

Review

Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

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Abstract

Background: Screening can detect prostate cancer in earlier, asymptomatic stages when treatments might be more effective.

Purpose: To update the 2002 and 2008 U.S. Preventive Services Task Force evidence reviews on screening and treatments for prostate cancer.

Data Sources: MEDLINE (2002 to July 2011) and the Cochrane Library Database (through second quarter of 2011).

Study Selection: Randomized trials of prostate-specific antigen-based screening, randomized trials and cohort studies of prostatectomy or radiation therapy versus watchful waiting, and large observational studies of perioperative harms.

Data Extraction: Investigators abstracted and checked study details and quality using predefined criteria.

Data Synthesis: Of 5 screening trials, the 2 largest and highest-quality studies reported conflicting results. One found screening was associated with reduced prostate cancer-specific mortality compared with no screening in a subgroup of men age 55 to 69 years after 9 years (relative risk, 0.80 [95% CI, 0.65 to 0.98]; absolute risk reduction, 0.07 percentage point). The other found no statistically significant effect after 10 years (relative risk, 1.1 [CI, 0.80 to 1.5]). After 3 or 4 screening rounds, 12% to 13% of screened men had false-positive results. Serious infections or urinary retention occurred after 0.5% to 1.0% of prostate biopsies. There were 3 randomized trials and 23 cohort studies of treatments. One good-quality trial found that prostatectomy for localized prostate cancer decreased risk for prostate cancer-specific mortality compared with watchful waiting through 13 years of follow-up (relative risk, 0.62 [CI, 0.44 to 0.87]; absolute risk reduction, 6.1%). Benefits appeared limited to men younger than 65 years of age. Treating approximately 3 men with prostatectomy or 7 men with radiation therapy instead of watchful waiting would each result in 1 additional case of erectile dysfunction. Treating approximately 5 men with prostatectomy would result in 1 additional case of urinary incontinence. Prostatectomy was associated with perioperative death (about 0.5%) and cardiovascular events (0.6% to 3%), and radiation therapy was associated with bowel dysfunction.

Limitation: Only English-language articles were included. Few studies evaluated newer therapies.

Conclusion: Prostate-specific antigen-based screening results in small or no reduction in prostate cancer-specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary.

Primary Funding Source: Agency for Healthcare Research and Quality.

Editors' Notes

Context

- Examining tradeoffs between potential benefits and harms of prostate screening is a hot topic.

Contribution

- This updated systematic review for the U.S. Preventive Services Task

Force found the following: screening based on prostate-specific antigen led to detection of more cases of prostate cancer; there was small to no reduction in prostate cancer-specific mortality after about 10 years; and several potential harms are related to false-positive tests and subsequent evaluations and therapies.

Caution

- Evidence regarding the mortality-associated benefits of screening conflicted.

Implication

- Clinical benefits of screening for prostate cancer remain uncertain. Consequences include evaluations and treatments that have associated complications and that may be unnecessary.

—The Editors

Editor's Note: The related draft recommendation statement will soon be available for public comment at www.uspreventiveservicestaskforce.org/. The USPSTF will consider all submitted comments when it finalizes its recommendation. To sign up for notification about the posting of draft recommendation statements, please visit the USPSTF Web site.

Prostate cancer is the most commonly diagnosed cancer in U.S. men (1–3). Prostate-specific antigen (PSA)-based screening can detect prostate cancers in earlier, asymptomatic stages, when treatments might be more effective.

The U.S. Preventive Services Task Force (USPSTF) last reviewed the evidence on prostate cancer screening (4) and issued recommendations in 2008 (5). Since then, large trials of prostate cancer screening have been published (6, 7). Benefits and harms of treatments for prostate cancer were last reviewed by the USPSTF in 2002 (8). This article summarizes 2 recent reviews commissioned by the USPSTF to synthesize the current evidence on screening (9) and treatments (10) for localized prostate cancer.

Methods

Scope of the Review

We followed a standardized protocol and developed an analytic framework that focused on the following key questions:

1. Does PSA-based screening decrease prostate cancer-specific or all-cause mortality?
2. What are the harms of PSA-based screening for prostate cancer?
3. What are the benefits of treatment of early-stage or screening-detected prostate cancer?
4. What are the harms of treatment of early-stage or screening-detected prostate cancer?

