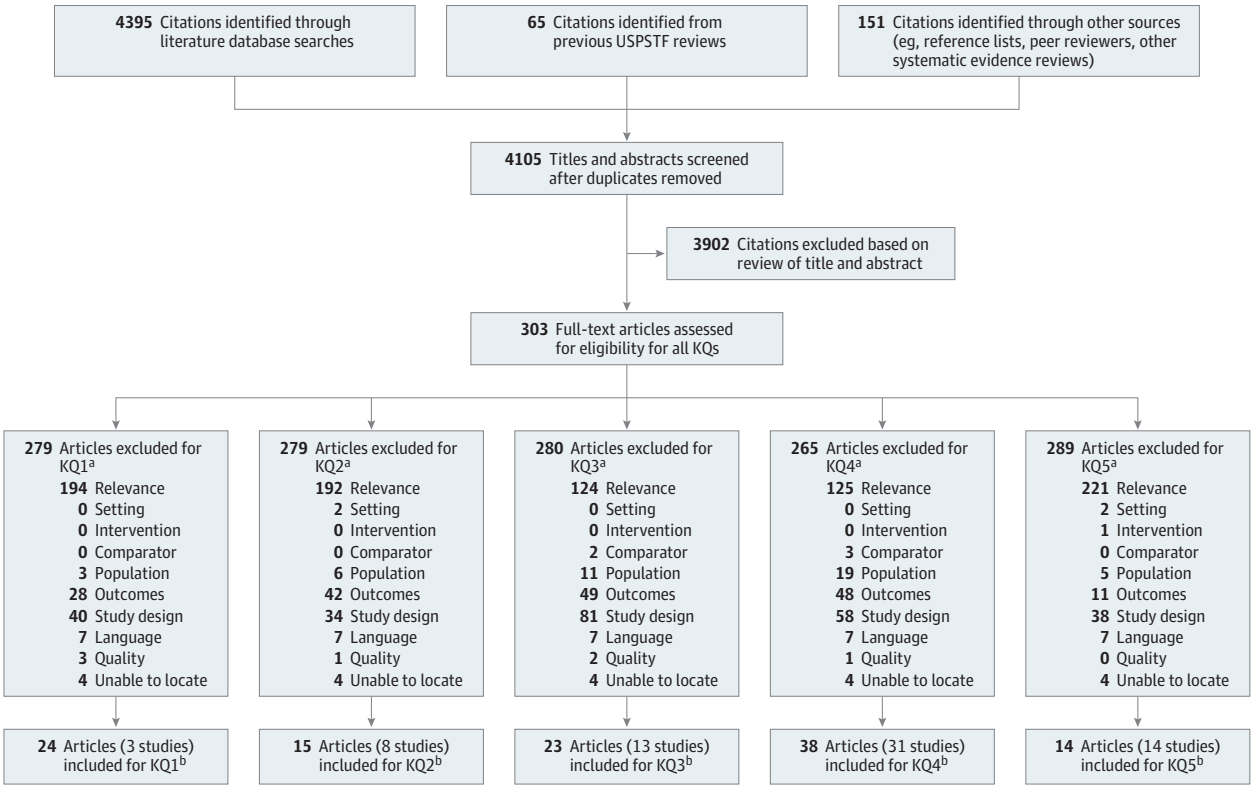
were limited to those published in English and were rated as fair or good quality using USPSTF quality rating standards (eTable 1 in the Supplement). Poor-quality studies contained a fatal flaw or multiple significant limitations that could invalidate the results. Three poor-quality RCTs of screening PSA were excluded.[24-26] Limitations of these studies included inadequate statistical power,[24-26] faulty analysis,[25] and potentially biased outcomes assessment.[24-26]

Data Synthesis and Analysis

For each key question, the study designs, population characteristics, screening and treatment details, and overall results were summarized using descriptive statistics. Pooled meta-analyses were not performed for outcomes of screening effectiveness (KQ1), screening harms (KQ2), or treatment effectiveness (KQ3), because data on these outcomes derived from few studies with variable populations and interventions. For KQ4, random-effects meta-analyses were performed using the method of DerSimonian and Laird to estimate pooled relative risks (RRs) of urinary incontinence (ie, daily use of a pad or worse) and erectile dysfunction (ie, erections insufficient for intercourse) among patients receiving radical prostatectomy or radiation therapy vs conservative management.

Statistical heterogeneity across studies was estimated using the I^2 statistic. Meta-analyses were performed using Stata version 14.2 (StataCorp). Pooled RRs were used to estimate the number of patients needed to be treated for 1 patient to be harmed (number needed to harm); in these calculations, the absolute risk of the harm in actively treated patients was estimated as

Figure 2. Literature Search Flow Diagram



KQ indicates key question; USPSTF, US Preventive Services Task Force.

[a] Reasons for article exclusion: Relevance: study aim not relevant to key question. Setting: study not conducted in a country relevant to US practice. Intervention: study of excluded screening or treatment approach. Comparator: study lacked comparator group receiving either no screening (KQ1 and KQ2) or conservative management (KQ3 and KQ4). Population: study not conducted in a population at average risk for prostate cancer. Outcomes: study did not report relevant outcomes. Study design: design did not meet inclusion criteria for key question. Language: study published in non-English language. Quality: study did not meet criteria for fair or good quality. Unable to locate: full-text article could not be located.

[b] There were 17 new articles since the 2011 USPSTF review for KQ1, 9 for KQ2, 11 for KQ3, 15 for KQ4, and 14 for KQ5.

the product of the pooled RR and the absolute risk among all men included in the conservative management control groups of included studies. Statistical tests were 2-sided, with $P < .05$ indicating statistical significance.

Results

Two reviewers independently assessed 4105 unique citations and 303 full-text articles for inclusion (**Figure 2**). Overall, 24 articles (3 studies) were included for KQ1, 15 articles (8 studies) were included for KQ2, 23 articles (13 studies) were included for KQ3, 38 articles (31 studies) were included for KQ4, and 14 articles (14 studies) were included for KQ5.

Effectiveness of PSA-Based Screening

Key Question 1. Is there direct evidence that PSA-based screening for prostate cancer reduces short- or long-term prostate cancer morbidity and mortality and all-cause mortality?

Key Question 1a. Does the effectiveness of PSA-based screening vary by subpopulation or risk factor (eg, age, race/ethnicity, family history, or clinical risk assessment)?

Three fair-quality RCTs (n = 647 906) assessed the effect of PSA screening on prostate cancer morbidity and mortality and all-cause mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,[27] the European Randomized Study of Screening for Prostate Cancer (ERSPC),[28] and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP)[15] (**Table 1**). Since the previous USPSTF review, the ERSPC[30] and PLCO[29] trials each reported results of extended follow-up; recent reports from 4 ERSPC sites (Goteborg-Sweden,[32] Finland,[37] the Netherlands,[35] and Spain[34]) were also included.

In the PLCO trial, 76 683 US men aged 55 to 74 years were recruited from 1993 to 2001 and randomized to either annual PSA screening for 6 years or usual care. When men had PSA levels of 4.0 ng/mL or greater, they and their clinicians were informed; community physicians coordinated diagnostic evaluations and treatments. The PLCO trial has been characterized as comparing the effectiveness of organized vs opportunistic screening,[40] because during the screening phase of the trial, approximately 46% of control group participants received routine screening PSA testing from community physicians during each year, compared with approximately 85% of men in the screening group.[41] PSA testing was also common in both trial groups during the 7 years after the screening phase.

