Evidence Synthesis

Number 154

Prostate-Specific Antigen–Based Screening for Prostate Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Investigators:
Joshua J. Fenton, MD, MPH
Meghan S. Weyrich, MPH
Shauna Durbin, MPH
Yu Liu, MS
Heejung Bang, PhD
Joy Melnikow, MD, MPH

This report does not include information from the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP), which was published on March 6, 2018 (Martin RM, Donovan JL, Turner EL, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. *JAMA*. 2018;319(9):883-95). However, results from this trial were considered by the U.S. Preventive Services Task Force during its deliberations and are included in an article summarizing this report (Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow H. Prostate-specific antigen-based screening for prostate cancer: evidence report and systematic review for the US Preventive Services Task Force [published online May 8, 2018]. *JAMA*. doi:10.1001/jama.2018.3712).

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

Director, Division of Cancer Prevention, National Cancer Institute (NCI); Eliseo Perez-Stable, MD, Director, National Institute on Minority Health and Health Disparities; Paul Pinsky, PhD, Acting Chief, Early Detection Research Branch, Division of Cancer Prevention, NCI; Philip Prorok, PhD, Chief of Biometry, Division of Cancer Prevention, NCI; Mary Roary, PhD, Program Director, National Institute of Nursing Research; and two anonymous reviewers from the Centers for Disease Control and Prevention; Michael LeFevre, MD, MSPH, Vice Chair of Family and Community Medicine, University of Missouri; Jennifer S. Lin, MD, MCR, Director, Kaiser Permanente EPC; Russell P. Harris, MD, MPH, Adjunct Professor of Epidemiology, University of North Carolina–Chapel Hill; and David Meyers, MD, Chief Medical Officer, AHRQ.

Suggested Citation

Structured Abstract

Background: Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death among U.S. men. U.S. prostate cancer incidence increased sharply with the dissemination of prostate-specific antigen (PSA) screening in the late 1980s, although it has been controversial whether the benefits of PSA-based screening outweigh potential harms.

Purpose: To update previous USPSTF systematic reviews regarding the benefits and harms of prostate cancer screening and treatments for screen-detected or localized prostate cancer, and to synthesize evidence on the utility of pre-biopsy risk calculators to identify men with clinically significant prostate cancers that are likely to progress to advanced disease.

Data Sources: We considered all studies included in prior USPSTF reviews, relevant English-language articles identified by searching PubMed, Embase, Web of Science and Cochrane Registries and Databases (through July 2017), and articles referenced in included articles or suggested by experts.

Study Selection: We included randomized controlled trials (RCTs) of PSA-based screening reporting prostate cancer morbidity, prostate cancer mortality, or all-cause mortality. For screening harms, we also considered cohort studies of men undergoing PSA screening and diagnostic followup. For treatment benefits and harms, we included RCTs and cohort studies of men with screen-detected or localized prostate cancer comparing outcomes of active treatments versus conservative management strategies (i.e., active surveillance, watchful waiting). We also included uncontrolled observational studies of treatment harms. For risk calculator studies, we included external validation studies of multivariable risk calculators that used PSA in addition to patient variables routinely available prior to prostate biopsy to predict the presence of prostate cancer (Gleason score ≥7 or stage T2b).

Data Extraction: One investigator abstracted study data, while a second checked data accuracy. Two investigators independently rated study quality based on pre-specified criteria.

Data Synthesis and Results: Fair-quality evidence on the impact of PSA screening on prostate cancer mortality and morbidity derives from two RCTs (the Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer [ERSPC] trial). During each year of the PLCO screening phase, approximately 46 percent of control arm participants received PSA screening, so the PLCO has been characterized as trial comparing organized versus opportunistic screening. After median followup of 14.8 and 13.0 years in the PLCO and ERSPC respectively, there was no difference in the risk of prostate cancer mortality in the screening versus control arms in the PLCO (RR, 1.04 [95% CI, 0.87 to 1.24]) but a 21 percent relative reduction in prostate cancer mortality in the ERSPC trial (RR, 0.79 [95% CI, 0.69 to 0.91]). Based on ERSPC incidence and mortality data, an estimated 27 men need to be diagnosed with prostate cancer to avert one prostate cancer death at 13 years of followup (95% CI, 17 to 66). Within the four ERSPC sites that reported it, randomization to screening was associated with 3.1 fewer cases of metastatic prostate cancer per 1,000 men randomized (95% CI, 1.8 to 4.4). In neither trial was screening associated with significantly reduced all-cause mortality.

In the ERSPC trial, there was a high rate of positive screening and biopsy (32.3 positive screens and 27.7 biopsies per 100 men randomized to screening). Biopsy-related harms include moderate to severe pain (7.3% at 35 days [95% CI, 5.7% to 9.1%]), infectious complications (range, 2% to 7%), and hospitalization (approximately 1%). Excess incidence data from the PLCO and ERSPC trials imply that between 20.7 percent and 50.4 percent of screen-detected cancers are overdiagnosed and would not have come to clinical attention in the absence of screening.

In the recently reported Prostate Testing for Cancer and Treatment (ProtecT) trial, prostate cancer survival was approximately 99 percent at 10-year followup among men with screen-detected prostate cancer in each of the three study arms (radical prostatectomy [RP], radiation therapy [RT] with neoadjuvant androgen deprivation therapy [ADT], or active surveillance [AS]), and there were no statistically significant differences in prostate cancer mortality. However, men randomized to active treatment (either RP or RT) were significantly less likely than men assigned to active surveillance to be diagnosed with metastatic disease (2.3% and 2.9% with RP and RT, respectively, vs. 6.0% with AS; NNT, 27 and 33 with RP and RT rather than AS, respectively, to prevent one case of metastatic disease at 10-year followup). Two prior RCTs of RP versus watchful waiting (WW) in localized prostate cancer also observed reduced long-term incidence of metastatic cancer with RP. In cohort studies, RP (7 cohorts) and RT (7 cohorts) were each associated with improved prostate cancer survival among men with localized prostate cancer compared to conservative management, while primary ADT for localized prostate cancer was associated with no significant differences in prostate cancer mortality or overall mortality compared to conservative management in a cohort study using instrumental variable analyses.

Based on pooled meta-analyses of RCT data, approximately 7.9 men would need to be treated with RP rather than conservative management for one additional man to experience urinary incontinence (95% CI, 5.4 to 12.2), and 2.7 men would need to be treated with RP rather than conservative management for one man to experience erectile dysfunction (95% CI, 2.2 to 3.6). In trials and cohort studies, approximately 7 percent of patients undergoing RP experienced major medical or surgical complications, and a median of 0.29 percent died within 30 days of surgery (8 studies). For every 6.9 men undergoing RT (95% CI, 5.1 to 10.7), one man will develop erectile dysfunction; bothersome bowel symptoms are also significantly increased with RT. As compared to conservative management, neither RP nor RT was associated with clinically significant impacts on generic measures of quality of life. In three cohort studies, primary ADT for localized prostate cancer was associated with erectile dysfunction in 73.8 percent to 85.8 percent of men; ADT has been associated with a range of systemic side effects in men with advanced cancer, including osteoporosis.

Two risk calculators have been externally validated for the prediction of significant prostate cancer in multiple biopsy cohorts: the Prostate Cancer Prevention Trial (PCPT) calculator (21 cohorts) and the ERSPC risk calculator (7 cohorts). In nearly all cohorts, the calculators discriminated between men with and without significant cancer better than PSA alone, although discrimination varied across cohorts. When assessed, risk calculator calibration was inconsistent across cohorts.

Limitations: Limitations of the screening trials include a high rate of PSA use in the PLCO control arm, biasing results toward the null, while the ERSPC trial was limited by differences in

treatments received by men diagnosed with similarly staged cancers in screening and control arms. Followup duration in trials may be insufficient to detect differences in prostate cancer mortality or to quantify overdiagnosis. Only one treatment trial (ProtecT) exclusively enrolled men with screen-detected prostate cancer, and low event rates in this trial resulted in low power for discerning differences in prostate cancer mortality by study arm. No RCTs have evaluated the benefits and harms of risk calculator use prior to biopsy decisions among men with abnormal PSA screening.

Conclusions: PSA screening for prostate cancer may reduce risk of prostate cancer mortality but is associated with harms including false-positive results, biopsy complications, and overdiagnosis in 20 percent to 50 percent of screen-detected prostate cancers. Early, active treatment for screen-detected prostate cancer may reduce the risk of metastatic disease, although the long-term impact of early, active treatment on prostate cancer mortality remains unclear. Active treatments for prostate cancer are frequently associated with sexual and urinary difficulties.

Table of Contents

Figures
Figure 1. Analytic Framework
Figure 2. Relative Risk of Urinary Incontinence After Radical Prostatectomy vs. Conservative Management for Treatment of Localized Prostate Cancer
Figure 3. Relative Risk of Erectile Dysfunction After Radical Prostatectomy vs. Conservative Management for Treatment of Localized Prostate Cancer
Figure 4. Relative Risk of Urinary Incontinence After Radiation Therapy vs. Conservative Management for Treatment of Localized Prostate Cancer
Figure 5. Relative Risk of Erectile Dysfunction After Radiation Therapy vs. Conservative Management for Treatment of Localized Prostate Cancer

Tables
Table 1. Prostate Cancer Tumor Staging
Table 2. Recommendations From Other Groups
Table 3. Study Characteristics of Randomized, Controlled Trials of PSA-Based Prostate Cancer Screening
Table 4. Study Characteristics of Cohort Studies of Physical or Psychological Harms of Prostate Cancer Screening
Table 5. The Effect of PSA-Based Screening on Prostate Cancer Incidence
Table 6. The Effect of PSA-Based Screening on Prostate Cancer-Specific and All-Cause Mortality
Table 7. The Effect of PSA-Based Screening on Prostate Cancer-Specific Mortality, by Subgroup and Risk Factor
Table 8. False-Positives, Complications, and Biopsy-Related Mortality Associated With PSA-Based Screening
Table 9. Estimates of Overdiagnosis of Prostate Cancer Based on Excess Incidence in the Screening Arms of Randomized, Controlled Trials
Table 10. Study Characteristics of Randomized, Controlled Trials of Prostate Cancer Treatment Benefits and Harms
Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms
Table 12. Study Characteristics of Uncontrolled Observational Studies of Prostate Cancer Treatment Harms
Table 13. Quality of Life Measures
Table 14. The Effect of Radical Prostatectomy Compared With Conservative Management on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality
Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor
Table 16. The Effect of Radiation Therapy Compared With Conservative Management on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

Chapter 1. Introduction

Condition Definition

Adenocarcinoma accounts for over 95% of all cancers of the prostate gland.[1] Prostate cancer is staged according to the criteria jointly established by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (IUCC).[2] This system stages prostate cancer based on the extent of the primary tumor (T), lymph node involvement (N), presence of distant metastases (M), serum prostate specific antigen (PSA) level, and Gleason score (**Table 1**).[3] Localized prostate cancer is classified as stages 1 (non-palpable) and 2 (palpable) and is confined within the prostate capsule. According to 2007 to 2013 data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program, the majority of prostate cancer cases (79%) are localized, while 12% involve regional lymph nodes and 5% involve distant metastases (4% unknown stage).[4] The likelihood of progression from localized to regional or metastatic disease is associated with the presence of more poorly differentiated cells and other histopathologic features, as reflected in the Gleason score (range, 6 [well-differentiated] to 10 [poorly-differentiated]). In addition to staging, risk assessment tools, such as the D'Amico risk classification or the Cancer of the Prostate Risk Assessment (CAPRA) score, are commonly used to categorize cancers as low-, intermediate-, or high-risk on the basis of clinical presentation and other risk factors (i.e., tumor size, Gleason score, PSA level, age).