Detailed methods and data for the review, including search strategies, multiple evidence tables with quality ratings of individual studies, and pooled analyses of some harms data, are available in the full report (10). Also of note, androgen deprivation therapy, cryotherapy, and high-intensity focused ultrasonography are reviewed in the full report (10) but are not presented in this manuscript.

Data Sources and Searches

We searched OVID MEDLINE from 2002 to July 2011, PubMed from 2007 to July 2011, and the Cochrane Database through the second quarter of 2011 and reviewed reference lists to identify relevant articles published in the English language.

Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. We restricted inclusion to published studies. We included randomized trials of screening for prostate cancer in asymptomatic men (including those with chronic, mild lower urinary tract symptoms) that incorporated 1 or more PSA measurements, with or without additional methods, such as digital rectal examination, and reported all-cause or prostate cancer-specific mortality or harms associated with screening. We also included randomized trials and cohort studies of men with screening-detected prostate cancer that compared radical prostatectomy or radiation therapy (the most common primary treatments for localized prostate cancer [11, 12]) with watchful waiting and reported all-cause mortality, prostate cancer-specific mortality, or prespecified harms (quality of life or functional status, urinary incontinence, bowel dysfunction, erectile

dysfunction, psychological effects, and surgical complications). We included studies of clinically localized (T1 or T2) prostate cancer because more than 90% of screening-detected prostate cancers are localized (6, 7, 13). We included only studies that reported risk estimates for mortality adjusted at a minimum for age at diagnosis and tumor grade (no study reported adjusted risk estimates for treatment harms). We also included large ($n > 1000$) uncontrolled observational studies of perioperative mortality and surgical complications.

We classified “no treatment,” “observation,” or “deferred treatment” as watchful waiting because patients probably received at least watchful waiting. We also grouped watchful waiting with active surveillance because studies of active surveillance provided insufficient information to determine whether more active follow-up actually occurred (14), and older studies used these terms interchangeably.

Data Extraction and Quality Assessment

One investigator abstracted details about the patient population, study design, analysis, duration of follow-up, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF (15) to rate the quality of each study as good, fair, or poor. Discrepancies were resolved through a consensus process.

Data Synthesis and Analysis

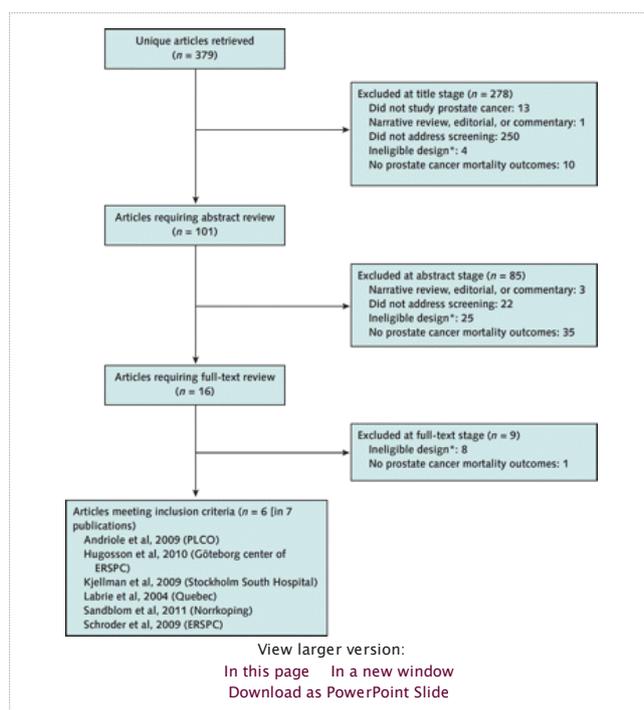
We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, and poor) using methods developed by the USPSTF on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence (15). We synthesized results of treatment studies descriptively, using medians and ranges, because few randomized, controlled trials (RCTs) were available and studies varied in the populations and interventions evaluated, methodologic quality, duration of follow-up, and other factors. We stratified results according to study type and qualitatively assessed effects of study quality, duration of follow-up, year of publication, and mean age on results.

Role of the Funding Source

This study was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Agency staff and USPSTF members helped develop the scope of this work and reviewed draft manuscripts. The draft systematic reviews were reviewed by external peer reviewers not affiliated with the USPSTF, then revised for the final version. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit.

Results

Appendix Figures 1 and 2 show the results of the search and study selection process.