Table 1. Results of Randomized Clinical Trials of PSA-Based Screening (Key Question 1)[a]

Source	No. of Participants		Age Range, y	PSA Screening Threshold, ng/mL	Screening Interval, y (Planned No. of Screening Rounds)	Median Follow-up, y	Prostate Cancer Incidence, No. (%)		No. of Prostate Cancer Deaths				RR (95% CI)	
									Per 10 000 Men		Per 10 000 Person-Years			
	Intervention	Control					Intervention	Control	Intervention	Control	Intervention	Control	Prostate Cancer Mortality	All-Cause Mortality
CAP,[15] 2018 (United Kingdom)	189 386	219 439	50-69	3.0	1 (1)	10.0	8054 (4.3)	7853 (3.6)	29.0	29.5	3.0	3.1	0.96 (0.85-1.08)	0.99 (0.94-1.03)
PLCO,[27,29] 2016 (United States)	38 340	38 343	55-74	4.0	1 (6)	13.0, 14.8[b]	4250 (11.1)	3815 (9.9)	66.5	63.6	4.8	4.6	1.04 (0.87-1.24)	0.98 (0.95-1.00)
ERSPC,[30,31] 2014[c] (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, Switzerland)[d]	72 891	89 352	55-69[e]	2.5-4.0[f]	2-4 (3-10)[f]	13.0	7408 (10.2)	6107 (6.0)	48.7	61.0	4.3	5.4	0.79 (0.69-0.91)	1.00 (0.98-1.02)
ERSPC-Goteborg,[32,33] 2015 (Sweden)	10 000	10 000	50-64	2.5-3.0	2 (10)	14.0, 18.0[g]	1396 (14.0)	962 (9.6)	79.0	122.0	NR	NR	0.58 (0.46-0.72)	Intervention: 19.8% Control: 19.8%
ERSPC-Spain,[34] 2014 (Spain)	2415	1861	45-70	3.0	4 (3)	15.2	161 (6.7)	80 (4.3)	20.7	26.9	4.8	4.6	0.76 (0.22-2.62)	0.92 (0.78-1.08)
ERSPC-Rotterdam,[35,36] 2013 (the Netherlands)	20 985	20 917	55-74	3.0-4.0	4 (5)	12.8	2674 (12.7)	1430 (6.8)	72.0	89.9	NR	NR	0.80 (0.65-0.99)	Intervention: 2.8% Control: 2.3%
ERSPC-Finland,[37,38] 2013 (Finland)	31 866	48 278	55-67	4.0	4 (3)	12.0	2883 (9.0)	3337 (6.9)	46.8	55.1	NR	NR	0.85 (0.69-1.04)[h]	0.99 (0.96-1.02)[h]

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; RR, relative risk.

[a] The comparator for each randomized clinical trial was a control group that was not offered prostate cancer screening. All studies in this table were fair quality, as assessed using criteria from the US Preventive Services Task Force.[6]

[b] PLCO incidence data are based on median follow-up of 13 years,[39] and mortality data are based on median follow-up of 14.8 years.[29]

[c] Results for the overall ERSPC trial are inclusive of all study locations, including those that have published site-specific results (Sweden, Spain, the Netherlands, Finland).

[d] France was excluded from all published ERSPC analyses of prostate cancer mortality because of incomplete follow-up.[30] Data presented are for all sites except France.

[e] ERSPC recruited men aged 50 to 74 years; however, most ERSPC reports, including the most recent update,[30] emphasize outcomes among men in the "core" age group of 55 to 69 years at randomization.

[f] The Belgium site initially used a PSA threshold of 10.0 ng/mL and a screening interval of 7 years but transitioned to a threshold of 4.0 ng/mL and a 4-year interval by the end of the study.

[g] ERSPC-Goteborg reported longest (rather than median) follow-up, which was 14.0 years for incidence and all-cause mortality and 18.0 years for prostate cancer mortality.

[h] ERSPC-Finland reported hazard ratio rather than relative risk.

In the ERSPC trial, 181 999 men aged 50 to 74 years were enrolled at 7 European centers from 1993 to 2003, although primary outcomes were reported among 162 243 men aged 55 to 69 years at randomization. The ERSPC screening interval was 4 years at all sites except in Sweden, which used a 2-year interval; the PSA threshold prompting biopsy recommendation was most commonly 3 ng/mL but varied across sites and over time within some sites. Contamination was not systematically assessed at all ERSPC sites, although 19.4% of control group participants had a screening PSA test during the screening phase at the Netherlands site.[36]

In the CAP trial, 408 825 UK men aged 50 to 69 years were randomized by primary care practice cluster (n = 573) to invitation (or no invitation) to a single PSA screen conducted from 2001 to 2009.[15] After invitation, 34% of men obtained a valid PSA screening test. Although PSA screening was not routine in UK practice during the study period, from 2002 to 2011, UK men aged 45 to 69 years had a 39.2% cumulative risk over 10 years of receiving at least 1 PSA test for screening or diagnostic purposes.[42]

Prostate Cancer Incidence

Cumulative incidences of prostate cancer in the screening and control groups were 11.1% and 9.9%, respectively, at 13 years of median follow-up in the PLCO trial (RR, 1.12 [95% CI, 1.07-1.17]), 10.2% and 6.0% at 13 years of median follow-up in the ERSPC trial (RR, 1.57 [95% CI, 1.51-1.62]), and 4.3% and 3.6% at 10 years of median follow-up in the CAP trial (RR, 1.19 [95% CI, 1.14-1.25]) (Table 1). Observed risk differences in prostate cancer incidence indicate a number needed to invite of 84 men in the PLCO trial (95% CI, 59-144), 26 men in the ERSPC trial (95% CI, 24-29), and 154 men in the CAP trial (95% CI, 128-192) for 1 additional man to be diagnosed with prostate cancer.[15,30,39]

Cumulative Incidence of Metastatic Disease

Within 4 ERSPC sites, the cumulative incidence of metastatic cancer (ie, metastases on imaging or a PSA level >100 ng/mL) at a median follow-up of 12.0 years was lower among men randomized to screening compared with control (RR, 0.70 [95% CI, 0.60 to 0.82]), and randomization to screening was associated with an absolute reduction in long-term risk of metastatic prostate cancer of 3.1 cases per 1000 men.[43] After accounting for the 55.6% relative increase in prostate cancer incidence in the screening vs control groups at these sites, the number needed to invite to avoid 1 case of metastatic cancer was 323 (95% CI, 227-556), and the number needed to diagnose with prostate cancer through screening to avert 1 case of metastatic cancer was 12 (95% CI, 9-21).[43]

Prostate Cancer Mortality

At a median follow-up of 14.8 years in the PLCO trial, the prostate cancer–specific mortality rate was 4.8 per 10 000 person-years among men in the intervention group and 4.6 per 10 000 person-years among men in the control group (RR, 1.04 [95% CI, 0.87-1.24]) (Table 1).[29] In the CAP trial, at a median follow-up of 10 years, prostate cancer–specific mortality was 3.0 per 10 000 person-years among men invited to screening and 3.1 per 10 000 person-years among men in the control group (RR, 0.96 [95% CI, 0.85-1.08]). Among men in the ERSPC core age group after a median of 13 years of follow-up, prostate cancer–specific mortality was 4.3 per 10 000 person-years in the intervention group and 5.4 per 10 000 person-years in control group (RR, 0.79 [95% CI, 0.69-0.91]; $P = .001$).[30] In the ERSPC trial, the absolute risk reduction in prostate cancer mortality associated with screening was 1.1 deaths per 10 000 person-years (95% CI, 0.5-1.8), or 1.3 fewer prostate cancer deaths per 1000 men; the number needed to invite to prevent 1 prostate cancer death was 781 (95% CI, 490-1929), and the number needed to diagnose was 27 (95% CI, 17-66). Across all ERSPC sites, prostate cancer mortality was statistically significantly reduced only at the sites in the Netherlands and Sweden, although point estimates were in favor of screening at all sites except Switzerland.