Prevalence and Burden of Disease

Prostate cancer is the most commonly diagnosed cancer in American men, with an estimated lifetime risk of approximately 12.9 percent.[4] Based on SEER data, an estimated 161,360 men will be newly diagnosed with prostate cancer in 2017 (annual incidence rate of 119.8 per 100,000 men),[4] accounting for 19 percent of new cancer cases in males.[5] Prostate cancer is diagnosed most often in men ages 55 to 74 years (71% of all new cases), with a median age at diagnosis of 66 years.[4] The prostate cancer incidence rate is highest among African American men (188.7 cases per 100,000 men), followed by whites (112.8 cases per 100,000 men), Asian/Pacific Islanders (62.9 cases per 100,000 men), and American Indian/Alaska Natives (59.9 cases per 100,000 men). Prostate cancer incidence is higher among non-Hispanic men compared to Hispanics (123.3 vs. 98.3 per 100,000 men, respectively);[4] however recent studies have shown that, when disaggregated, certain Latino groups (i.e., Cuban and Puerto Rican men) have comparable or slightly higher incidence rates than non-Hispanic whites.[6]

Prostate cancer is the second leading cause of cancer death among U.S. men, and the third leading cause of cancer death in the general population.[7] The lifetime risk of dying from prostate cancer among U.S. men is 2.5 percent. While the 5-year survival rate among men with localized or regional prostate cancer is nearly 100 percent, the 5-year survival for prostate cancer with distant metastases is 29.8 percent.[4] Nearly 68 percent of all prostate cancer deaths occur among U.S. men aged 75 years and older, with a median age at death of 80 years.[4] The prostate cancer death rate is highest among African American men (42.0 deaths per 100,000 men), more than double the prostate cancer death rate of American Indian/Alaska Natives (19.4 per 100,000),

whites (18.7 per 100,000), and Asian/Pacific Islanders (8.8 per 100,000).[4] Because prostate cancer mortality rates are much lower than incidence rates, the large majority of men who are diagnosed with prostate cancer die of causes other than prostate cancer.[4]

Etiology and Natural History

The etiology of prostate cancer is not completely understood. Men with 5-alpha-reductase deficiency do not develop prostate cancer, suggesting that androgenic hormones play a role in pathogenesis.[8] The higher incidence in African American men points to genetic or other predispositions that vary by race/ethnicity.

Many prostate cancers never become clinically evident in the absence of screening. In addition, many prostate cancers progress slowly, such that clinically significant progression may not occur during a man's lifetime. In autopsy studies of men dying of other causes, the prevalence of localized prostate cancer increases with age, from 5 percent in men aged 30 years and younger to 15 percent in men ages 40 to 50 years and 59 percent in men aged 79 years and older.[9] Tumor grade, typically assessed using the Gleason score, is an important marker of tumor aggressiveness. Tumors that remain localized to the prostate are often asymptomatic but may cause symptoms of bladder outlet obstruction. Tumors that remain localized generally do not affect survival. In contrast, tumors that spread beyond the prostate to invade local structures or metastasize can have severe negative impacts on quality of life and may result in mortality.[10]

Risk Factors

Prostate cancer risk is associated with both unmodifiable risk factors (e.g., age, race, and genetics)[4, 11, 12] and modifiable risk factors (e.g., diet, tobacco use).[13-16] Based on autopsy studies and epidemiological data, prostate cancer risk is strongly tied to both age and race/ethnicity. According to 2010 to 2014 SEER data, men aged 54 years and younger accounted for only an estimated 10 percent of all diagnosed prostate cancer, while men ages 55 to 74 accounted for 71 percent of all cases.[4] After 75 years of age, the incidence of diagnosed prostate cancer begins to decline (approximately 19% of all new cases),[4] which may be due in part to reduced PSA-based screening in older men.[17, 18] SEER data also show that the incidence of prostate cancer among African Americans is significantly higher than other racial/ethnic groups. Similarly, African American men have the highest prostate cancer mortality rates,[4] consistent with earlier age of cancer onset, more advanced cancer stage at diagnosis, and other factors related to poor disease prognosis (i.e., worse Gleason scores, higher serum PSA levels).[19-22] Differential access to care may contribute to lower adherence with diagnostic followup after abnormal PSA screening among African American men compared to white men, potentially contributing to relatively higher prostate cancer mortality among African American men.[23] Prostate cancer risk is significantly greater among men with one or more first-degree relatives with prostate cancer.[11] One Scandinavian study of twins estimated that hereditary factors may account for up to 42 percent of prostate cancer risk.[12] Among modifiable risk factors, diets high in fat and low in vegetable consumption are associated with increased prostate cancer risk.[13-15] While not consistently shown to increase risk of prostate cancer incidence, cigarette smoking is associated

with higher risk of prostate cancer mortality.[16]

Current Clinical Practice in the United States

Screening Strategies

The purpose of screening for prostate cancer is to identify high-risk, localized prostate cancer that can be successfully treated, thereby preventing the morbidity and mortality associated with advanced or metastatic prostate cancer. Screening for prostate cancer can be done through prostate-specific antigen (PSA) screening, with or without digital rectal examination (DRE). Measuring PSA levels is done through multiple approaches, including single-threshold testing, adjusted threshold testing, velocity, and doubling time.

Single-threshold testing measures serum PSA levels against a single threshold for all men. **Age-adjusted thresholds** attempt to improve the sensitivity and specificity of PSA testing by raising the threshold in older men (with a goal of reducing the potential for overdiagnosis) and lowering the threshold in younger men (with a goal of increasing the likelihood of early detection).[24] **PSA velocity** and **PSA doubling time** both measure the rate of change in PSA levels, with velocity measuring the change in PSA over time and doubling time measuring the time it takes (usually measured in months) for a certain PSA level to double.[25]

While elevated PSA levels may indicate prostate cancer, elevated PSA levels can also accompany benign conditions, such as benign prostatic hyperplasia and prostatitis.[26] Also, PSA levels in men without evidence of prostate cancer vary by race/ethnicity,[27] and race-specific PSA reference ranges have been proposed with the goal of improving sensitivity.[28]

Several adjunctive serum or urinary tests have been developed with the goal of improving the sensitivity or specificity of PSA screening. **Appendix F** summarizes evidence regarding adjunctive tests that are increasingly used in concert with PSA screening.

Treatment Approaches

Common therapeutic options for men with localized prostate cancer include both active treatments and conservative approaches.

Active treatment approaches for prostate cancer include surgery (radical prostatectomy), radiation therapy, hormone therapy (i.e., androgen deprivation therapy), or ablation (i.e., cryotherapy and high-intensity focused ultrasound). **Radical prostatectomy** (RP) is a surgical technique intended to remove all prostate tissue. **Radiation therapy** (RT), either in the form of *external beam radiation therapy (EBRT)* or *brachytherapy*, is typically used for localized, low-risk prostate cancer. *External beam radiation therapy* uses an external source of radiation to treat the prostate gland and may affect adjacent, healthy tissue. *Brachytherapy* implants a radioactive source within the prostate gland with the goal of reducing radiation exposure to adjacent, healthy tissue.[29] **Androgen deprivation therapy** (ADT), typically used in combination with other treatments rather than as monotherapy, reduces the levels of male hormones, or androgens (e.g.,

testosterone and dihydrosterone) in order to shrink the tumors or cause the tumor to grow more slowly.[30] Neo-adjuvant ADT is provided prior to other active treatments, such as RP or EBRT, with the goal of improving the chances of complete tumor eradication. **Cryotherapy** is a form of ablation that is applied to the entire prostate gland or a specific portion affected by the tumor and destroys the prostate tissue through freezing. **High-intensity focused ultrasound** (HIFU) is another form of ablative therapy that destroys the prostate tissue by generating local thermal energy.[29]

Active surveillance and watchful waiting are both conservative approaches that involve postponing immediate treatment.[31] **Active surveillance** (AS) involves deferring treatment indefinitely unless evidence of disease progression is uncovered during regular monitoring with physical examination, serial PSA, or repeat biopsy. The goal of active surveillance is to avert or postpone treatment-related harms among men with indolent cancers or with cancer that may not progress during their lifetimes. Optimal candidates for active surveillance are older men with low-risk tumors who have life expectancies exceeding 10 to 15 years.[32] In contrast, **watchful waiting** involves no immediate treatment with the provision of palliative therapies if and when patients become symptomatic. Watchful waiting is typically recommended for men who are unlikely to benefit from active treatments due to limited life expectancy.[31]

Factors influencing treatment choice include the likelihood of cancer metastasis or recurrence (based on tumor characteristics) as well as patient age, comorbidities, life expectancy, patient preferences, and clinical practice. A study of U.S. veterans with screen-detected prostate cancer diagnosed in 2003 (n=5,220)[33] found that men were more likely to receive curative treatments (58%) rather than hormone therapy (24%) or no treatment (18%). In an analysis of U.S. men with early-stage prostate cancer (n=11,892) diagnosed between 1990 and 2007, most men selected RP (49.9%) or RT (24.9% [EBRT, 11.6%, brachytherapy, 13.3%]), followed by primary ADT (14.4%) and cryotherapy (4.0%); comparatively, only 6.8 percent of men chose a surveillance-based treatment approach.[34] HIFU is currently rarely employed in U.S. practice.