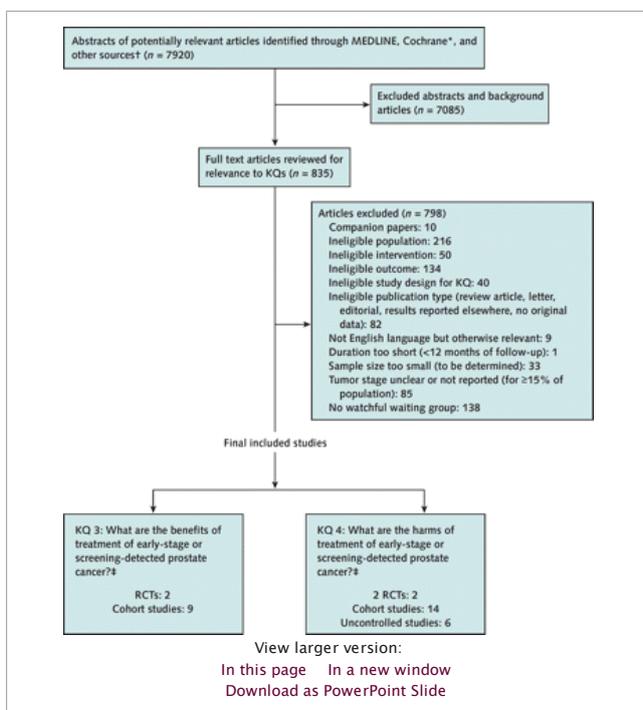


Appendix Figure 1. Summary of literature search and selection: effectiveness and harms of screening. [↗ Web-Only](#)

BMJ = British Medical Journal; ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian study.

* Not a randomized, controlled trial; systematic review; or meta-analysis; or was a nonrandomized analysis of a randomized, controlled trial.

† These meta-analysis are not covered in this manuscript but are evaluated in a separate review (9).



Appendix Figure 2. Summary of literature search and selection: effectiveness and harms of treatment. [↗ Web-Only](#)

KQ = key question; RCT = randomized, controlled trial.

* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

† Identified from reference lists, suggested by experts, or other methods.

‡ Excluding studies of androgen deprivation therapy, cryotherapy, and high-intensity focused ultrasonography (see the full technical report [10]).

We identified 2 fair-quality (6, 7) and 3 poor-quality (16–20) randomized trials of PSA-based screening (Appendix Table 1). We also included a report describing results from a single center (21) participating in a fair-quality trial (7). Sample sizes ranged from 9026 to 182 160 and maximum follow-up from 11 to 20 years (median, 6 to 14 years).

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Appendix Table 1. Randomized, Controlled Trials of Prostate-Specific Antigen-Based Screening [↗ Web-Only](#)

We identified 11 studies (2 RCTs [22–29] and 9 cohort studies [30–38]) on benefits of prostate cancer treatments and 16 studies (2 RCTs [39–42] and 14 cohort studies [43–58]) on harms (Appendix Table 2). Sample sizes ranged from 72 to 44 630 and duration of follow-up from 1 to 23 years. Four studies were rated good quality (23, 42, 52, 56, 58), 1 poor quality (29), and the remainder fair quality. Frequent methodologic shortcomings were failure to describe loss to follow-up (6 cohort studies and all 3 RCTs met this criterion) and inadequate

blinding of outcome assessors (no cohort studies and 1 RCT met this criterion). Only 2 studies (33, 40) clearly described the control group intervention (Appendix Table 1). We also included 6 observational studies (59–64) of surgical complications after prostatectomy.

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Appendix Table 2. Studies of Treatments [Web-Only](#)

Key Question 1: Does PSA-Based Screening Decrease Prostate Cancer–Specific or All-Cause Mortality?

The fair-quality U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial randomly assigned 76 693 men between 55 and 74 years of age to annual PSA screening in combination with digital rectal examination versus usual care (6). After 7 years' (complete) follow-up, screening was associated with increased prostate cancer incidence (relative risk [RR], 1.2 [95% CI, 1.2 to 1.3]) but no effect on prostate cancer–specific (RR 1.1 [CI, 0.75 to 1.7]) or all-cause (RR, 0.98 [CI, 0.92 to 1.0]) mortality. Similar results were observed after 10 years (67% of sample; RR, 1.1 [CI, 0.80 to 1.5]). Up to 52% of men assigned to usual care underwent a PSA test at some point during the trial, and 44% of trial participants had undergone PSA screening before entry.