Randomization to screening was not associated with statistically significant reductions in prostate cancer mortality among men aged 65 to 74 years at baseline in the PLCO trial (RR, 1.02 [95% CI, 0.77-1.37])[29] or among men aged 70 to 74 years at baseline in the ERSPC trial (RR, 1.17 [95% CI, 0.82-1.66]).[30] No reports on differences in outcomes by race/ethnicity within the PLCO or ERSPC trials were found, and the sample size of 3370 non-Hispanic black men randomized in the PLCO trial (4.4% of the overall population) was relatively small. Among white men in the PLCO trial who reported of a family history of prostate cancer (n = 4833), the multivariable-adjusted hazard ratio for prostate cancer death among men randomized to screening was lower relative to control participants but was not statistically significant (HR, 0.49 [95% CI, 0.22-1.10]).[44]

All-Cause Mortality

After median follow-up periods ranging from 10 years in the CAP trial to 14.8 years in the PLCO trial, randomization to screening (relative to control) was not associated with statistically significantly reduced all-cause mortality in any of the 3 trials (CAP trial: RR, 0.99 [95% CI, 0.94-1.03]; ERSPC trial: RR, 1.00 [95% CI, 0.98-1.02]; PLCO trial: RR, 0.98 [95% CI, 0.95-1.00]) (Table 1).[15,29,30]

Harms of Screening

Key Question 2. What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up?

Evidence on the harms of PSA screening and diagnostic follow-up derives from the PLCO, CAP, and ERSPC trials (n = 647 906), as well as 2 good-quality and 3 fair-quality cohort studies (n = 297 971).[15,27,29,30,45-55]

False-Positive Testing and Diagnostic Biopsies

Among men who underwent at least 1 PSA screen during the initial 4 (of 6) PLCO screening rounds (n = 32 576), 10.4% received at least 1 false-positive PSA screening result,[56] compared with 17.8% of men who were screened at least once within 5 ERSPC centers (n = 61 604).[50] Across all PLCO screening rounds, 12.6% of men randomized to screening underwent 1 or more biopsies, resulting in a total of 6295 biopsies (16.4 biopsies per 100 men randomized to screening). Within ERSPC, the rate of biopsies among men randomized to screening was higher (27.7 biopsies per 100 men). Of biopsies performed in the 3 trials, 67.7%, 75.8%, and 60.6% did not result in a prostate cancer diagnosis in the PLCO, ERSPC, and CAP trials, respectively.[15,30,52]

Among men undergoing a single round of PSA screening within the Veterans Affairs health system (n = 295 645), 8.5% had a PSA level of 4 ng/mL or greater; of these, 32.9% underwent

subsequent prostate biopsy.[55] Of biopsies performed, 37.2% did not result in a prostate cancer diagnosis.

Physical and Psychological Harms of Screening and Diagnostic Follow-up

Among men who underwent biopsy in the PLCO trial (n = 4861), 2.0% experienced complications consisting predominately of infection, bleeding, or urinary difficulties, while 5.6% of 8313 men undergoing biopsy experienced similar complications in the Veterans Affairs cohort.[55] Among men undergoing biopsy after abnormal PSA screening results, postbiopsy hospitalization ranged from 0.5% to 1.6% in 1 trial and 2 cohorts.[53,55,57] Within approximately 1 month of biopsy within a UK cohort (n = 1147),[53] 7.3% of men experienced moderate or serious pain and 5.5% experienced moderate or severe fevers. Prostate biopsy has not been associated with statistically significantly increased risk of death.[47,52,53] Within 3 cohorts (n = 1179),[46,48,49,51] men who had abnormal PSA screening results followed by normal biopsy results had increased prostate cancer–specific worry up to 1 year after biopsy but no increase in depression or trait anxiety.

Overdiagnosis

The percentage of detected cancers that were overdiagnosed was estimated using the excess incidence method applied to screening trials data (eTable 2 in the Supplement).[18] When overdiagnosis was estimated as a percentage of all prostate cancers diagnosed, 16.4% of prostate cancers were overdiagnosed in the PLCO trial, 33.2% in the ERSPC trial, and 40.7% in the CAP trial. When estimated as a percentage of cancers detected by screening during the 2 trials reporting such data, 20.7% of cancers were overdiagnosed in the PLCO trial and 50.4% in the ERSPC trial. The extent of overdiagnosis varied across ERSPC sites, with higher rates of overdiagnosis occurring at 2 sites that also reported statistically significantly reduced prostate cancer mortality with screening.[33,35]

Benefits of Early Detection

Key Question 3. Is there evidence that various treatment approaches for early-stage or screen-detected prostate cancer reduce morbidity and mortality?

Three RCTs (n = 2524)[9,58,59] and 7 cohort studies (n = 64 965)[11,60-65] assessed morbidity and mortality with radical prostatectomy compared with conservative management, and 1 RCT (n = 1090)[58] and 7 cohort studies (n = 60 585)[11,60-65] compared radiation therapy with conservative management (**Table 2**). Conservative management in these studies consisted of observation without treatment, active surveillance, watchful waiting, or a combination of these approaches. Comparative studies of benefits and harms associated with other treatment modalities are summarized in the full evidence report.

The ProtecT trial randomized men with localized, screen-detected prostate cancer to radical prostatectomy, radiation therapy (with neoadjuvant androgen deprivation therapy), or active surveillance (consisting of periodic PSA monitoring without surveillance biopsy).[58] During a median follow-up of 10 years, 54.8% of men randomized to active surveillance received treatment, mostly commonly radical prostatectomy; prostate cancer survival was approximately 99% in each group, with no statistically significant differences in prostate cancer mortality or all-cause mortality.

In the Scandinavian Prostate Cancer Group Trial-4 (SPCG-4), which included men with clinically diagnosed, predominately palpable cancers, radical prostatectomy was associated with statistically significantly reduced prostate cancer mortality (RR, 0.56 [95% CI, 0.41-0.77]) and all-cause mortality (RR, 0.71 [95% CI, 0.59-0.86]), compared with watchful waiting.[59] In the US Prostate Cancer Intervention vs Observation Trial (PIVOT), in which 50% of men had screen-detected rather than clinically detected cancers, radical prostatectomy did not significantly reduce either prostate cancer mortality (RR, 0.65 [95% CI, 0.41-1.03]) or all-cause mortality (RR, 0.92 [95% CI, 0.82-1.02]), compared with conservative management.[9]

In the ProtecT trial, incidence of metastatic disease among men randomized to active surveillance (6.3 cases per 1000 person-years) was higher than among men randomized to radical prostatectomy or radiation therapy (2.4 and 3.0 cases per 1000 person-years; $P = .004$ for overall difference across groups). Approximately 27 (95% CI, 16-77) and 32 (95% CI, 18-143) men with screen-detected localized cancer would need to be treated with radical prostatectomy and radiation therapy (rather than active surveillance), respectively, to prevent 1 man from progressing to metastatic disease within 10 years. In both the SPCG-4 and PIVOT trials, radical prostatectomy was also associated with reduced progression to metastatic or systemic disease (SPCG-4: RR, 0.57 [95% CI, 0.44-0.75]; PIVOT: HR, 0.64 [95% CI, 0.42-0.97]).[9,59]

Compared with conservative management, radical prostatectomy and radiation therapy were associated with reduced prostate cancer mortality and all-cause mortality in several fair- to good-quality cohort studies (Table 2).[60-65] However, cohort study estimates often diverged from RCT estimates, and cohort studies of treatments may be susceptible to residual confounding.