Although conservative, surveillance-based approaches (i.e., active surveillance or watchful waiting) are less common than active treatment for early-stage prostate cancer, several recent assessments indicate that initial use of conservative approaches is rapidly increasing.[34-39] In a consortium of 45 U.S. urology practices, use of surveillance for men with low-risk prostate cancer has increased sharply (from ~10% in 2005-2009 to 40.4% in 2010-2013).[40] Nevertheless, approximately half of men diagnosed with low-risk prostate cancer in 2010-2013 received RP. [40] Among men aged 75 years and older, active surveillance or watchful waiting was used in over three-quarters of men with low-risk prostate cancer from 2010-2013 (76.2%).[40]

Clinical Guidelines

Prostate cancer screening recommendations from other groups are summarized in **Table 2**. The American Academy of Family Physicians (AAFP),[41] American College of Preventive Medicine (ACPM),[42] and the Canadian Task Force on Preventive Health Care[43] recommend against routine, population-based screening for prostate cancer. Strategies based on shared decision-making and individualized screening based on patient risk are recommended by the ACPM, the European Association of Urology (EAU),[44] the American College of Physicians (ACP), the

American Cancer Society (ACS)[45] and the American Urological Association (AUA).[17] The National Comprehensive Cancer Network (NCCN) recommends that clinicians perform screening PSA on men aged 45 to 75 years, and that the frequency of subsequent screening based on baseline PSA or DRE results (if performed).[46] The ACS and ACPM include specific recommendations for African American men or those with a family history of prostate cancer; ACS recommends that these men should discuss screening with their doctor between ages 40 and 45 years, while ACPM emphasizes that clinicians provide information about the benefits and harms of screening and that the choice to screen should be individualized. A recent review of national survey data from 2013 found that PSA-based screening decreased from 31.8 percent in 2008 to 24.2 percent in 2013 among U.S. men. Additionally, between 2010 and 2013, decreases were observed among all screening-relevant age groups: PSA testing decreased from 33.2 percent to 24.8 among men ages 50 to 59 years, 51.2 percent to 43.6 percent for men 60 to 74 years, and 43.9 percent to 37.1 percent for men 75 years and older.[18]

Previous USPSTF Recommendation

In 2012, the USPSTF concluded that there was sufficient evidence to recommend against PSA-based screening for prostate cancer in men in all age groups (D recommendation). The USPSTF found convincing evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer, and that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime.

The USPSTF found that the benefits of PSA-based screening for prostate cancer did not outweigh the harms. Clinical trials indicated that the reduction in prostate cancer mortality 10 years after PSA-based screening was, at most, very small, even for men aged 55 to 69 years. The harms of PSA screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm from false-positive test results, and harms related to overdiagnosis, such as treatment of prostate cancer that would not cause symptoms. Harms of treatment were noted to include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk of premature death. Because of the inability to reliably distinguish tumors that remain indolent from those destined to be lethal, the harms of treatment would affect men with screen-detected cancers that would never have become symptomatic.

Chapter 2. Methods

Scope and Purpose

This systematic review will provide updated evidence regarding the benefits and harms of PSA-based screening for prostate cancer, and subsequent treatments for screen-detected or localized prostate cancer. The USPSTF will use this review to update its 2012 recommendation on this topic.[47] This review included studies from the previous review that met current inclusion and exclusion criteria, as well as newly identified studies.

Key Questions and Analytic Framework

Using USPSTF methods,[48] we developed an analytic framework (**Figure 1**) and five Key Questions (KQs) in consultation with members of the USPSTF. These KQs were adapted from questions addressed in the previous review;[49, 50] however, KQ5, related to the utility of pre-biopsy risk calculators, is new to this review.

KQs

1. Is there direct evidence that prostate-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 (e.g., age, race/ethnicity, family history, or clinical risk assessment)?
2. What are the harms of PSA-based screening for prostate cancer and diagnostic followup?
   a. Do the harms of PSA-based screening for prostate cancer and diagnostic followup vary by subpopulation or risk factor (e.g., 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 (e.g., 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 (e.g., 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 pre-biopsy prostate cancer risk calculator, in combination with PSA-based screening, accurately identifies men with clinically significant prostate cancer (i.e., cancer that is more likely to cause symptoms or lead to advanced disease) compared to PSA-based screening alone?

Data Sources and Searches

In addition to considering studies from the previous review for inclusion in the current review, we performed a comprehensive search of MEDLINE/PubMed, Embase, Web of Science, and the Cochrane Database of Systematic Reviews. We worked with a medical librarian to develop our search strategy (**Appendix A**). All searches were limited to articles published in the English language. For evidence related to the effect of screening and treatment on health outcomes, we searched for studies published between January 2011 and July 2017, building upon the literature published since the previous review. For evidence related to the use of risk calculators, we searched for studies published between January 2006 and July 2017. We limited the search for KQ5 to this time span based on a preliminary scan of the evidence, which revealed that the earliest publication on risk calculators was based on the Prostate Cancer Prevention Trial (published in 2006).[51] All other relevant publications were published more recently.

To ensure comprehensiveness of our search strategy, we reviewed reference lists of included studies and relevant systematic reviews and meta-analyses to identify potentially relevant articles that were published before our search dates or were not identified in our literature searches. We also obtained references from outside experts, and searched federal agency trial registries for ongoing trials (**Appendix C**). We managed literature search results using EndNote version X7.5 (Thomson Reuters, New York, NY).

Study Selection

Two reviewers independently reviewed titles and abstracts of identified articles to determine if studies met inclusion criteria for design, population, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated full-text articles of potentially relevant studies to assess whether they met inclusion or exclusion criteria. Disagreements in the abstract or full-text review were resolved by discussion and consultation with a third reviewer. A list of excluded studies after full-text review, including the reasons for exclusion, is available in **Appendix B**.

We developed an a priori set of criteria for inclusion and exclusion of studies based on criteria from the previous review and our understanding of the literature (**Appendix A Table 1**). We excluded studies where the majority of participants were from countries that are not designated as having a very high Human Development Index, as defined by the United Nations Development Programme.[52] Studies conducted in other settings are less likely to offer evidence that would translate to U.S primary care settings.

For the screening questions (KQ1-2), we included studies of asymptomatic men, defined as men without symptoms that were suspicious for prostate cancer. For screening effectiveness (KQ1), we examined studies that compared PSA-based screening to either non-PSA-based methods of prostate cancer screening (e.g., DRE) or no screening. For KQ1, we included studies reporting all-cause and prostate cancer-specific mortality, and prostate cancer-related morbidity, such as bone pain from metastases, and progression to advanced-stage cancer. Although prostate cancer screening trials were not powered to detect a decrease in overall (all-cause) mortality, we

included this outcome because screening may conceivably either decrease overall mortality (if the impact on prostate cancer-specific mortality is very large) or increase overall mortality (if screening increases rates of treatment harms). For screening harms (KQ2), which includes the harms of subsequent diagnostic followup, we included studies reporting false positives, physical harms of screening or biopsy (e.g., infection), psychological harms (e.g., anxiety), and deleterious effects on health-related quality of life. For studies of men undergoing biopsy, we required that men were undergoing prostate biopsy as a result of an elevated screening PSA; we excluded studies of men undergoing biopsy if the reason for prostate biopsy was not specified. We also assessed randomized trials of screening for evidence of overdiagnosis. We excluded ecological studies that examined the rising incidence of prostate cancers over time, the prevalence of subclinical prostate cancers, and autopsy studies as studies with these designs do not directly assess screened populations and often include many subjects whose cancers were identified without screening. For KQ1, we limited the study design to randomized, controlled trials (RCTS); for KQ2, we also included cohort studies of men undergoing screening PSA or biopsy.

For the questions of treatment-related benefits and harms (KQ3-4), we included studies of men with screen-detected or early-stage prostate cancer (defined as stages T1-T2). We did not consider studies of treatment benefits and harms for men with later-stage prostate cancer (stages III or IV), because large, population-based screening trials have primarily detected early-stage cancer (90-96% of cancers detected) and the treatment-related consequences of screening will chiefly derive from treatments of early-stage disease.[53, 54] We excluded studies that did not adequately report baseline tumor stage or that enrolled more than 10 percent of patients with stage T3 tumors or higher, unless results were stratified according to tumor stage at baseline. We also excluded studies that evaluated patients with recurrent or refractory prostate cancer. Studies that described the population as having localized prostate cancer were included even if they did not report specific tumor stage information, as this term typically refers to T1 and T2 cancer.[55]

We included studies that compared outcomes of active treatments with conservative management, defined as watchful waiting, active surveillance, observation, deferred treatment, or no treatment. Active treatment options for men with early-stage prostate cancer include radical prostatectomy (retropubic, perineal, and laparoscopic), radiation therapy (external beam radiation therapy, brachytherapy), androgen deprivation therapy (ADT), cryotherapy, or high-intensity focused ultrasound (HIFU). For treatment effectiveness (KQ3), we included studies reporting all-cause and prostate cancer-specific mortality, and prostate cancer-related morbidity, such as bone pain from metastases, and progression to metastatic cancer. For treatment harms (KQ4), we included studies reporting surgical complications and other physical harms of treatment (e.g., urinary, sexual, bowel function), psychological harms (e.g., depression), and impacts on generic- or health-related quality of life. For KQ3, we limited study designs to RCTs and comparative cohort studies. For KQ3, we excluded comparison studies of active treatments unless a conservative management group was included. For KQ4, we broadened our criteria to include uncontrolled observational studies of harms, in addition to RCTs and comparative cohort studies. We limited our inclusion of uncontrolled studies of harms to those studies with sample sizes of 100 men or greater. We prioritized uncontrolled studies with a sample size of at least 1,000 men, and included uncontrolled studies with smaller sample sizes only if RCTs, cohort studies, and larger uncontrolled studies (sample sizes greater than 1,000 men) were not available.

For KQ 5, we included external validation studies of multivariable risk calculators that used PSA in addition to patient variables routinely available prior to prostate biopsy to predict the presence of clinically significant prostate cancer. We defined prostate cancers as clinically significant if either high-grade (Gleason score ≥7) or clinical stage T2b or higher, as these tumor characteristics are associated with five-year, post-treatment recurrence risk of 25 to 50 percent.[56] We defined external validation as evaluation of the discrimination and calibration of the risk calculator in a population other than the population from which it was derived. We excluded internal validation studies (e.g., using a random- or split-sample of the derivation population) as these are prone to bias and overfitting.[57] We also excluded studies of tools designed to predict any prostate cancer, rather than clinically significant prostate cancer as defined above. For KQ5, we limited the included study designs to RCTs and cohort studies. We did not include studies of novel serum biomarkers, such as the 4Kscore[58] or the Prostate Health Index (PHI),[59] or imaging studies, such as multiparametric magnetic resonance imaging (MP-MRI),[60] because results of these studies would not be routinely available prior to biopsy in most U.S. urology practices. Evidence on these modalities is summarized in **Appendix F**.