The fair-quality European Randomized Study of Screening for Prostate Cancer (ERSPC) randomly assigned 182 000 men age 50 to 74 years from 7 countries to PSA testing every 2 to 7 years (depending on center and year) or to usual care (7). Data from 2 other study centers were excluded for reasons not specified in the study protocol. Levels of PSA for diagnostic evaluation ranged from 2.5 to 4.0 mcg/L (1 center used 10 mcg/L for several years). Recruitment and randomization procedures and age eligibility also varied. After a median of 9 years, prostate cancer incidence was higher in the screened group (net increase, 34 per 1000 men), but there was no statistically significant difference in prostate cancer–specific mortality (RR, 0.85 [CI, 0.73 to 1.0]). A prespecified subgroup analysis of 162 243 men age 55 to 69 years found that screening was associated with reduced prostate cancer–specific mortality (RR, 0.80 [CI, 0.65 to 0.98]; absolute risk reduction, 0.07 percentage point), for an estimated 1410 men invited to screening and 48 treated to prevent 1 prostate cancer–specific death.

After the publication of the main ERSPC results, 1 participating center (Göteborg, Sweden) reported results separately (21). It found PSA screening (threshold, 2.5 to 3.0 mcg/L) every 2 years in 20 000 men age 50 to 64 years to be associated with increased prostate cancer incidence (hazard ratio [HR], 1.6 [CI, 1.5 to 1.8]) and decreased risk for prostate cancer–specific mortality (RR, 0.56 [CI, 0.39 to 0.82]; absolute risk reduction, 0.34 percentage point) after a median of 14 years. Outcomes for 60% of participants were included in the main ERSPC report (7). Although no other center separately reported results, only exclusion of the Swedish center data from the overall ERSPC analysis resulted in loss of the statistically significant effect of screening on prostate cancer–specific mortality (RR, 0.84 [CI, 0.70 to 1.01]), suggesting better results than the other centers (7).

Three poor-quality trials (number of men invited to screening ranged from 1494 to 31 333) found no difference between screening–invited and control groups in prostate cancer–specific mortality risk (16, 17, 20). Two of the trials (17, 19) were included in the 2008 USPSTF review (4); results after 5 years' additional follow-up are now available from 1 of the trials (20). Methodologic shortcomings in these trials included failure to describe adequate randomization or allocation concealment methods, poorly described loss to follow-up, and unclear masking of outcomes assessors. One trial used a high PSA cut-point (10 mcg/L) (16).

Key Question 2: What Are the Harms of PSA-Based Screening for Prostate Cancer?

Direct harms of PSA-based screening were reported in the ERSPC and PLCO trials (6, 7). The Finnish center of the ERSPC trial found that 12% of men received at least 1 false-positive result after 3 rounds of PSA testing (cutoff, 4.0 mcg/L) (65). For the entire ERSPC trial, 76% of prostate biopsies for an elevated PSA level identified no cancer (7). In the PLCO trial, the cumulative risk for at least 1 false-positive result was 13% after 4 PSA tests (cutoff, 4.0 mcg/L), with a 5.5% risk for undergoing at least 1 biopsy due to a false-positive test result (66).

Physical harms of screening in the PLCO trial included bleeding or pain from digital rectal examination (0.3 event per 10 000 screened); bruising or fainting due to venipuncture (26 events per 10 000 screened); and biopsy complications, such as infection, bleeding, and urinary difficulties (68 events per 10 000 evaluations) (6). The Rotterdam, Netherlands, center of the ERSPC trial reported that among 5802 biopsies performed, 200 men (3.5%) developed a fever, 20 (0.4%) experienced urinary retention, and 27 (0.5%) required hospitalization for

signs of prostatitis or urosepsis (67).

None of the RCTs of PSA-based screening provided information on potential psychological harms, such as anxiety or adverse effects on health-related quality of life. The 2008 USPSTF review found evidence that false-positive PSA test results are associated with adverse psychological effects but could not estimate their magnitude (4).

Key Question 3: What Are the Benefits of Treatment of Early-Stage or Screening-Detected Prostate Cancer?