Harms of Treatment

Key Question 4. What are the harms of the various treatment approaches for early-stage or screen-detected prostate cancer?

Three RCTs (n = 2524)[66-68] and 11 cohort studies (n = 8809)[10,11,69-78] compared harms among men treated with radical prostatectomy compared with conservative management, and 6 uncontrolled studies of surgical harms related to radical prostatectomy were included.[79-84] Two RCTs (n = 1198)[66,67,85] and 12 cohort studies (n = 4762)[10,11,69-78,86] compared harms among men treated with radiation therapy compared with conservative management, and 1 uncontrolled observational study of radiation therapy was included (n = 3180).[87]

Both urinary incontinence and erectile dysfunction occurred more commonly in men who underwent radical prostatectomy than in men receiving conservative management (**Figure 3** and **Figure 4**). Pooled relative risks of incontinence with radical prostatectomy were 2.27 (95% CI, 1.82-2.84; $I^2 = 0.0\%$) in 3 RCTs and 2.75 (95% CI, 1.78-4.23; $I^2 = 63.0\%$) in 6 cohort studies. Based on risk differences estimated from RCT data, 7.9 men (95% CI, 5.4-12.2) would need to be treated with radical prostatectomy rather than conservative management for 1 additional man to develop incontinence.

In pooled meta-analyses of the 3 RCTs, there was marked statistical heterogeneity in the relative risk of erectile dysfunction with radical prostatectomy ($I^2 = 87.5\%$), which was attributable to a disparate outcome from the ProtecT trial, in which many men

Table 2. Prostate Cancer and All-Cause Mortality With Radical Prostatectomy or Radiation Therapy (Intervention) Compared With Conservative Management (Control) (Key Question 3)[a]

Source	Study Design (Quality)[b]	No. of Participants		Age Range, y	Median Follow-up, y	Prostate Cancer Mortality			All-Cause Mortality		
						Deaths, No. (%)			Deaths, No. (%)		
		Intervention	Control			Intervention	Control	RR (95% CI)	Intervention	Control	RR (95% CI)
Radical Prostatectomy											
ProtecT,[58] 2016 (United Kingdom)	RCT (good)	553	545	49-69	10.0	5 (0.9)	8 (1.5)	0.63 (0.21-1.93)[c]	55 (9.9)	59 (10.8)	0.93 (0.65-1.35)[c]
SPCG-4,[59] 2014 (Sweden, Finland, Iceland)	RCT (good)	347	348	NR	13.4	63 (17.7)	99 (28.7)	0.56 (0.41-0.77)	200 (56.1)	247 (68.9)	0.71 (0.59-0.86)
PIVOT,[9] 2017 (United States)	RCT (good)	364	367	40-75	12.7	27 (7.4)	42 (11.4)	0.65 (0.41-1.03)	223 (61.3)	245 (66.8)	0.92 (0.82-1.02)
Barocas et al,[11] 2017 (United States)	Cohort (good)	1523	429	<80	3.3	1 (0.1)	0	NR	18 (1.3)	12 (2.9)	NR
Ladjevardi et al,[60] 2010 (Sweden)	Cohort (fair)	12 950	12 645	<75	4.4	NR	NR	NR	NR	NR	0.36 (0.32-0.40)[c]
Schymura et al,[61] 2010 (United States)	Cohort (fair)	1310	614	NR	5.0[d]	NR	NR	NR	6.3[e]	24.5[e]	NR
Stattin et al,[62] 2010 (Sweden)	Cohort (fair)	3399	2021	<70	8.2	56 (1.7)	58 (2.9)	0.49 (0.34-0.71)	286 (8.4)	413 (20.4)	0.49 (0.41-0.57)
Zhou et al,[63] 2009 (United States)	Cohort (fair)	936	2306	≥65	7.0[d]	NR	NR	0.25 (0.13-0.48)[c]	NR	NR	0.32 (0.25-0.41)[c]
Albertsen et al,[64] 2007 (United States)	Cohort (fair)	802	114	≤75	13.3	64 (8.0)	18 (16.0)	0.29 (0.17-0.52)[c]	216 (27.0)	65 (57.0)	NR
Wong et al,[65] 2006 (United States)	Cohort (good)	13 292	12 608	65-80	12.0[d]	NR	NR	NR	NR	NR	0.50 (0.47-0.53)
Radiation Therapy											
ProtecT,[58] 2016 (United Kingdom)	RCT (good)	545	545	49-69	10.0	4 (0.7)	8 (1.5)	0.51 (0.15-1.69)[c]	55 (10.1)	59 (10.8)	0.94 (0.65-1.36)[c]
Barocas et al,[11] 2017 (United States)	Cohort (good)	598	429	<80	3.3	2 (0.3)	0	NR	21 (3.9)	12 (2.9)	NR
Ladjevardi et al,[60] 2010 (Sweden)	Cohort (fair)	6308	12 645	<75	4.4	NR	NR	NR	NR	NR	0.54 (0.49-0.59)[c]
Schymura et al,[61] 2010 (United States)	Cohort (fair)	1037	614	NR	5.0[d]	NR	NR	NR	14.0[e]	24.5[e]	NR
Stattin et al,[62] 2010 (Sweden)	Cohort (fair)	1429	2021	<70	8.2	40 (2.8)	58 (2.9)	0.70 (0.45-1.09)	196 (13.7)	413 (20.4)	0.68 (0.57-0.82)
Zhou et al,[63] 2009 (United States)	Cohort (fair)	879	2306	≥65	7.0[d]	NR	NR	0.66 (0.41-1.04)[c]	NR	NR	0.63 (0.53-0.75)[c]
Albertsen et al,[64] 2007 (United States)	Cohort (fair)	702	114	≤75	13.3	126 (18.0)	18 (16.0)	0.65[c]	393 (55.0)	65 (57.0)	0.83 (0.67-1.11)[c]
Wong et al,[65] 2006 (United States)	Cohort (good)	18 249	12 608	65-80	12.0[d]	NR	NR	NR	NR	NR	0.81 (0.78-0.85)[c]

Abbreviations: CM, conservative management, NR, not reported; PIVOT, Prostate Cancer Intervention vs Observation Trial; ProtecT, Prostate Testing for Cancer and Treatment trial; RCT, randomized clinical trial; RR, relative risk.

[a] The comparator for each study was a control group receiving conservative management (ie, active surveillance, watchful waiting, deferred treatment or no treatment).

[b] Assessed using criteria from the US Preventive Services Task Force.[6]

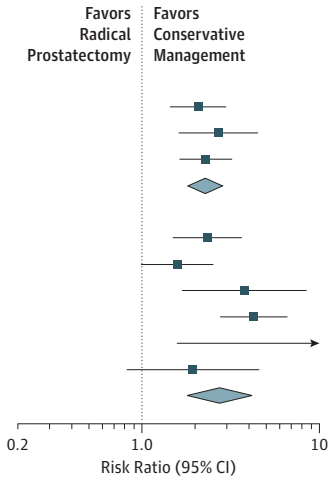
[c] Study reported only hazard ratios (HRs). Confidence intervals are excluded when not reported.

[d] Maximum follow-up (ie, duration of study period).

[e] Study reported only percentages.