Quality Assessment and Data Abstraction

Two investigators independently assessed the methodological quality of each included study using predefined criteria developed by the USPSTF[48] and supplemented with criteria from the Newcastle-Ottawa Scale,[61] and the National Institute for Health and Care Excellence methodology checklists for observational studies.[62] Each study was assigned a final quality rating of good, fair or poor. Disagreements in quality were resolved through discussion.

Good-quality studies included all or most of the following: adequate randomization procedures or cohort selection, allocation concealment, blinding of outcome assessors, reliable outcome measures, comparable groups at baseline (with specified eligibility criteria), low attrition, acceptable statistical methods, adjustment for potential confounders, adequate adherence to the intervention, and low rates of contamination. We rated studies as fair quality if they were unable to meet the majority of the good-quality criteria or one or two flaws were of sufficient magnitude to undermine confidence in the results. We rated studies as poor quality if they contained major flaws (i.e., attrition >40%, differential attrition of >20% between groups) or the cumulative effects of multiple minor flaws or the extent of missing information was significant enough to raise serious doubts about the validity of study results.

As there is no widely accepted quality rating tool for studies of risk prediction models, we critically appraised risk prediction studies (KQ5) using the checklists and principles articulated in the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews for Prediction Modeling Studies (CHARMS)[57] and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.[63] For KQ5, we required that the study include biopsy results from all men as a key quality indicator, and excluded studies that did not meet this criterion. Studies of risk prediction models were not formally rated as good versus fair quality because of the absence of standardized rating methods for studies with this objective.

One reviewer extracted data from all included studies into a REDCap[64] (Research Electronic Data Capture) electronic database (Vanderbilt University, Nashville, TN) and a second reviewer checked the data for accuracy. We abstracted study design characteristics, population demographics, screening and treatment details, prostate cancer outcomes (stage at diagnosis, incidence, mortality), health outcomes (quality of life, functioning, health status), and adverse events.

Approach to Assessing Overdiagnosis

For this analysis, we define overdiagnosis as a screen-detected cancer that would not have been clinically detected during the patient's lifetime in the absence of screening. Overdiagnosis is a harm of screening because men who are overdiagnosed by definition do not benefit from early detection yet may suffer the harms of diagnosis and treatment. In this report, we synthesize evidence on overdiagnosis from randomized trials of PSA screening.

Randomized trials can yield an estimate of the number of overdiagnosed cancers in the screening group by comparing the number of cancers diagnosed in the screening group with the number diagnosed in the control group after extended followup of both groups. Two different denominators have been used when reporting on the "frequency" or "extent" of overdiagnosis – all screen-detected prostate cancers during the screening phase of the trial and all prostate cancers detected during the screening phase.[65] In a randomized trial, the numerator for both computations is the absolute excess number of cancer cases diagnosed in the screening arm during long-term followup. The first approach estimates that percentage of screen-detected cancers that are overdiagnosed. The second approach estimates the percentage of all cancer diagnosed during the screening phase that are overdiagnosed. If randomization is not 1:1, as in some ERSPC subsites and in the overall ERSPC trial, appropriate weights to incident cases can be applied to estimate excess incidence if randomization had been 1:1. This methodology has yielded estimates of overdiagnosis in randomized trials of breast and lung cancer screening.[65-68]

Measures of Risk Prediction Model Performance

We abstracted study data on three metrics of risk model performance: discrimination, calibration, and clinical utility. Discrimination, usually expressed as the area under the receiver operator curve (AUC or *c* statistic), is a measure of the probability that the model will correctly distinguish a case from a non-case (ranging from 0.5 [no better than chance] to 1.0 [perfect discrimination]). We abstracted available data on AUCs both with the risk assessment tool and with PSA alone, allowing judgment of the extent to which the risk assessment tool may improve biopsy recommendations based on PSA alone.

Calibration refers to the extent to which the risk model accurately predicts observed risk. Statistical tests, such as the Hosmer-Lemeshow test, can quantify model fit, but calibration plots directly portray the extent to which model-predicted risk matches observed risk in a population.

Finally, we abstracted available qualitative data from decision curve analyses, which provide information on the expected benefits and harms of applying the risk assessment tools in biopsy

decisions at varying pre-biopsy risk thresholds for undergoing biopsy.[69] In the decision curve analyses, expected benefits are the number of patients with significant prostate cancer who are detected (true-positives), while expected harms are the number of patients without significant prostate cancer who undergo biopsy (weighted based on the probability threshold above which the patient would undergo treatment regardless of biopsy results). A decision curve analysis suggests that use of a risk calculator will yield net benefit at a given pre-biopsy risk threshold if the expected benefits exceed the expected harms (or net harm if expected harms exceed expected benefits).

Data Synthesis and Analysis

We created separate tables for the results for each KQ and additional summary tables that included key study characteristics. We used these tables and forest plots of results to examine data for consistency, precision, and relationship of effect size with key potential modifiers, such as age or tumor stage.

For all outcomes, we synthesized data descriptively using medians and ranges. We did not perform pooled meta-analyses for outcomes of screening effectiveness (KQ1), screening harms (KQ2) or treatment effectiveness (KQ3) because data derived from relatively few trials, variability in populations and interventions, and varying measures of treatment effectiveness across cohort studies. For commonly reported treatment-related harms (i.e., urinary incontinence and erectile dysfunction), we used DerSimonian-Laird random-effects meta-analyses to estimate pooled relative risks (RRs) of these complications among patient receiving radical prostatectomy or radiation therapy as compared to conservative management. Heterogeneity was first assessed graphically, and if meta-analysis was performed, it was quantified using I^2. As none of the cohort studies reported adjusted risk estimates, we used raw event rates. We performed sensitivity analyses assessing the potential impact of shorter versus longer followup times within studies and the potential impact of individual studies on observed heterogeneity. When multiple time points were reported within studies, we included the latest time point in meta-analyses. For one study that reported results from the same cohort at 30 to 41 months' followup[70] and 10 years' followup,[71] we used the earlier data, since it was more complete (n=108 vs. n=54) and pooled estimates using either results were similar in sensitivity analyses. We used pooled RRs to estimate the number of patient needed to be treated for one patient to be affected by harms (NNH); in these calculations, the absolute risk of the complication in actively treated patients was estimated as the product of the pooled RR and the median absolute risk in the conservatively managed control group.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center approach[72] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[73] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an

estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., lack of replication of interventions, non-reporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF Web site for public comment from October 29 to November 15, 2015. In response, we expanded the scope of KQs 1 through 4 to include assessment for evidence of differential impact of screening within high-risk subgroups, and a separate group was commissioned to summarize results of statistical modeling studies for the USPSTF. A final version of the research plan was posted on the USPSTF website in April 2016. A draft version of this report was reviewed by invited external experts and federal partners listed in the acknowledgements. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report. Additionally, a draft of the full report was posted on the USPSTF Web site from April 11 through May 8, 2017. In response to these comments, we included a summary of evidence on the psychological harms of screening. We also included results of studies identified during ongoing literature surveillance through February 2018, including extended followup from the PIVOT trial,[74] two cohort studies reporting longitudinal outcomes among U.S. men receiving treatment for localized prostate cancer,[75, 76] and three studies of multivariable risk calculators.[77-79]

USPSTF Involvement

This research was funded by AHRQ under a contract to support the USPSTF. The authors consulted with USPSTF members at key points throughout the review process to develop and refine the scope, analytic framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. AHRQ had no role in study selection, quality assessment or synthesis. AHRQ staff provided oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside experts, including representatives of professional societies and federal agencies.

Chapter 3. Results

Literature Search

Our literature search yielded 4,148 unique citations. From these, we provisionally accepted 302 articles for review based on titles and abstracts (**Appendix A Figure 1**). After screening the full-text articles, 2 trials (23 publications)[53, 54, 80-100] were judged to have met the inclusion criteria for KQ1; 2 trials and 5 cohort studies (14 publications)[33, 53, 90, 96, 101-113] were included for KQ2; 3 trials and 10 cohort studies (23 publications)[74, 75, 114-136] were included for KQ3; 4 trials, 14 cohort studies and 14 uncontrolled observational studies (38 publications)[70, 71, 74-76, 121, 126, 132, 133, 136-166] were included for KQ 4, and; 13 studies (14 publications)[77-79, 167-177] were included for KQ5. The remaining articles were excluded (**Appendix B**).

KQ1. 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?

We identified 2 fair-quality randomized controlled trials (RCTs) investigating the benefits of PSA-based screening for prostate cancer for the prevention of prostate cancer-specific morbidity and mortality and all-cause mortality (**Tables 3** and **5-7**). In the 2012, the USPSTF considered evidence from the Prostate, Lung, Colorectal, and Ovarian (PLCO)[53] Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC)[54] trial, as well as separately published reports from the Goteborg center of the ERSPC trial.[85] In 2012, the USPSTF also reviewed updated evidence from three trials previously rated as poor-quality,[178, 179] as well as results from a 2010 systematic review and meta-analysis[180] and a 2011 updated Cochrane meta-analysis.[181] The current review summarizes updated results with extended followup from the PLCO trial,[80, 106] the overall ERSPC trial,[96] and separate updated reports from four ERSPC sites (Sweden,[81] Finland,[87] Netherlands,[92] and Spain[89]). Subjects included in the site-specific ERSPC reports were also included in the overall trial results, so we interpret site-specific outcomes as ancillary, subgroup analyses of the main trial. We also summarize trial evidence on the potential differential impact of screening on subgroups of men with elevated prostate cancer risk (**Table 8**). As previously mentioned, the USPSTF previously reviewed three poor-quality randomized controlled trials in their prior assessment of the effectiveness of PSA-based screening for prostate cancer; due to their poor quality, we excluded these trials and briefly summarize the findings of these studies in **Appendix D**.

Summary

Fair-quality evidence on the impact of PSA screening on prostate cancer mortality and morbidity derives from two randomized trials of screening: the PLCO and the ERSPC trials.[96, 106] The PLCO has been characterized as a trial comparing the effectiveness of organized versus opportunistic screening, whereas the ERSPC trial assessed the impact of PSA screening chiefly among men who have not previously been screened.[182] The PLCO was limited mainly by the

high rate of PSA use among control subjects during the screening and post-screening phases of the trial, which would be expected to bias study outcomes toward the null.[106] The ERSPC trial was limited by unexplained post-randomization differences in prostate cancer treatments in the two study arms; a greater percentage of screening arm subjects with higher-risk cancers underwent radical prostatectomy than control subjects with similar cancers, which may have biased study results in favor of screening.[97] Randomization to PSA screening in both trials was associated with an appreciable increase in the incidence of prostate cancer. In the ERSPC trial, 28.7 men aged 55 to 69 years needed to be invited to multiple rounds of screening over a 13-year period for one additional man to be diagnosed with prostate cancer.[96] Within four sites of ERSPC, randomization to screening was associated with reduced incidence of metastatic prostate cancer during a median followup of 12 years (relative risk [RR], 0.70 [95% CI, 0.60 to 0.82]).[94] After accounting for the 56 percent relative increase in overall incidence of prostate cancer in the screening versus the control arms at these four ERSPC sites, an estimated 12 men would need to be diagnosed with prostate cancer through screening to avert one case of metastatic cancer.