Prostatectomy

Prostatectomy was compared with watchful waiting in 1 good-quality RCT ($n = 695$) of men with localized (stage T1b, T1c, or T2) prostate cancer (Appendix Table 3) (22–24, 28). It did not specifically enroll men with screening-detected prostate cancer, and about 75% of cancers were palpable (stage T2). By comparison, 36% of localized cancers in the ERSPC screening trial were stage T2 (7). The 2002 USPSTF review included results through 6 years of follow-up (28). Data now available through 15 years showed a sustained decrease in risk for prostate cancer-specific mortality (15% vs. 21%; RR, 0.62 [CI, 0.44 to 0.87]; absolute difference, 6.1 percentage points [CI, 0.2 to 12 percentage points]) and all-cause mortality (RR, 0.75 [CI, 0.61 to 0.92]; absolute difference, 6.6 percentage points [CI, –1.3 to 14 percentage points]) (23). In subgroup analyses, benefits were restricted to men younger than 65 years of age (RR, 0.49 [CI, 0.31 to 0.79] for prostate cancer-specific mortality; RR, 0.52 [CI, 0.37 to 0.73] for all-cause mortality). One other small ($n = 142$), poor-quality RCT found no difference between prostatectomy and no prostatectomy for localized prostate cancer on overall survival through 23 years (29). It did not report prostate cancer-specific mortality.

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Appendix Table 3. Watchful Waiting vs. Prostatectomy [Web-Only](#)

Eight cohort studies (median $n = 2264$ [range, 316 to 25 900]) with duration of follow-up ranging from 4 to 13 years consistently found prostatectomy for localized prostate cancer to be associated with decreased risk for all-cause mortality (6 studies; median adjusted HR, 0.46 [range, 0.32 to 0.67] [31, 33–37]) and prostate cancer-specific mortality (5 studies; median adjusted HR, 0.32 [range, 0.25 to 0.50] [30, 33, 35, 36, 38]) compared with watchful waiting (Appendix Table 3). The largest was a fair-quality, propensity-adjusted analysis of data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program ($n = 25 900$) of men 65 to 80 years of age that found decreased risk for all-cause mortality after 12 years (adjusted HR, 0.50 [CI, 0.66 to 0.72]) (37). Another large ($n = 22 385$), fair-quality Swedish cohort study also found prostatectomy to be associated with decreased risk for all-cause mortality after 4 years of follow-up, after adjustment for age, Gleason score, and PSA level (adjusted HR, 0.41 [CI, 0.36 to 0.48]) (31).

Radiation Therapy

No RCTs compared radiation therapy versus watchful waiting. Five cohort studies (median $n = 3441$ [range, 334 to 30 857]) with follow-up ranging from 4 to 13 years consistently found that radiation therapy (external-beam radiation therapy or unspecified modality) for localized prostate cancer was associated with decreased risk for all-cause mortality (5 studies; median adjusted HR, 0.68 [range, 0.62 to 0.81] [31, 35–38]) and prostate cancer-specific mortality (5 studies; median adjusted HR, 0.66 [range, 0.63 to 0.70]) compared with watchful waiting (Appendix Table 3) (30, 35–38). The largest study, a previously described analysis of SEER data, found radiation therapy to be associated with decreased propensity-adjusted risk for all-cause mortality (adjusted HR, 0.81 [CI, 0.78 to 0.85]) (37). A large Swedish cohort study (also described earlier) found radiation therapy to be associated with decreased risk for all-cause mortality (adjusted HR, 0.62 [CI, 0.54 to 0.71]) (31).

Key Question 4: What Are the Harms of Treatment of Early-Stage or Screening-Detected Prostate Cancer?

Prostatectomy

Urinary Incontinence and Erectile Dysfunction. Prostatectomy was associated with increased risk for urinary incontinence compared with watchful waiting in 1 RCT (RR, 2.3 [CI, 1.6 to 3.2]) (41) and 4 cohort studies (median RR, 4.0 [range, 2.0 to 11]) (Appendix Table 4) (47, 49, 53, 56). In the RCT, the absolute increase in risk for urinary incontinence with surgery was 28 percentage points (49% versus 21%) (41). In the cohort studies, the median rate of urinary incontinence with watchful waiting was 6% (range, 3% to 10%), with prostatectomy associated with a median increase in absolute risk of 18 percentage points (range, 8 to 40 percentage

points) (47, 49, 53, 56).