Figure 3. Risk of Urinary Incontinence After Radical Prostatectomy Compared With Conservative Management (Key Question 4)[a]

Source	No. of Patients With Urinary Incontinence/Total No. of Patients (%)		ARD, %	Risk Ratio (95% CI)
	Radical Prostatectomy	Conservative Management		
RCT				
Donovan et al,[66] 2016	79/455 (17.4)	38/453 (8.4)	9.0	2.07 (1.44-2.98)
Wilt et al,[68] 2012	49/287 (17.1)	18/284 (6.3)	10.7	2.69 (1.61-4.51)
Johansson et al,[88] 2011	79/162 (48.8)	33/155 (21.3)	27.5	2.29 (1.63-3.22)
Subtotal (I^2 = 0.0%)	207/904 (22.9)	89/892 (10.0)	14.5	2.27 (1.82-2.84)
Cohort study				
Barocas et al,[11] 2017	175/1307 (13.4)	20/349 (5.7)	7.7	2.34 (1.49-3.65)
Chen et al,[10] 2017	58/360 (16.1)	21/206 (10.2)	5.9	1.58 (0.99-2.53)
Smith et al,[77] 2009	111/981 (11.3)	6/200 (3.0)	8.3	3.77 (1.68-8.46)
Hoffman et al,[69] 2003	484/1373 (35.3)	19/230 (8.3)	27.0	4.27 (2.76-6.60)
Schapira et al,[75] 2001	16/36 (44.4)	1/25 (4.0)	40.4	11.11 (1.57-78.47)
Litwin,[73] 1995	19/98 (19.4)	6/60 (10.0)	9.4	1.94 (0.82-4.58)
Subtotal (I^2 = 63.0%)	863/4155 (20.8)	73/1070 (6.8)	14.6	2.75 (1.78-4.23)

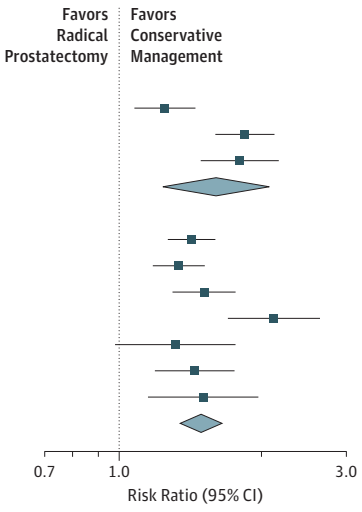


ARD indicates absolute risk difference; RCT, randomized clinical trial; RR, relative risk.

[a] Conservative management encompasses management strategies in which active treatment is deferred or postponed indefinitely (ie, active surveillance, watchful waiting, or no treatment).

Figure 4. Risk of Erectile Dysfunction After Radical Prostatectomy Compared With Conservative Management (Key Question 4)[a]

Source	No. of Patients With Erectile Dysfunction/Total No. of Patients (%)		ARD, %	Risk Ratio (95% CI)
	Radical Prostatectomy	Conservative Management		
RCT				
Donovan et al,[66] 2016	227/457 (49.7)	174/437 (39.8)	9.9	1.25 (1.08-1.45)
Wilt et al,[68] 2012	231/285 (81.1)	124/281 (44.1)	36.9	1.84 (1.59-2.12)
Johansson et al,[88] 2011	128/159 (80.5)	71/158 (44.9)	35.6	1.79 (1.48-2.16)
Subtotal (I^2 = 87.5%)[b]	586/901 (65.0)	369/876 (42.1)	27.3	1.60 (1.23-2.07)
Cohort study				
Barocas et al,[11] 2017	893/1307 (68.3)	168/349 (48.1)	20.2	1.42 (1.27-1.59)
Chen et al,[10] 2017	285/373 (76.4)	130/227 (57.3)	19.1	1.33 (1.18-1.51)
Smith et al,[77] 2009	695/981 (70.8)	94/200 (47.0)	23.8	1.51 (1.29-1.76)
Hoffman et al,[69] 2003	757/1373 (55.1)	60/230 (26.1)	29.0	2.11 (1.69-2.64)
Schapira et al,[75] 2001	33/37 (89.2)	17/25 (68.0)	21.2	1.31 (0.98-1.76)
Siegel et al,[76] 2001	353/392 (90.1)	40/64 (62.5)	27.6	1.44 (1.19-1.75)
Litwin,[73] 1995	76/98 (77.6)	31/60 (51.7)	25.9	1.50 (1.15-1.96)
Subtotal (I^2 = 59.2%)	3092/4561 (67.8)	540/1155 (46.8)	23.6	1.49 (1.34-1.65)



ARD indicates absolute risk difference; RCT, randomized clinical trial; RR, relative risk.

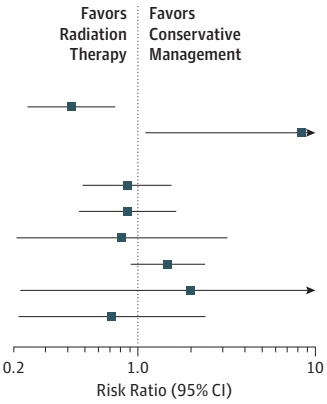
[a] Conservative management encompasses management strategies in which active treatment is deferred or postponed indefinitely (ie, active surveillance, watchful waiting, or no treatment).

[b] Data from Donovan et al[66] are the source of marked heterogeneity, potentially because of the crossover of many active surveillance patients to radical treatments during the 6 years of median follow-up. Excluding those data and pooling only data from Wilt et al[68] and Johansson et al[88] results in RR = 1.82 (95% CI, 1.62-2.04; I^2 = 0.0%).

randomized to active surveillance received radical treatments during the comparatively long 6 years of median follow-up for harms (Figure 4).[66] After excluding the ProtecT trial from the RCT meta-analysis, the pooled relative risk of erectile dysfunction associated with radical prostatectomy vs conservative management was 1.82 (95% CI, 1.62-2.04; I^2 = 0.0%). Based on estimated risk differences from this pooled analysis, 2.7 men (95% CI, 2.2-3.6) need to be treated with radical prostatectomy rather than conservative management for 1 additional man to develop erectile dysfunction.

Figure 5. Urinary Incontinence After Radiation Therapy Compared With Conservative Management (Key Question 4)[a]

Source	No. of Patients With Urinary Incontinence/Total No. of Patients (%)		ARD, %	Risk Ratio (95% CI)
	Radiation Therapy	Conservative Management		
RCT[b]				
Donovan et al,[66] 2016	16/452 (3.5)	38/453 (8.4)	-4.8	0.42 (0.24-0.75)
Fransson et al,[85] 2001	10/59 (16.9)	1/49 (2.0)	14.9	8.31 (1.10-62.63)
Cohort study[b]				
Barocas et al,[11] 2017	24/482 (5.0)	20/349 (5.7)	-0.8	0.87 (0.49-1.55)
Chen et al,[10] 2017	15/168 (8.9)	21/206 (10.2)	-1.3	0.88 (0.47-1.65)
Smith et al,[77] 2009	3/123 (2.4)	6/200 (3.0)	-0.6	0.81 (0.21-3.19)
Hoffman et al,[69] 2003	71/583 (12.2)	19/230 (8.3)	3.9	1.47 (0.91-2.39)
Schapira et al,[75] 2001	3/38 (7.9)	1/25 (4.0)	3.9	1.97 (0.22-17.92)
Litwin,[73] 1995	4/56 (7.1)	6/60 (10.0)	-2.9	0.71 (0.21-2.40)



ARD indicates absolute risk difference; RCT, randomized clinical trial; RR, relative risk.

[a] Conservative management encompasses management strategies in which active treatment is deferred or postponed indefinitely (ie, active surveillance, watchful waiting, or no treatment).

[b] Meta-analysis not performed because of observed variability in the plots; no pooled estimates available.

In 5 longitudinal studies,[9-11,66,77] mean urinary and sexual function scores decreased to a nadir in the initial year after radical prostatectomy with some longer-term improvement, although urinary and sexual function typically remained statistically significantly lower than baseline up to 6 years after the procedure.