After a median followup of 14.8 years in the PLCO, there was no difference in the risk of prostate cancer mortality in the screening versus control arms (RR, 1.04 [95% CI, 0.87 to 1.24]). After 13.0 years of median followup in the ERSPC trial, randomization to screening versus control was associated with a 21 percent reduction in prostate cancer mortality (RR, 0.79 [95% CI, 0.69 to 0.91]). Based on ERSPC incidence and mortality data, an estimated 27 men need to be diagnosed with prostate cancer to avert one prostate cancer death (95% CI, 17 to 66). In neither trial was screening associated with significantly reduced all-cause mortality. Trial evidence regarding the differential impact of screening on morbidity and mortality within patient subgroups (age, race/ethnicity, comorbidity, prostate cancer risk) was limited or absent. In the PLCO, sample sizes of African-American men (n=3,370) and men with a family history of prostate cancer (n=5,326) were small, limiting power for relevant subgroup analyses.

Study Characteristics

The ERSPC trial was conducted in asymptomatic men identified by population-based registries in Europe,[96] while the PLCO enrolled men at participating screening centers in the U.S.[106] Both trials randomized participants to either receive PSA-based screening (with or without digital rectal examination [DRE]) or no screening. During the screening phases of the trials, 83 percent of men randomized to screening in the ERSPC trial had at least one PSA tests,[96] while average annual adherence to PSA screening in the intervention arm of the PLCO was 85 percent.[99] Characteristics of both trials are presented in **Table 3**.

PLCO Trial

In the prostate component of the PLCO trial, 76,683 U.S. men aged 55 to 74 years were recruited from 1993 to 2001 and randomized to either annual PSA screening for six years (with DRE for the first four screening rounds) or usual care. Abnormal screening results (either a PSA level ≥4.0 ng/mL or an abnormal DRE) were forwarded to primary care physicians, who coordinated further diagnostic evaluation. Incident cancers and deaths were ascertained by annual participant questionnaires, supplemented with medical records review, and linkage with the National Death Index.[91] A 2012 report from the PLCO provides results after a median followup of 13 years,[80]

while a recent publication provides mortality results at a median followup of 14.8 years.[106]

The ages of men in the PLCO screening and control arms were well-matched; 32.3 percent of men were aged 55 to 59 years, 31.3 percent were aged 60 to 64 years, 23.2 percent were aged 65 to 69 years, and 13.2 percent were aged 70 to 74 years.[53] The majority of men were non-Hispanic white (86.2% of the screening arm and 83.8% of the control arm); only 4.4 percent of the PLCO population was non-Hispanic black. About one in five men enrolled in the study had an enlarged prostate or benign prostatic hyperplasia and approximately 7 percent had a family history of prostate cancer. Approximately one-third of men in both arms received either a PSA test or DRE within the past three years, and 4.3 percent of men had previously received a prostate biopsy.[53]

The PLCO has been characterized as a trial comparing the effectiveness of organized versus opportunistic screening,[182] because an estimated 46 percent of control participants received routine screening PSA from community physicians in the prior year during the screening phase of the trial, and 78 percent of control subjects received PSA testing for some purpose during the screening phase of the trial (**Appendix E Table 1**). Nevertheless, during the six-year screening phase of the trial, the extent of PSA testing exposure was greater in the screening than the control arm (mean of 5.3 vs. 3.1 tests, respectively).[99] During the seven years following the screening phase of the trial, between one-half and two-thirds of men in both trial arms reported PSA testing within the prior year in annual surveys of random samples of PLCO participants. Twelve years after randomization, 91 of 100 of surveyed control arm subjects (95% CI, 83.6% to 95.8%) reported having at least one out-of-trial PSA test.[183] Because of the extent of PSA use in the PLCO control arm, we rated the overall quality of the trial as fair.

ERSPC Trial

The ERSPC trial was initiated in 1993 in the Netherlands and Belgium. Five additional centers joined the study between 1994 and 1998 (Sweden, Finland, Italy, Spain, and Switzerland), and two French centers began in 2000 and 2003. Eligible men were aged 50 to 74 years and were recruited through 2003 (2005 in France). However, most ERSPC reports, including the most recent update,[96] emphasize outcomes among the 162,388 randomized men in the "core" age group of 55 to 69 years, which was pre-specified based on consideration of rising prostate cancer incidence in the mid-fifties and lower likelihood of definitive treatment in men over age 70 years.[98] In the core age group, the median age at randomization among men across all sites (excluding France) was 60.2 years.[96]

Recruitment methods differed across sites; four sites obtained informed consent from all men prior to randomization (Belgium, Netherlands, Spain, and Switzerland), while all other sites randomized men from population rolls and only contacted men randomized to screening. Screening PSA protocols varied across ERPSC sites. Most screening intervals were four years, with the exception of Sweden, which used a two-year interval. PSA thresholds prompting biopsy recommendation ranged from 2.5 ng/mL (in later Swedish screening rounds) to 10.0 ng/mL (in the early screening rounds in Belgium); by the end of trial, most sites had adopted a threshold of 3.0 ng/mL. Notably, the Swedish site combined the most intensive screening schedule (biennial) with the lowest positive PSA threshold (2.5 ng/mL). Recently reported mortality results also exclude men from France due to incomplete mortality data from this site. Details of screening

protocols by ERSPC sites are provided in **Table 3**.

ERSPC has been characterized as a trial of PSA screening chiefly among men who have not previously been screened[182] because PSA screening was uncommon in community practice when the trial was initiated. However, the extent of contamination in the control arm was not assessed at all sites; it was estimated to be approximately 20 percent in Netherlands control arm.[82] In Finland, baseline contamination among screening subjects was 13.8 percent in 1999. Among control arms subjects in Italy in 1999, 36.6 percent of control arms subjects reported PSA in the prior year.[84] Due to the rising prevalence of PSA-detected cancers (i.e., stage T1c), recent ERSPC reports suggest substantial opportunistic screening has occurred at some sites during later followup years, although direct measures of out-of-trial screening are lacking.[81, 84, 96, 184]

Since the 2012 USPSTF recommendation, ERSPC centers in Sweden (n=19,899),[81] Finland (n=80,144),[87] the Netherlands (n=42,376)[92] and Spain (n=4,276)[89] have reported results of extended followup of their individual study populations (**Table 3**). In brief, the Swedish (Goteborg) trial was initiated in 1995 as a stand-alone, population-based screening trial but joined the Swedish arm of ERSPC soon after in 1996. Of the 19,899 men aged 50 to 70 years in the Goteborg trial, 11,852 (59.5%) were included in analyses of the overall ERSPC core-age group (ages 55 to 69 years). Screening continued through 2008 for up to eight rounds of biennial screening or until men were over age 69 years. Incident cancers and prostate cancer deaths were ascertained by linkage with national cancer and death registries with cause of death adjudicated by causes of death committees blinded to group assignment. In the most recent report from the trial, followup for mortality outcomes was up to 18.0 years. The Finnish, Netherlands, and Spain ERSPC sites have reported followup at medians of 12.0, 12.8, and 15.2 years, respectively.

We rated the ERSPC trial as fair quality on the basis of several considerations. First, recruitment strategies and inclusion criteria differed across sites, yielding potentially heterogeneous study populations. Second, screening and diagnostic protocols differed across sites and over time. Overall, men in the intervention group were screened a mean of 2.3 times, ranging from 1.6 times in Belgium to 3.5 in Sweden. Third, contamination rates in the control arm were not systematically assessed at all sites.[96] Fourth, among men diagnosed with non-metastatic prostate cancer, a greater proportion of men in the screening arm underwent radical prostatectomy (41.3%) than in the control arm (32.8%), while the opposite was the case for androgen deprivation therapy.[97] While treatment differences by screening arm would arise if screening produces a shift toward more localized stages, treatment differences across ERSPC study arms persisted even with stratification by clinical stage and tumor grade (**Appendix E Table 2**). Screening may also induce favorable shifts in tumor characteristics within-stage, and analyses of ERSPC data show that patient and tumor characteristics (age, PSA, tumor size, nodal status, and grade) were much stronger predictors of treatment approach than study arm.[185] Nevertheless, even after adjusting for these factors, patients randomized to screening were significantly more likely to be treated with prostatectomy as compared to radiotherapy or hormonal therapy.[97] It remains unclear why risk-adjusted treatment differences emerged in the ERSPC study arms, but the location of screening centers within academic rather than community institutions may have played a role. It is conceivable that treatment differences could have influenced long-term study outcomes independent of screening in the ERSPC trial.

Findings

Prostate Cancer Incidence

After up to 13.0 years of followup, incidence rates of prostate cancer in the screening and control arms of the PLCO trial were 108.4 and 97.1 cases per 10,000 person-years, respectively (RR, 1.12 [95% CI, 1.07 to 1.17]) (**Table 5**). After a median followup of 13.0 years, incidence rates of prostate cancer in the screening and controls arms of the ERSPC trial were 95.5 and 62.3 cases per 10,000 person-years, respectively (RR, 1.57 [95% CI, 1.51 to 1.62]), or an absolute rate difference of 34.8 cancers per 1000 men (**Table 5**). The observed risk differences in prostate cancer incidence per 1,000 men imply a number needed to invite (NNI) of 88.0 men in the PLCO trial and 28.7 men in the ERSPC trial for one additional man to be diagnosed with prostate cancer.[80, 96]

At all ERSPC sites with separate reports (Sweden, Netherlands, Finland, and Spain), prostate cancer incidence was statistically significantly greater in the screening versus control arms (**Table 5**).[81, 87, 89, 92] In the Swedish (Goteborg) trial, observed cumulative incidences of prostate cancer over 18.0 years of followup in the screening and control arms were 16 percent and 11 percent, respectively, compared to expected incidences of approximately 7 percent in the absence of organized (in the screening arm) and opportunistic (in the control arm) screening.[81] Absolute differences in the percentage of men diagnosed with prostate cancer in the screening and controls arms at three other ERSPC sites with separate reports ranged from 2.1 percent in Finland[87], 2.4 percent in Spain,[89] and 6.1 percent in the Netherlands.[92]