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Appendix Table 4. Harms of Radical Prostatectomy, Radiation, and Androgen Deprivation Therapy vs. Watchful Waiting [Web-Only](#)

Prostatectomy was also associated with an increased risk for erectile dysfunction compared with watchful waiting in 1 RCT (RR, 1.8 [CI, 1.5 to 2.2]) (41) and 5 cohort studies (median RR, 1.5 [range, 1.3 to 2.1]) (Appendix Table 4) (47, 49, 53, 54, 56). In the RCT, the absolute increase in risk for erectile dysfunction with surgery was 36 percentage points (81% versus 45%) (41). In the cohort studies, the median rate of erectile dysfunction with watchful waiting was 52% (range, 26% to 68%), with prostatectomy associated with a median increase in absolute risk of 26 percentage points (range, 21 to 29 percentage points) (47, 49, 53, 54, 56).

Differences in study quality, duration of follow-up, or year of publication did not appear to explain differences in estimates across studies. The studies provided few details about the specific surgical procedures evaluated, although open retropubic radical prostatectomy was the dominant procedure when most of the studies were conducted (68). One observational study stratified estimates for erectile dysfunction and urinary incontinence by use of nerve-sparing ($n = 494$; 68% and 9.4%, respectively) versus non-nerve-sparing ($n = 476$; 87% and 15%, respectively) techniques (56).

Consistent with the studies reporting dichotomous outcomes, 8 cohort studies that evaluated urinary and sexual function outcomes by using continuous scales found that prostatectomy was associated with worse outcomes compared with watchful waiting (Appendix Table 4 [43, 46, 48, 51, 53, 55-57]).

Quality of Life. Nine studies reported generic quality of life (43, 46, 48, 50, 51, 53, 55, 56). Two studies reported very similar Short-Form 36 (SF-36) physical and mental component summary scores after prostatectomy and watchful waiting (Appendix Table 5) (43, 56). On specific SF-36 subscales, prostatectomy was associated with better physical function (6 studies; median difference, 9 points [range, 2 to 16 points]) (43, 46, 48, 51, 53, 55) and emotional role function subscale scores (7 studies; median difference, 8 points [range, 5 to 13 points]) (43, 46, 48, 50, 51, 53, 55), with small or no clear differences on other SF-36 subscales.

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Appendix Table 5. Summary Scores for Disease-Specific and Generic Health-Related Quality of Life [Web-Only](#)

Surgical Complications. The largest ($n = 101\ 604$) study of short-term (≤ 30 -day) complications after prostatectomy reported a 30-day perioperative mortality rate of 0.5% in Medicare claimants (60); 3 other large observational studies reported similar findings (59, 61, 62). Advanced age and increased number of serious comorbid conditions were associated with higher perioperative mortality, although absolute rates were less than 1% even in men at higher risk. In the Medicare database study, perioperative rates of serious cardiovascular events were 3% and rates of vascular events (including pulmonary embolism and deep venous thrombosis) were 2% (60). In 2 other studies ($n = 1243$ [63] and 11 010 [59]), rates of cardiovascular events were 0.6% and 3% and rates of vascular events 1% and 2%, respectively. Serious rectal or ureteral injury due to surgery ranged from 0.3% to 0.6% (60, 63).

Other Harms. Five studies (reported in 6 publications) found no clear differences between prostatectomy and watchful waiting in risk for bowel dysfunction (41, 42, 46, 47, 49, 56). One RCT found no difference between prostatectomy and watchful waiting in risk for high levels of anxiety, depression, or worry after 4 years (42).

Radiation Therapy

Urinary Incontinence and Erectile Dysfunction. Radiation therapy was associated with increased risk for urinary incontinence compared with watchful waiting in 1 small RCT, but the estimate was very imprecise (RR, 8.3 [CI, 1.1 to 63]) because of small numbers of events (1 in the watchful waiting group) (Appendix Table 4) (39). There was no clear increase in risk in 4 (total $n = 1910$) cohort studies (median RR, 1.1 [range, 0.71 to 2.0]) (47, 49, 53, 56).

Radiation therapy was associated with increased risk for erectile dysfunction compared with watchful waiting in 6 cohort studies, with similar estimates across studies (median RR, 1.3 [range, 1.1 to 1.5]) (Appendix Table 4) (47, 49, 53, 54, 56,

58). Rates of erectile dysfunction ranged from 26% to 68% (median, 50%) with watchful waiting; radiation therapy was associated with a median increase in pooled absolute risk of 14 percentage points (range, 7 to 22 percentage points).