Data on surgical complications and perioperative mortality associated with radical prostatectomy are summarized in eTable 3 in the Supplement. In a cohort of US men undergoing radical prostatectomy, 1.7% experienced major medical complications (most commonly cardiac or pulmonary) and 5.3% experienced major surgical complications (requiring reintervention) within 30 days of surgery.[82] Across 2 trials and 6 cohort studies, the median perioperative mortality with radical prostatectomy was 0.29% (range, 0.0%-0.52%).

There was marked variability across 8 studies comparing incidence of urinary incontinence with radiation and conservative management, so these were not meta-analyzed (**Figure 5**). In the ProtecT trial, the prevalence of erectile dysfunction at 6 years of median follow-up was similar among men randomized to radiation therapy vs active surveillance (39.8% vs 36.2%; RR, 0.91 [95% CI, 0.77-1.08]), likely attributable to the substantial crossover to radical treatment of men randomized to active surveillance.[66] In contrast, in 8 cohort studies, the prevalence of erectile dysfunction was more common in men treated with radiation therapy compared with men receiving conservative management (pooled RR, 1.31 [95% CI, 1.20-1.42]; I^2 = 22.1%) (**Figure 6**).[10,11,69,73,75-77,86] Based on the cohort data, 6.9 men (95% CI, 5.1-10.7) would need to be treated with radiation therapy rather than conservative management for 1 additional man to develop erectile dysfunction. Although 2 US studies observed longitudinal improvement in adverse effects of radiation therapy on sexual function,[10,11] initial decrements in sexual function associated with radiation therapy persisted throughout a 3-year follow-up period in an Australian cohort.[77]

In the ProtecT trial, 10.4% of men randomized to radiation therapy experienced bothersome bowel symptoms (eg, loose stools, fecal incontinence) at 6-month follow-up, which tended to diminish during the 6-year follow-up.[66] Two US cohort studies suggest a similar pattern,[10,11] in contrast to an Australian cohort study in which adverse bowel effects of radiation therapy persisted during 3 years of follow-up.[77]

In 3 trials comparing radical prostatectomy with conservative management,[9,66,88] randomization to radical prostatectomy was not associated with differences in anxiety, depression, or physical or mental health status. Cohort studies[11,70-72,74,75,77,78] also found no evidence of an adverse effect of radical prostatectomy on generic quality-of-life measures compared with conservative management. Similarly, 2 trials[66,67] and 9 cohort studies[11,70-73,75,77,78,86] suggest no substantive adverse effect of radiation therapy on general measures of physical, mental, or global health status compared with conservative management.

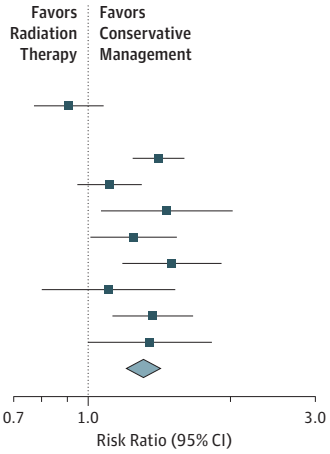
Accuracy of Risk Calculators

Key Question 5. Is there evidence that use of a prebiopsy prostate cancer risk calculator, in combination with PSA-based screening, accurately identifies men with clinically significant prostate cancer compared with PSA-based screening alone?

Fourteen articles (n = 48 234)[12-14,89-99] provided evidence on discrimination or calibration of risk assessment tools for prediction of clinically significant prostate cancer (either Gleason score ≥7 or Stage 2b or higher) among men undergoing prostate biopsy (**Table 3**). All were external validation studies of either the Prostate Cancer Prevention Trial (PCPT) risk calculator or the ERSPC risk calculator. Most cohorts consisted of men referred to tertiary or academic centers and typically included both symptomatic men and asymptomatic men with abnormal screening results. No RCTs evaluated the clinical effect of risk calculator use on patient outcomes.

Figure 6. Erectile Dysfunction After Radiation Therapy Compared With Conservative Management (Key Question 4)[a]

Source	No. of Patients With Erectile Dysfunction/Total No. of Patients (%)		ARD, %	Risk Ratio (95% CI)
	Radiation Therapy	Conservative Management		
RCT				
Donovan et al,[66] 2016	162/447 (36.2)	174/437 (39.8)	-3.6	0.91 (0.77-1.08)
Cohort study				
Barocas et al,[11] 2017	326/482 (67.6)	168/349 (48.1)	19.5	1.41 (1.24-1.59)
Chen et al,[10] 2017	120/189 (63.5)	130/227 (57.3)	6.2	1.11 (0.95-1.30)
Thong et al,[86] 2010	43/63 (68.3)	28/60 (46.7)	21.6	1.46 (1.06-2.01)
Smith et al,[77] 2009	72/123 (58.5)	94/200 (47.0)	11.5	1.25 (1.01-1.54)
Hoffman et al,[69] 2003	228/583 (39.1)	60/230 (26.1)	13.0	1.50 (1.18-1.91)
Schapira et al,[75] 2001	30/40 (75.0)	17/25 (68.0)	7.0	1.10 (0.80-1.52)
Siegel et al,[76] 2001	269/315 (85.4)	40/64 (62.5)	22.9	1.37 (1.12-1.66)
Litwin,[73] 1995	39/56 (69.6)	31/60 (51.7)	18.0	1.35 (1.00-1.82)
Cohorts subtotal (I^2 = 22.1%)	1127/1851 (60.9)	568/1215 (46.7)	14.9	1.31 (1.20 , 1.42)



ARD indicates absolute risk difference; RCT, randomized clinical trial; RR, relative risk.

[a] Conservative management encompasses management strategies in which active treatment is deferred or postponed indefinitely (ie, active surveillance, watchful waiting, or no treatment).

Both calculators usually discriminated better than PSA alone between men with and without clinically significant prostate cancer (median area under the curve [AUC] with PCPT calculator, 0.72 [range across 21 cohorts, 0.51-0.88]; median AUC with ERSPC calculator, 0.74 [range across 7 cohorts, 0.69-0.78]; median AUC with PSA alone, 0.68 [range across 16 cohorts, 0.59-0.82]). However, calibration was mixed with underestimation or overestimation of actual risk in several cohorts for each calculator.

Discussion

Table 3 summarizes the evidence contained in this review. Direct evidence from 3 fair-quality trials demonstrates that PSA screening increases prostate cancer detection, especially of localized, less aggressive cancers,[30,39] and evidence from 4 ERSPC sites suggests that screening can reduce the long-term incidence of metastatic disease.[43] While the PLCO and CAP trials found no association between randomization to screening invitation and reduced prostate cancer mortality, the overall ERSPC trial found a relative risk of 0.79 for prostate cancer mortality with screening.[30] Differences in trial outcomes may have been attributable to greater baseline exposure to PSA testing and contamination in the PLCO trial, low adherence to invitation to a single PSA screen in the CAP trial, and higher adherence to screening and biopsy in the ERSPC trial. A recent analysis of individual patient data from both the PLCO and the ERSPC trials suggests that results from both trials are consistent with approximately 25% to 30% relative reduction in the risk of prostate cancer death with screening vs no screening after accounting for differences in baseline risk, screening adherence, contamination, and the intensity of postscreening diagnostic evaluation.[100] In the ERSPC trial, 27 men needed to be diagnosed (and potentially treated) to prevent 1 prostate cancer death, underscoring the potential for overdiagnosis and overtreatment with PSA screening.[30] Evidence is limited on the benefit of screening among men older than 70 years or the differential benefits among African American men or men with a family history of prostate cancer.