Cumulative Incidence of Metastatic Cancer

While the PLCO has not reported on cumulative incidence of prostate cancer metastases, the cumulative incidence of metastatic cancer was assessed within four ERSPC sites (Sweden, Netherlands, Finland, and Switzerland).[94] Among randomized men at these sites, the risk of developing metastatic prostate cancer was 30 percent lower among men randomized to screening as compared to control at a median followup of 12.0 years (RR, 0.70 [95% CI, 0.60 to 0.82]; p=0.001). The absolute reduction in long-term risk of metastatic prostate cancer associated with screening was 3.1 cases per 1,000 men randomized. This absolute reduction in cumulative metastatic disease incidence is less than 10 percent as large in magnitude as the absolute increase in total prostate cancer incidence in the overall ERSPC trial (3.1 fewer metastatic cases vs. 34.8 additional prostate cancers diagnosed per 1,000 men). After accounting for the 55.6 percent relative increase in overall incidence of prostate cancer in the screening versus the control arms at these four ERSPC sites, the number needed to invite to screening (NNI) to avoid one case of metastatic cancer was 328, and the number needed to diagnose with prostate cancer through screening (NND) to avert one case of metastatic cancer was 12.[94]

Prostate Cancer-Specific Mortality

At a median followup 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 to 1.24]) (**Table 6**).[106]

Among men in the core age group (ages 55 to 69 years at enrollment) in the ERSPC trial after a median of 13.0 years of followup, the prostate cancer-specific mortality rate 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 to 0.91]; p=0.001) (**Table 6**).[96] The absolute risk reduction in prostate cancer mortality associated with screening was -0.11 deaths per 1,000 person-years (95% CI: -0.18 to -0.05), or 1.28 fewer prostate cancer deaths per 1,000 men. The relative risk of prostate cancer-specific mortality in the intervention arm as compared to the control arm did not diverge from 11 to 13 years of median followup (RR at 11 years, 0.78 [95% CI, 0.66 to 0.91]; p=0.002).[95] With followup truncated at 13.0 years, the NNI to prevent one prostate cancer death was 781 (95% CI, 490 to 1929) and the NND was 27 (95% CI, 17 to 66). When men of all ages were included (ages 50 to 74 years at enrollment) in the analyses, randomization to screening was still significantly associated with reduced prostate cancer mortality (RR, 0.83 [95% CI, 0.73 to 0.94]; p=0.004).

The screening-associated impact on prostate cancer-specific mortality differed across ERSPC sites with separate updated reports (**Table 6**). Within the Netherlands site after a median followup of 12.8 years, men randomized to screening had 20 percent reduced risk of prostate cancer mortality (RR, 0.80 [95% CI, 0.65 to 0.99]; p=0.04).[92] In the Swedish (Goteborg) trial after up to 18.0 years followup, men randomized to screening had 42 percent reduced risk of prostate cancer mortality compared to men randomized to control (RR, 0.58 [95% CI, 0.46 to 0.72]).[81] However, at both sites, the absolute risk reduction in prostate cancer mortality was much lower than the excess incidence of prostate cancer associated with screening; the NNI and NND to prevent one death from prostate cancer were 392 and 24 for men in the Netherlands core age group and 139 and 13 for all men in the Swedish (Goteborg) trial, respectively.

Prostate cancer specific mortality was not statistically significantly different in the screening and control groups in the Finnish and Spanish ERSPC sites. After 12.0 years of median followup in the Finnish site, the hazard ratio of prostate cancer death in the screening versus control arms was 0.85 (95% CI, 0.69 to 1.04; p=0.10).[87] After a median 15.2 years of followup in the Spanish ERSPC site, the prostate cancer mortality rate was 1.4 and 1.9 per 10,000 person-years in the screening and control arms, respectively (p=0.67).[89]

At 13.0 years of median followup, a test for statistical heterogeneity in prostate cancer mortality results across ERSPC sites was not statistically significant (p=0.43) (**Appendix E Table 5**). Across all ERSPC sites, prostate cancer mortality was statistically significantly reduced at the Netherlands and Swedish sites, although point estimates were in favor at screening at all sites except Switzerland.

All-Cause Mortality

After a median followup of 14.8 years, the all-cause mortality rate in the PLCO trial (excluding deaths due to colorectal and lung cancers) was 172.8 per 10,000 person-years in the intervention group and 176.9 per 10,000 person-years in the control arm (RR, 0.98 [95% CI, 0.95 to 1.00]; p=0.11) (**Table 6**).[106] This difference was not statistically significant and was not explained by lower rates of prostate cancer death or by clearly lower death rates within any other diagnostic group.

In the ERSPC trial after a median of 13.0 years of followup, overall mortality was 186.0 and 189.0 death per 10,000 person-years in the screening and control groups respectively (RR, 1.00 [95% CI, 0.98 to 1.02]; p=0.82).[96] Overall mortality was also similar in screening and control arms in the Netherlands, Swedish, Finnish, and Spanish ERSPC sites (**Table 6**).

KQ1a. Does the Effect of PSA Screening Vary Between a Priori Subgroups: Age, Race/Ethnicity, Family History, or Clinical Risk?

Age

Both the PLCO and the ERSPC assessed the differential impact of screening on prostate cancer-specific mortality by age at randomization (**Table 7**). At a median followup of 13.0 years within the PLCO, prostate cancer mortality rates were 2.35 and 1.97 per 10,000 person-years in intervention and control arms, respectively, among men aged 55 to 64 years at randomization (RR, 1.19 [95% CI, 0.83 to 1.72]); the analogous rates for men aged 65 to 74 years were 6.17 and 6.02 per 10,000 person-years (RR, 1.01 [95% CI, 0.77 to 1.37]). However, a test for interaction between patient age and trial arm with respect to prostate cancer mortality was not statistically significant (p=0.81).[80]

Within the ERSPC, the relative risk of prostate cancer-specific mortality associated with screening compared with no screening stratified by age at randomization was 0.84 among men ages 50 to 54 years (95% CI, 0.28 to 2.49), 0.81 among men ages 55 to 59 years (95% CI, 0.93 to 1.03; p=0.09), 0.90 among men ages 60 to 64 years (95% CI, 0.71 to 1.15; p=0.41), 0.69 among men ages 65 to 69 years (95% CI, 0.55 to 0.87), and 1.17 among men aged 70 years or older (95% CI, 0.82 to 1.66). A formal statistical test for heterogeneity in risk ratios across these age groups was non-significant (p=0.18).[96]

Race/Ethnicity

Neither the PLCO nor the ERSPC investigators have reported whether screening effects differed by racial/ethnic group. Although potentially greater benefits of screening among African-American men have been postulated,[186] the sample size of 3,370 non-Hispanic black men who were randomized in the PLCO trial (4.4% of the overall population) was relatively small.

Family History

In the PLCO trial, Liss et al. (2015) assessed whether PSA screening was associated with reduced prostate cancer mortality among white men who reported a family history of prostate cancer on baseline questionnaires (n=4,833, or 7.4% of the total study population). The analysis excluded non-white men due to concerns about small sample sizes and an absence of prostate cancer deaths among non-Hispanic black men with a family history of prostate cancer. After a median followup of 11.6 years, the multivariate hazard ratio for prostate cancer death among

men with a family history of prostate cancer who were randomized to screening was lower relative to control subjects, although not statistically significantly so (HR, 0.49 [95% CI, 0.22 to 1.10]; p=0.08) (**Table 7**).[88] However, the analysis lacked a formal test of statistical interaction between randomization to screening versus control and family history.

The impact of family history on screening outcomes has not been reported within the overall ERSPC trial. Within the Finnish site, Saarimaki, et al. reported on incidence rates, PSA test performance, and cancer characteristics among men randomized to screening with and without a first-degree relative with prostate cancer. However, data on family history were lacking for men randomized to the control arm, so the differential impact of screening among men with and without a family history could not be assessed.[93]

Clinical Risk Assessment

With a median followup of 13 years, PLCO investigators assessed whether comorbidity modified the effect of screening versus control assignment on prostate cancer mortality. Comorbidity was assessed using medical history information from a baseline questionnaire and was classified as 0 versus ≥1 comorbidities using a modification of the Charlson comorbidity index (CCI). Overall, 30 percent of PLCO subjects were classified as having one or more comorbidities. The relative risk of prostate cancer mortality among screening versus control arm subjects was 1.00 (95% CI, 0.76 to 1.31) among men with a CCI score of 0 as compared to 1.11 (95% CI, 0.72 to 1.71) among men with a CCI score ≥1; however this interaction was not statistically significant (p=0.68).[80]

Neither trial reported on the differential effects of screening among men by other clinical risk factors; ethical and practical concerns may preclude pre-planned subgroup analyses by baseline PSA as this would require obtaining and withholding PSA results from the control subjects.[187]

KQ2. What Are the Harms of PSA-Based Screening for Prostate Cancer and Diagnostic Followup?

We identified two fair-quality RCTs and five cohort studies (two good- and three fair-quality) that examined the harms associated with PSA-based screening and associated diagnostic followup (**Tables 3, 4, 8,** and **9**).[33, 53, 90, 96, 101-105, 109-113] Below we summarize evidence on the potential downstream harms that may be triggered by PSA screening, ranging from short-term consequences, such as false-positive biopsy, to longer-term consequences, such as overdiagnosis. Within each potential adverse consequence, we also summarize evidence on variation in adverse effects by patient subgroup.

Summary

Evidence on the harms of PSA screening and diagnostic followup derives from two fair-quality randomized trials of screening and five cohort studies (two good- and three fair-quality). Among men randomized to screening in the U.S. PLCO trial, 28.2 percent had at least one positive

screening during up to six annual screening rounds, and 13.4 percent underwent prostate biopsy, over two-thirds of which (67.7%) were negative for prostate cancer.[103] Compared to the PLCO, rates of positive screening tests and biopsy in the ERSPC trial were higher (32.3 positive screens and 27.7 biopsies per 100 men randomized to screening), and three-quarters of ERSPC biopsies (75.8%) did not reveal prostate cancer.[101] Cohort studies suggest that men who receive abnormal PSA screening but normal biopsy results have increased worry about prostate cancer for at least one year after biopsy. Trial and cohort data suggest that 2 to 5 percent of men undergoing biopsy will have infectious or non-infectious complications, requiring hospitalization in 0.5 to 1 percent.[33, 102, 103] Subgroup analyses from the ERSPC trial demonstrate that men older than age 70 years are at higher risk of having false-positive PSA screening (20.6%) compared to men younger than age 55 years (3.5%).[101] In the PLCO and one U.S. cohort study, non-white men were at increased risk of infectious complications after biopsy compared to white men.[33, 101] Based on excess incidence data from the two trials, 20.7 percent and 50.4 percent of cancer detected by PSA screening in the PLCO and ERSPC trials, respectively, were estimated to be overdiagnosed.[53, 96]

Study Characteristics

We included results from the two screening RCTs (PLCO[106] and ERSPC[96]) as well as five cohort studies[33, 102, 110-113] that reported on the downstream physical or psychological harms resulting from a positive PSA screening test (**Tables 3** and **4**).