Five of the six studies did not provide details about the type of radiation therapy (for example, external-beam radiation therapy [EBRT] versus brachytherapy) or dosing regimen. One good-quality cohort study reported a 7.0% rate of urinary incontinence after high-dose brachytherapy ($n = 47$), 5.4% after low-dose brachytherapy ($n = 58$), and 2.7% after EBRT ($n = 123$) (56). Rates of erectile dysfunction were 72%, 36%, and 68%, respectively.

Consistent with the studies reporting dichotomous outcomes, 8 cohort studies found radiation therapy to be associated with worse sexual function compared with watchful waiting based on continuous scales, although no clear differences were seen in sexual bother scores and measures of urinary function (Appendix Table 4) (40, 43, 46, 48, 51, 53, 55-58).

Quality of Life. Ten studies reported generic quality of life (40, 43, 46, 48, 50, 51, 53, 55, 58). Three studies found no differences between radiation therapy and watchful waiting in SF-36 physical (median difference, 0 points [range, -3 to 0 points]) or mental (median difference, 0 points [range, -2 to 1 points]) component summary scores (Appendix Table 4) (43, 56, 58). Results favored watchful waiting on the physical role function subscale (7 studies; median difference, -9 points [range, -22 to 1 points]) (43, 46, 48, 51, 53, 55, 58), with no clear differences on other SF-36 subscales.

Other Harms. Six cohort studies consistently found radiation therapy associated with worse Prostate Cancer Index bowel bother (median difference, -6 points [range, -10 to -2 points]) and function (median difference, -8 points [range, -15 to -3 points]) compared with watchful waiting (43, 48, 51, 53, 56). In studies that evaluated bowel function serially, effects appeared most pronounced in the first few months after radiation therapy and gradually improved (40, 46, 51, 57). This might help explain the inconsistent results among studies that reported dichotomous outcomes. Although 1 study found radiation therapy associated with substantially increased risk for bowel urgency after 2 years (3.2% vs. 0.4%; RR, 7.5 [CI 1.0 to 56]) (47), 2 studies with longer duration of follow-up (5.6 [49] and 3 years [56]) found no increased risk.

One cohort study reported similar effects of EBRT and brachytherapy on Prostate Cancer Index bowel function and bother (43). One other study found low-dose brachytherapy to be associated with smaller effects on bowel bother (about 3-point change from baseline) compared with high-dose brachytherapy (9-point change) or EBRT (8-point change) (56).

No study reported effects of radiation therapy versus watchful waiting on anxiety or depression.

Discussion

The Table depicts our summary of the evidence. Screening based on PSA identifies additional prostate cancers, but most trials found no statistically significant effect on prostate cancer-specific mortality. Recent meta-analyses of randomized trials included in this review found no pooled effect of screening on prostate cancer-specific mortality (69, 70). However, the 2 largest and highest-quality trials reported conflicting results (6, 7). The ERSPC trial found PSA screening every 2 to 7 years to be associated with a 20% relative reduction in risk for death from prostate cancer in a prespecified subgroup of men age 55 to 69 years (7), whereas the PLCO trial found no effect (6). High rates of previous PSA screening and contamination in the control group of the PLCO trial may have reduced its ability to detect benefits, although these factors do not explain the trend toward increased risk for prostate cancer-specific mortality in the screened group. The proportion of men in the PLCO trial who initially chose active surveillance or expectant management instead of curative treatment was lower than in the ERSPC trial (10% versus 19%), and the PLCO trial evaluated a shorter screening interval (annual versus every 4 years), suggesting that more conservative screening and treatment strategies might be more effective than more aggressive ones. Chance could also explain the apparent discrepancy between the 2 trials because the risk estimate confidence intervals overlapped. Additional follow-up might help resolve the discrepancy, given the long lead time (10 to 15 years) that may be necessary to fully understand the effect of PSA-based screening.

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Table. Summary of Evidence

Treatment studies can help inform screening decisions by providing information

about potential benefits of interventions once prostate cancer is detected. However, only 1 good-quality randomized trial compared an active treatment for localized prostate cancer versus watchful waiting (23). It found that prostatectomy was associated with decreased risk for all-cause and prostate cancer-specific mortality after 15 years of follow-up, although benefits appeared limited to younger men based on subgroup analyses. Because the RCT did not enroll men specifically with screening-detected prostate cancers, its applicability to screening is uncertain. Although cohort studies consistently found prostatectomy and radiation therapy to be associated with decreased risk for all-cause and prostate cancer-specific mortality compared with watchful waiting, estimates are susceptible to residual confounding, even after statistical adjustment.