Trial data demonstrate that abnormal PSA screening test results are common and that most men referred for biopsy after abnormal screening results will not have prostate cancer.[15,30,52] Biopsy harms include pain, bleeding, and infection,[53] but perhaps the most serious harm of prostate cancer screening is overdiagnosis, because overdiagnosis burdens men with the potential harms of diagnosis and treatment without improving life expectancy or quality of life. It was estimated that 16.4% to 50.4% of prostate cancers were overdiagnosed during the 3 trials, consistent with estimates based on ecological or modeling studies.[4,101-104]

This review assessed both the immediate harms of screening as well as the consequent adverse effects of prostate cancer treatments. Most men undergoing radical prostatectomy will experience long-term sexual difficulties and approximately 17% will experience urinary difficulties, while approximately 36% of men receiving radiation therapy experience erectile problems and many will experience adverse bowel symptoms.[66] Nevertheless, compared with conservative management, active treatments for localized prostate cancer did not clearly compromise overall quality of life or global physical or mental health status, despite adverse sexual, urinary, and bowel effects.[11,66,70-72,74,75,77,86]

The ProtecT trial found similarly high prostate cancer survival among men with screen-detected, early-stage prostate cancer randomized to radical prostatectomy, radiation therapy, or active surveillance. Of men assigned to active surveillance, 45.2% remained under surveillance without receiving active treatment during the 10-year follow-up period, although an increase in the incidence of metastatic disease was observed in the active surveillance group (approximately 6% with active surveillance vs 2 to 3% with active treatment). In contrast to the ProtecT active surveillance protocol

Table 3. Summary of Evidence[a]

Test or Treatment	Study Design	No. of Studies (No. of Participants)	Summary of Findings	Body of Evidence Limitations	Applicability	Overall Quality
Key Question 1: Effectiveness of Screening						
PSA-based screening	RCT	3 (647 906)	RR = 0.79 for prostate-specific mortality in ERSPC; no significant reduction in PLCO or CAP trials. No trial observed significant reduction in all-cause mortality. Within 4 ERSPC sites, screening associated with 3.1 fewer cases of metastatic disease per 1000 men at 12-y follow-up.	Contamination in PLCO control group, and low adherence with single PSA screening in CAP. Variable protocols across ERSPC sites, and ERSPC screening group enrollees with cancer more likely to be treated with radical prostatectomy than similar controls.	Uncertain applicability of ERSPC results to US practice because of lower rate of baseline screening, lower biopsy thresholds (usually PSA ≥3 ng/mL), and higher rate of biopsy than is usual in US practice.	Fair
Key Question 2: Harms of Screening						
PSA-based screening	RCT	3 (647 906)	Cumulative incidence of false-positive results, 10.4%-17.8% among screened men. Among biopsied men, 60.6%-75.8% of biopsies were negative for cancer. In trials, 20.7%-50.4% of screen-detected cancers were overdiagnosed. In PLCO, 20.2 complications per 1000 biopsies (mostly infectious); no increase in mortality with biopsy.	ERSPC sites with variable PSA thresholds for positive test results. Lower biopsy rate after positive screen result in PLCO vs ERSPC (44.8 vs 85.6%). Limited follow-up in the trials (median, 10-13 y) may exaggerate overdiagnosis estimates. Small sample sizes inhibit ability to detect increased mortality after biopsy.	Results from the PLCO trial generalizable to US practice. Rates of biopsy in US practice may be lower than reported by PLCO or ERSPC, as many men may undergo monitoring (eg, repeat PSA testing) instead of biopsy.	Fair
	Cohort	5 (297 971)	Within 7 d of biopsy, 20.0%, 5.7%, and 4.0% of men reported moderate or severe hematospermia, pain, or fevers, respectively; 0.5% to 1.6% of men were hospitalized after biopsy; 10.4% sought outpatient care. Men with abnormal PSA screen results have increased prostate cancer-specific worry up to 1 y; no increase in state anxiety or depression.			
Key Question 3: Effectiveness of Treatments						
Radical prostatectomy	RCT	3 (2524)	1 of 3 trials reported statistically significant reductions in prostate cancer mortality with radical prostatectomy relative to conservative management, and this trial enrolled strictly men with clinically detected, palpable cancers. All 3 trials reported significantly reduced risk of progression to metastatic disease with radical prostatectomy relative to conservative management.	Only the ProtecT trial exclusively randomized men with screen-detected cancer; PIVOT and SPCG-4 included men with higher-risk, clinically detected cancers. Low event rate in ProtecT led to imprecise estimates for prostate cancer and all-cause mortality. Cohort studies vulnerable to confounding by unmeasured patient characteristics.	Active surveillance in ProtecT consisted chiefly of PSA monitoring, which may not be applicable to US settings, where surveillance biopsy may be routine in most active surveillance protocols.	Fair to good
	Cohort	7 (64 965)	Radical prostatectomy associated with statistically significantly reduced prostate cancer mortality in 3 cohorts; 4 of 7 cohorts reported reduced all-cause mortality with radical prostatectomy relative to conservative management.			

(continued)

Table 3. Summary of Evidence[a] (continued)

Test or Treatment	Study Design	No. of Studies (No. of Participants)	Summary of Findings	Body of Evidence Limitations	Applicability	Overall Quality
Radiation therapy	RCT	1 (1090)	ProtecT trial found no significant reductions in prostate cancer or all-cause mortality with radiation therapy vs active surveillance. Radiation therapy associated with significantly reduced risk of progression to metastatic disease (3.0 vs 6.3 per 1000 person-years with radiation therapy and conservative management, respectively).	Only 1 trial (ProtecT) assessed the effectiveness of radiation therapy and was not powered to detect differences in all-cause mortality. Only the ProtecT trial assessed effect of radiation therapy on metastatic disease.	Active surveillance in ProtecT consisted chiefly of PSA monitoring, which may not be applicable to US settings, where surveillance biopsy may be routine in most active surveillance protocols.	Fair to good
	Cohort	7 (60 585)	Radiation therapy was associated with significant reductions in all-cause mortality in 4 of 7 cohorts.	Cohort studies vulnerable to confounding by unmeasured patient characteristics.		
Androgen deprivation therapy	Cohort	3 (103 382)	In instrumental variable analysis, ADT not associated with reduced prostate cancer mortality vs conservative management (HR, 1.01 [95% CI, 0.90-1.14]) or all-cause mortality (HR, 1.04 [95% CI, 0.99-1.09]). Mortality results from other cohorts were mixed.	Small number of cohort studies available. Potential confounding by indication in cohort studies of treatment effectiveness.	Potential bias in study estimates may limit applicability to US clinical practice.	Fair
Key Question 4: Harms of Treatment						
Radical prostatectomy	RCT	3 (2524)	Pooled RR of urinary incontinence with radical prostatectomy vs conservative management, 2.3 (95% CI, 1.8-2.8; I^2 = 0.0%). Pooled RR of erectile dysfunction, 1.6 (95% CI, 1.2-2.1; I^2 = 87.5%). No adverse effect of radical prostatectomy on physical or mental health status, anxiety, or depression relative to conservative management.	Inclusion of ProtecT in meta-analysis of erectile dysfunction may have increased heterogeneity because of (1) relatively long 6-y follow-up; and (2) crossover of >50% of men from conservative management to active treatment. Studies had varying outcome definitions, inconsistent timing of follow-up measurements. Many studies included predominately retropubic rather than robot-assisted radical prostatectomies.	Likely generalizable to US clinical practice.	Fair to good
	Cohort	11 (8809)	Pooled RR of urinary incontinence with radical prostatectomy vs conservative management, 2.75 in 6 cohorts (95% CI, 1.78-4.23; I^2 = 63.0%). Pooled RR of erectile dysfunction, 1.49 in 7 cohorts (95% CI, 1.34-1.65; I^2 = 59.2%). Radical prostatectomy not associated with decrement in generic measures of quality of life vs conservative management.			
	RCT or uncontrolled observational	2 RCTs and 6 cohorts (150 001)	Median perioperative mortality after radical prostatectomy, 0.29% (range across 8 studies, including cohort studies and RCTs, 0.0% to 0.52%). Thromboembolic or cardiovascular complications of radical prostatectomy ranged from 0.4%-9.0%. Surgical complications required reintervention in ≈5% (US cohort).			