RCTs

PLCO Trial

The design of the PLCO trial has been described previously; three publications[53, 103, 107] reported harms among men in the screening arm of the trial. In the PLCO, a PSA threshold of 4.0 ng/mL or a positive DRE resulted in notification of patients' primary care physicians regarding the need for diagnostic followup.[103] After a median followup of 11.5 years, Andriole et al. (2009) reported immediate harms stemming from the PSA screening procedure itself,[53] while Pinsky et al (2014) compared the rate of biopsy-related complications and mortality among men randomized to the screening arm who had at least one prostate biopsy compared to men who did not receive a biopsy.[103] Crosswell et al. (2009) reported on the frequency of false-positive PSA screening during the first four rounds of screening among men randomized to the PLCO screening arm.[107] Men receiving a positive PSA and biopsy were slightly older (63.7 years versus 62.4 years) and were more likely to have prostatic enlargement (34.0% versus 23.2%) than men with a negative screen and no biopsy, but were less likely to be a current or former smoker and had lower comorbidity rates.[103] We rated the overall PLCO trial as fair quality, mainly due to contamination in the control arm, although this limitation would not be expected to bias estimates of screening-related harms in the screening arm of the trial.

ERSPC Trial

The design of the ERSPC trial has been described previously; four publications[101, 104, 105, 108] reported harms among cohorts of men randomized to the screening arm of the ERSPC trial. In

this trial, diagnostic referral and intervention protocols varied among ERSPC sites. For most ERSPC sites, a PSA threshold of 3.0 ng/mL was used for biopsy indication, although some sites initially used higher thresholds, findings from DRE or transrectal ultrasound (TRUS), or ratio of free to total PSA. After one year of followup, Carlsson et al. (2011)[104] assessed the rate of excess mortality after prostate biopsies among first-time screen-positive men from three sites (Finland, Sweden and the Netherlands) compared with a cohort of first-time screen-negative men. Kilpelainen et al. (2011)[101] reported on false-positive screens among men randomized to the screening arm of five sites (Finland, Sweden, the Netherlands, Belgium, and Italy). Raajimakers et al. (2002)[108] reported on complications of initial prostate biopsies prompted by abnormal PSA screening tests within the Rotterdam site. Vasarainen et al (2013)[105] reported the effects of PSA screening on health-related quality of life in the Finnish arm of the ERSPC. We rated the overall ERSPC as fair quality, in part due to the variability in screening protocols and thresholds for biopsy referral.

Cohort Studies

Embedded within the multicenter Prostate Testing for Cancer and Treatment (ProtecT) trial, the Prostate Biopsy Effect (ProBE) cohort study recruited asymptomatic men referred for biopsy at eight U.K. centers due to elevated PSA screening tests (PSA concentrations 3.0 to 19.9 ng/mL).[102] All men completed questionnaires regarding symptoms, health status, and healthcare utilization at baseline, immediately after biopsy, and at 7 and 35 days post-biopsy. Men had a mean age of 62.1 years (standard deviation [SD], 5.1 years) and mean PSA of 4.2 ng/mL (interquartile range [IQR], 3.5 to 5.8).

In a fair quality cohort study using electronic health record data, Walter et al. (2013)[33] identified a cohort of Veterans Affairs health system patients (n=295,645) who had a single PSA screening test in 2003. Among this cohort, potential biopsy candidates were identified based on PSA results exceeding 4.0 ng/mL; the study prospectively followed this cohort for up to five years. Among men in this cohort, the mean age was 73.0 years, nearly 90% of men were white, and 62.4% had no comorbidities.

The 2008 USPSTF review identified two prospective cohort studies[110, 111, 113] and one cross-sectional study evaluating psychological harms of PSA screening.[112] In a good-quality study within one U.S. academic medical center,[110, 111] a cohort of men undergoing PSA screening were identified and surveyed by mail regarding worry and concern about prostate cancer at 6 weeks, 6 months, and 12 months after either normal PSA screening (n=193) or benign biopsy (n=287). In a fair-quality prospective cohort study embedded as part of case-finding for the ProtecT trial,[113] men aged 50 to 69 years who were attending a clinic for PSA screening (n=7,344) completed questionnaires regarding baseline depression, anxiety, and general health status, and the subsample of men with abnormal screening results completed the same measures prior to biopsy (n=569). Lastly, in a fair-quality cross-sectional study within a single U.S. academic institution,[112] men were surveyed regarding anxiety, worry about prostate cancer, and general health status by telephone either 2 months after a normal PSA screening results (n=101) or after a benign biopsy prompted by abnormal PSA screening (n=109).

Findings

Exposure to Followup Testing and False Positives

Followup Testing

Among men randomized to screening in the PLCO who had at least one screening test (n=35,870), 10,798 men (28.2%) had at least one elevated PSA screen (≥4.0 ng/mL) during up to six screening rounds. Of men with elevated PSA tests, 4,836 (44.8% of men with positive screens, 12.6% of men randomized to screening) underwent one or more biopsies, resulting in a total of 6,295 biopsies (16.4 biopsies per 100 men randomized to screening). Of 6,295 biopsies performed on these 4,836 men, 67.7% did not result in a prostate cancer diagnosis.[103]

Among men randomized to screening in the ERSPC core age group (n=72,891), men were screened on average 1.9 times over a median followup of 13.0 years. During this period, there were 23,574 positive PSA tests (0.32 positive tests per man randomized to screening). Among men with positive screening tests, there were 20,188 prostate biopsies performed (27.7 biopsies per 100 men randomized to screening). Of the 20,188 biopsies performed, 15,305 (75.8%) did not result in a prostate cancer diagnosis.[96]

In the fair-quality VA cohort study of men undergoing a single PSA screening test, 8.5 percent of screened men (n=25,208) had a PSA exceeding 4.0 ng/mL. Of those men, most (51.2%) underwent further PSA testing without biopsy, and 8,313 underwent biopsy (32.9% of men with elevated PSA). Of men undergoing biopsy, 37.2% did not have prostate cancer.[33] The higher positive predictive value of biopsy in this cohort (62.8%) compared to the two trials (24.2% and 32.3% in ERSPC and PLCO, respectively) may be attributable to the older age of men in the cohort as well as the selection of men for biopsy based on repeated PSA or other clinical features.

False-Positive Testing

Among men who underwent at least one PSA screen during the initial four PLCO screening rounds (n=32,576), the cumulative incidence of false-positive PSA screening was 10.4 percent (defined as a PSA>4 ng/mL with the absence of a prostate cancer diagnosis within three years of positive screening) (**Table 8**).[107] After four rounds of screening, the risk of undergoing biopsy on account of a false-positive PSA screen was 5.5 percent (95% CI, 4.6% to 6.5%).

Longitudinal post-biopsy followup was reported for five ERSPC centers (Belgium, Finland, Italy, Netherlands, and Sweden), enabling classification of abnormal PSA screening results as true- versus false-positive (**Table 8**).[101] False-positive screening results were defined as elevated PSA results without a histological prostate cancer diagnosis occurring within one year of the screen. Each site reported results for three screening rounds, while Sweden reported results of six screening rounds. Among men randomized to screening who were screened at least once (n=61,604), 17.8 percent (n=10,972) had at least one false-positive screening test. Cumulative false-positive rates were lower at sites with a higher screen-positive PSA threshold of 4.0 ng/mL (9.0% in Italy and 11.9% in Finland), as compared to sites with lower thresholds of 2.5 to 3.0

ng/mL (cumulative false-positive rates of 15.6%, 27.8%, and 44.9% in Belgium, Netherlands, and Sweden, respectively). In addition to the lower screen-positive threshold, there were up to six biennial screening rounds at the Swedish site (as compared to a maximum of three rounds every fourth year at the other sites), which contributed to the higher cumulative false-positive rate at the Swedish site.

Physical and Psychological Harms of PSA Screening and Diagnostic Followup

PSA Testing

PSA screening requires venipuncture, and the PLCO reported rare adverse effects of this procedure, including bleeding (0.3 events per 10,000 men screened) and dizziness, fainting, or bruising (26.2 events per 10,000 men screened) (**Table 8**).[53]

Complications of Diagnostic Followup

Among 4,836 men who underwent biopsy within the PLCO, biopsy complications occurred at a rate of 20.2 per 1,000 biopsies (approximately 2% overall), including 7.8 infectious and 13.0 non-infectious complications per 1,000 biopsies (non-infectious complications consisted predominately of bleeding or urinary difficulties) (**Table 8**). Biopsy was not associated with increased short-term (120-day) mortality relative to men with negative PSA screens (RR, 0.49 [95% CI, 0.2 to 1.1]).[103]

Among 5,676 men undergoing prostate biopsy after abnormal PSA at the ERSPC Rotterdam site, 22.6 percent experienced hematuria lasting more than 3 days, 7.5 percent reported significant post-biopsy pain, 3.5 percent experience fever, and 0.5 percent were hospitalized (the large majority due to infectious complications).[108] Among men randomized at three ERSPC centers (Finland, Netherlands, and Sweden), prostate biopsy was not associated with overall mortality during a one-year post-biopsy followup as compared to screen-negative men who did not undergo biopsy.[104]

Among men in the ProBE cohort (n=1,147), 7.4 percent reported moderate or severe hematuria immediately after biopsy (95% CI, 6.0% to 9.1%), and 89.4 percent (87.4% to 91.1%) reported one or more infective/hemorrhagic symptoms within 7 days of biopsy. During the 35 days after biopsy, 7.3 percent of men (95% CI, 5.7% to 9.1%) reported pain to be a moderate or serious problem, 5.5 percent experienced fevers that were a moderate or serious problem (95% CI, 4.2% to 7.1%), and 26.6 percent considered hemoejaculation to be a moderate or serious problem (95% CI, 23.3% to 30.2%). Within 35 days of biopsy, 1.3 percent of men were admitted to hospital for biopsy-related complications (95% CI, 0.8% to 2.1%), including 0.6 percent of men who were admitted for sepsis within 3 days of biopsy. Overall, 10.4 percent of men sought outpatient care for biopsy-related symptoms (95% CI, 8.7% to 12.3%). There were no biopsy related deaths (95% CI, 0% to 0.4%).