Screening is associated with potential harms, including serious infections or urinary retention in about 1 of 200 men who undergo prostate biopsy as a result of an abnormal screening test result. False-positive screening results occurred in 12% to 13% of men randomly assigned to PSA-based screening (65, 66), with 1 trial reporting no prostate cancers in three quarters of screening-triggered biopsies (7). Screening also is likely to result in overdiagnosis because of the detection of low-risk cancers that would not have caused morbidity or death during a man's lifetime, and overtreatment of such cancers, which exposes men to unnecessary harms (71). Over three quarters of men with localized prostate cancer (about 90% of screening-detected cancers are localized) undergo prostatectomy or radiation therapy (11, 12). On the basis of data from the ERSPC trial, the rate of overdiagnosis with screening was estimated to be as high as 50% (72), and 48 men received treatment for every prostate cancer-specific death prevented (7). Treating approximately 3 men with prostatectomy or 7 with radiation therapy instead of watchful waiting would each result in 1 additional case of erectile dysfunction, and treating approximately 5 men with prostatectomy instead of watchful waiting would result in 1 additional case of urinary incontinence. Prostatectomy and radiation therapy were not associated with worse outcomes on most measures related to general health-related quality of life compared with watchful waiting, suggesting that negative effects related to specific harms may be offset by positive effects (perhaps related to less worry about untreated prostate cancer). Prostatectomy was also associated with perioperative (30-day) mortality (about 0.5%) and cardiovascular events (0.6% to 3%), and radiation therapy was associated with bowel dysfunction.

The evidence on treatment-related harms reviewed for this report appeared most applicable to open retropubic radical prostatectomy and EBRT, although details about specific surgical techniques or radiation therapy techniques and dosing regimens were frequently lacking. We found little evidence with which to evaluate newer techniques for prostatectomy (including nerve-sparing approaches that use laparoscopy, either robotic-assisted or free-hand) compared with watchful waiting, but found no pattern suggesting that more recent studies reported different risk estimates than older studies. Limited data suggest that low-dose brachytherapy may be associated with fewer harms than high-dose brachytherapy or EBRT (56). A potential harm of radiation therapy not addressed in this review is secondary post-treatment carcinogenic effects (73, 74).

Other treatments used for localized prostate cancer are reviewed in the full report, available on the AHRQ Web site (10). Although androgen deprivation is the next most commonly used therapy for localized prostate cancer after prostatectomy and radiation therapy (11), its use is comparatively infrequent, and it is not recommended as primary therapy (75, 76) because of evidence suggesting ineffectiveness (32), as well as an association with important adverse events, such as coronary heart disease, myocardial infarction, diabetes, and fractures, when given for more advanced prostate cancer (77-79).

Our study has some limitations. We excluded non-English-language articles, which could result in language bias, although we identified no non-English-language studies that would have met inclusion criteria. We included cohort studies of treatments, which are more susceptible to bias and confounding than well-conducted randomized trials. However, confounding by indication may be less of an issue in studies that evaluate harms (80), and analyses stratified by study design did not suggest differential estimates. If patients are selected for a specific prostate cancer treatment, in part because of a lower perceived risk for harms, the likely effect on observational studies would be to underestimate risks. For mortality outcomes, which may be more susceptible to confounding by indication, we included only studies that performed statistical adjustment. Finally, studies did not distinguish well between active surveillance and watchful waiting. Active surveillance might be associated with more harms (due to repeat biopsies or subsequent interventions) compared with watchful waiting, and studies with well-described active surveillance interventions that are consistent with current definitions for this therapy are needed (14).

In summary, PSA-based screening is associated with detection of more prostate cancers; small to no reduction in prostate cancer-specific mortality after about 10 years; and harms related to false-positive test results, subsequent evaluation,

and therapy, including overdiagnosis and overtreatment. If screening is effective, optimal screening intervals and PSA thresholds remain uncertain. The ERSPC trial evaluated longer screening intervals (2 to 7 years) and in some centers lower PSA thresholds (2.5 to 4.0 mcg/L) as compared with typical U.S. practice (6). When available, results from the Prostate Cancer Intervention Versus Observation Trial, which compared prostatectomy with watchful waiting for screening-detected cancer, may help clarify which patients would benefit from prostatectomy or other active treatments, potentially reducing harms from unnecessary treatment (81).

Article and Author Information

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