(continued)

Table 3. Summary of Evidence[a] (continued)

Test or Treatment	Study Design	No. of Studies (No. of Participants)	Summary of Findings	Body of Evidence Limitations	Applicability	Overall Quality
Radiation therapy	RCT	2 (1198)	Radiation therapy not clearly associated urinary incontinence across 2 RCTs. In ProtecT, radiation therapy not associated with erectile dysfunction vs active surveillance (RR, 0.9 [95% CI, 0.8-1.1]). Bowel dysfunction more common with radiation therapy than conservative management in both trials. No adverse effect of radiation therapy on physical or mental health status, anxiety, or depression, compared with conservative management (1 trial).	54.8% of men in ProtecT who were randomized to conservative management crossed over to active treatment, which may have increased rate of adverse effects in conservative management group. Studies had varying outcome definitions, inconsistent timing of follow-up measurements. Most studies of external-beam radiation therapy; relatively few studies of brachytherapy.	Likely generalizable to US clinical practice.	Fair to good
	Cohort	12 (4762)	Marked variability across studies in estimates of risk of urinary incontinence with radiation therapy vs conservative management. Pooled RR of erectile dysfunction with radiation therapy vs conservative management, 1.31 in 8 cohorts (95% CI, 1.20-1.42; I^2 = 22.1%). Bowel dysfunction more common with radiation therapy vs conservative management (5 cohorts). Radiation therapy not associated with decrement in generic measures of quality of life vs conservative management.			
Androgen deprivation therapy	Cohort	3 (4662)	Increased risk of erectile dysfunction with ADT (RR, range in RR, 1.6-2.9). Worse function across several SF-36 domains (eg, physical function, vitality, emotional role).	Few studies; small sample sizes; varying outcome definitions; inconsistent timing of follow-up measurements.	Likely generalizable to US clinical practice.	Fair
High-intensity focused ultrasound	Uncontrolled observational	7 (2239)	Grade 2 urinary incontinence (ie, leaking with mild activity) or worse ranged from 0.0%-7.3%. Among men with baseline potency, 37.3%-52.7% had erectile dysfunction after treatment (3 studies).	No studies compared HIFU with conservative management; only 1 study had a sample size exceeding 1000 men.	Likely generalizable to US clinical practice.	Fair
Key Question 5: Prebiopsy Risk Calculators to Predict Significant Prostate Cancer						
PCPT and ERSPC risk calculators	Cohort	14 (total 28 cohorts of men) (48 234 biopsies)	Median AUC of PCTP, 0.72 (range, 0.51-0.88 across 21 cohorts) and 0.74 (range, 0.69-0.78 across 7 cohorts) for the ERSPC calculator, vs median AUC of 0.68 with PSA alone (range, 0.59-0.82 across 6 cohorts). Calibration and decision curve analyses mixed for each calculator.	Most cohorts included many symptomatic men in addition to men referred for biopsy after abnormal PSA screening result. ERSPC calculator derived with prostate volume determined by ultrasound rather than digital rectal examination. No RCTs of calculator use.	Results may not generalize to men referred for biopsy after abnormal PSA screening result. Unclear how risk information from calculators would influence biopsy decisions by actual physicians and patients. Effects on long-term prostate cancer outcomes unknown.	Fair

Abbreviations: ADT, androgen deprivation therapy; AUC, area under the curve; HIFU, high-intensity focused ultrasound; HR, hazard ratio; PCPT, Prostate Cancer Prevention Trial; PSA, prostate-specific antigen; RCT, randomized clinical trial; RR, relative risk; SF-36, 36-Item Medical Outcomes Study Short Form Health Survey.

[a] For evidence pertaining to subgroups (eg, age, race/ethnicity, etc.) and general and disease-specific quality of life, please refer to the full evidence synthesis.

that consisted of periodic PSA monitoring, many active surveillance protocols include surveillance biopsy or imaging, which might reduce metastatic disease risk, albeit with added harms associated with repeated biopsy. In contemporary case series, prostate cancer–specific survival estimates for patients receiving active surveillance have been as high as 99% at 10 years of follow-up, although since relatively few men in these series have had extended follow-up, uncertainty remains about long-term outcomes.[105]

This review demonstrates that prebiopsy risk calculators can discriminate between men with and without high-risk cancer better than PSA screening alone, but net clinical benefit of routine calculator use in biopsy decisions is not established by existing evidence. Diagnostic or surveillance strategies based on serum or urine tests or multiparametric magnetic resonance imaging are under study, and some have been recommended by the National Comprehensive Cancer Network.[106] Further research is needed to elucidate whether the use of adjunctive tests can improve the balance of benefits and harms of PSA-based prostate cancer screening in community settings.

Because the lead time for prostate cancer may be very long, current screening trials (with <15 years of median follow-up) might underestimate mortality benefits. Limited follow-up duration from trials may also exaggerate estimates of overdiagnosis based on extra incidence, although estimates based on longer-term follow-up may be influenced by posttrial PSA testing. In the PLCO trial, contamination among control group participants would be expected to bias trial results toward the null. The ERSPC trial, in contrast, was limited by unexplained stage-adjusted differences in prostate cancer treatments by study group that may have biased results in favor of screening.[107] There was also variation across ERSPC sites in recruitment methods, screening intervals, use of ancillary testing, and PSA thresholds for biopsy referral. The CAP trial was limited by the low adherence of intervention participants to the invitation to a single PSA screen. Across all studies, relatively few men older than 70 years were enrolled, and there is limited evidence about the differential benefits or harms of screening for men at higher risk.

Of 4 randomized trials comparing the effectiveness and harms of treatments for localized prostate cancer, only the ProtecT trial exclusively enrolled men with screen-detected cancer, and prostate cancer–specific and all-cause mortality were extremely low in that study.[58] Other treatment RCTs enrolled many or mostly men with clinically detected prostate cancer.[59,68,85] Thus, uncertainty remains about the generalizability of treatment trial results to US men with early-stage prostate cancer detected by PSA screening.

Limitations

This review may be limited by language or publication biases. Aside from uncontrolled studies of treatment harms, few or no studies were found on comparative effectiveness of new or novel treatment modalities, such as alternative surgical approaches (eg, nerve-sparing or robotic surgery), cryotherapy, or high-intensity focused ultrasound. Because of the limited use and variable definitions of active surveillance during the time periods of most included studies, active surveillance and watchful waiting were grouped in analyses, although outcomes may differ between these conservative approaches.

Conclusions

PSA screening may reduce prostate cancer mortality risk but is associated with false-positive results, biopsy complications, and overdiagnosis. Compared with conservative approaches, active treatments for screen-detected prostate cancer have unclear effects on long-term survival but are associated with sexual and urinary difficulties.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fenton, Weyrich, Durbin.
Critical revision of the manuscript for important intellectual content: Fenton, Durbin, Liu, Bang, Melnikow.
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