Of men with abnormal PSA screens who underwent prostate biopsy and were followed in the fair-quality VA cohort study, (n=8,313), 5.6 percent had infectious or urinary complications within seven days of biopsy, and 1.6 percent were hospitalized (**Table 8**); comparison rates for a

non-biopsy control group were not provided.[33]

Psychological Harms of PSA Screening

In a prospective cohort study[110, 111] and a cross-sectional study,[112] men who had abnormal PSA screening tests but benign biopsy results had significantly increased worry about prostate cancer at both six- to eight-week as well as one-year followup compared to men with normal PSA screening results. At 12 months followup, 33 percent of men with a benign biopsy after abnormal screening thought about prostate cancer either "a lot" or "some" as compared to 18 percent of men who had normal PSA screening (p=0.005). However, in a U.K. prospective cohort study, men who had received abnormal PSA screening results had no increase in anxiety or depression relative to baseline prior to PSA screening and similar scores on the Mental Health Component of the SF-12.[113] Likewise, in a comparative, cross-sectional U.S. study (n=210), men with benign biopsies after abnormal PSA screening did not have statistically significantly greater trait anxiety than men who received normal results approximately two months after receiving final test results.[112]

Impact on Health-Related Quality of Life

Within the Finnish arm of the ERSPC trial, a subsample of men randomized to the screening arm were asked to complete the SF-36 health and functional status assessments at invitation, after PSA screening, after receiving a PSA result, after DRE, and after TRUS with biopsy (n, range: 215 to 386). As compared to status at invitation, health and functional status were essentially unchanged at every other point in the screening process. While prostate biopsy is an invasive procedure that is associated pain and discomfort, within the sub-sample of men who underwent TRUS and biopsy after positive PSA (n=319), biopsy was not associated with any change in the SF-36 bodily pain subscale as compared to pre-biopsy.[105] In a cross-sectional study of U.S. men,[112] overall SF-36 scores (as well subscale scores) were similar among men who had normal PSA screening results and men who had abnormal PSA screening results with subsequent benign biopsies.

Overdiagnosis of Prostate Cancer

Using the approach described in the Methods, we assessed the rate of overdiagnosis using data from the PLCO, the overall ERSPC trial, and four ERSPC sites reporting extended followup (Sweden, Netherlands, Finland and Spain). The PLCO and overall ERSPC reported excess incidence after a median of 13.0 years followup, while median followup at ERSPC subsites ranged from 12.0 years (Finland) to 15.2 years (Spain).

As shown in **Table 9** when overdiagnosis is estimated as a percentage of all prostate cancers diagnosed, 16.4 percent and 33.2 percent of prostate cancers were overdiagnosed in PLCO and overall ERSPC trials, respectively. When estimated as a percentage of cancers detected by screening during the screening phase, 20.7 percent and 50.4 percent of cancers were overdiagnosed in the PLCO and ERSPC trials, respectively.

The extent of overdiagnosis varied across ERSPC sites (**Table 9**). When estimated as a

percentage of all prostate cancers diagnosed, the extent of overdiagnosis within ERSPC subsites ranged from 23.6 percent to 47.9 percent in Finland and the Netherlands, respectively. At these two sites, we could identify the number of cancers detected by screening, and the extent of overdiagnosis of screen-detected cases was 25.6 percent in Finland and 58.9 percent in the Netherlands. The two ERSPC sites with the largest extent of overdiagnosis (Sweden and Netherlands) were those with relatively more intensive screening protocols (PSA biopsy thresholds of 2.5 to 3.0 ng/mL at each site, biennial screening in Sweden and every four years in the Netherlands, and comparatively high rates of biopsy). Sweden and the Netherlands were also the only ERSPC sites to report statistically significant reductions in prostate cancer mortality, suggesting that a reduction in prostate cancer mortality with PSA screening may necessitate a higher level of overdiagnosis.[85, 92]

These estimates of overdiagnosis should be interpreted cautiously for several reasons.[188] Due to the long lead-time of prostate cancer, the duration of post-screening followup may be insufficient for incident cases to accrue fully in control arms. For example, at the ERSPC sites with screening rounds every four years (Netherlands, Finland, and Spain), the 12 to 15 year median followup period would allow approximately 4 to 7 years of followup after the third and final screening rounds. Estimates of overdiagnosis could be lower with longer-term followup. However, use of screening in the control arm during and after the screening phase of the trial may reduce the excess incidence that would be observed with strict adherence to screening protocol and cessation of screening in both trial arms at the end of the screening phase.[67] In both the PLCO and ERSPC, there was evidence of substantial PSA screening in both screening and control groups during post-trial followup.[86, 96, 183] The use of PSA screening during and after the screening phase among control subjects would reduce trial-based estimates of overdiagnosis. Thus, the precise extent of overdiagnosis in the PLCO and ERSPC may be difficult to discern even after many additional years of post-trial followup.

KQ2a. Do the Harms of PSA Screening Vary Between a Priori Subgroups: Age, Race/Ethnicity, Family History, or Clinical Risk?

Age

Among ERSPC participants, false-positive rates were higher among older as compared to younger men, ranging from 3.5 percent in men younger than 55 years to 20.6 percent in men older than 70 years during the first screening round.[101]

In the VA cohort study, the proportion of PSA tests exceeding 4.0 ng/mL that resulted in a prostate biopsy was higher among younger men (50.5% among men aged 65 to 69 years) compared with older men (25.4%, 16.5% and 10.0% among men aged 75 to 79 years, 80 to 84 years, and older than 85 years, respectively).[33]

Biopsy complications in the PLCO were more common in men aged 70 years or older compared to men younger than age 70 years (28.2 vs. 17.7 complications per 1000 biopsies, respectively),

although this difference did not reach statistical significance in adjusted analyses (OR, 1.4 [95% CI, 0.9 to 2.4]; p=0.06).[103]

Race/Ethnicity

Two studies compared the risk of biopsy complications by race/ethnicity. In the PLCO trial, infectious complications were significantly more common in black men as compared to non-black men (OR, 7.1 [95% CI, 2.7 to 18.0]; p<0.001); however, the same was not true for non-infectious complications (OR, 0.5 [95% CI, 0.1 to 3.6]; p=0.08).[103] Due the small sample size of biopsies among black men in the PLCO (n=142), confidence intervals were wide around the odds ratio for infectious complications, and it is unclear why black men would be at elevated risk for infectious biopsy complications.

Family History

No studies assessed the risk for screening or diagnostic-related harms based on family history of prostate cancer.

Clinical Risk Assessment

The PLCO trial did not find any significant difference in total, infectious, or non-infectious complications based on level of comorbidity.

No studies assessed the risk for screening or diagnostic-related harms based other measures of clinical risk, such as baseline PSA.

KQ3. Is There Evidence That Various Treatment Approaches for Early-Stage or Screen-Detected Prostate Cancer Reduce Morbidity and Mortality?

Three good-quality RCTs[74, 116-119, 121-124, 132, 133, 136] and 10 cohort studies (3 good-quality and 7 fair-quality)[75, 114, 115, 125, 127-131, 134, 135] compared the benefits of various active treatments to conservative management for early-stage or screen-detected prostate cancer (**Tables 10, 11,** and **16-19**). Of the three RCTs, only the recently published Prostate Testing for Cancer and Treatment (ProtecT) trial assessed the impact of various treatment approaches on long-term outcomes of screen-detected prostate cancer, while patient samples in prior trials included men with clinically-detected rather than screen-detected cancers.

Summary

The ProtecT trial randomized men with localized, screen-detected prostate cancer to one of three study arms (radical prostatectomy [RP; n=553], radiation therapy [RT; n=545] with neoadjuvant androgen deprivation therapy [ADT], and active surveillance [AS; n=545]).[126, 136] In each arm,

prostate cancer survival was approximately 99 percent at median followup of 10.0 years, and no statistically significant differences were observed in the primary outcome of prostate cancer mortality. During the 10-year followup, the incidence of metastatic disease among men randomized to AS (6.3 cases per 1,000 person-years) was higher than among men randomized to RP or RT (2.4 and 3.0 cases per 1,000 person-years; p=0.004 for overall difference across arms). Approximately 27 and 33 men with screen-detected localized cancer would need to be treated with RP and RT (rather than AS), respectively, to prevent one man from progressing to metastases within 10 years. In earlier RCTs that included men with clinically diagnosed rather than screen-detected prostate cancer, RP was associated with statistically significantly reduced prostate cancer mortality compared to watchful waiting among all men in the SPCG-4 (median followup, 13.4 years; RR, 0.56 [95% CI, 0.41 to 0.77])[117] but not in the U.S. Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial (median followup, 12.7 years; HR, 0.63 [95% CI, 0.39 to 1.02)]).[136] In both the SPCG-4 and the PIVOT trials, RP was also associated with reduced progression to metastatic or systemic disease (SPCG-4 at 13.4 y median followup: RR, 0.57 [95% CI, 0.44 to 0.75]; PIVOT at 12.7 median followup: HR, 0.64 [95% CI, 0.42 to 0.97)]).[117, 136] Thus, randomized trial evidence to date suggests that active treatment with RP or RT for early-stage, screen-detected prostate cancer is likely to reduce risk of clinical progression and metastatic disease and likely reduces prostate cancer mortality in men similar to those in the SPCG-4 with clinically detected or palpable tumors. The long-term impact of active treatments on prostate cancer mortality among men with screen-detected, lower-risk cancer remains unclear. We found no RCTs evaluating long-term outcomes of primary androgen deprivation therapy (ADT) for early-stage prostate cancer.

In eight cohort studies of RP[75, 115, 125, 129-131, 134, 135] and eight cohort studies of RT,[75, 114, 115, 125, 129, 130, 134, 135] both treatment approaches were predominately associated with improved prostate-cancer survival for men with early-stage prostate cancer, including studies that used propensity score or instrumental variable approaches to address potential unmeasured confounding. In a fair-quality cohort study using instrumental variable analyses, primary androgen deprivation therapy for early-stage prostate cancer was associated with no significant differences in prostate cancer mortality or overall mortality compared to conservative management.[127] Interpretation of the cohort data, however, is difficult because many studies included men with both screen-detected cancers and cancer detected due to clinical symptoms. In addition, providers may select healthier men for active treatments and sicker men for primary ADT or conservative management; even with careful multivariate adjustment, residual confounding may affect cohort results.

Study Characteristics

Overall, we identified three randomized controlled trials[117, 121, 133] and ten cohort studies[75, 114, 115, 125, 127, 129-131, 134, 135] reporting all-cause mortality, prostate cancer-specific mortality, or morbidity for active prostate cancer treatments compared with conservative management strategies (i.e., active surveillance, watchful waiting, or observation) (**Tables 10** and **11**). We identified three RCTs[117, 121, 133] and eight cohort studies[75, 115, 125, 129-131, 134, 135] that compared RP with conservative management, and one RCT[121] and eight cohort studies[75, 114, 115, 125, 129, 130, 134, 135] that compared RT with conservative management. One RCT, the VACURG trial, which was graded poor quality and only discussed descriptively in the 2012 review, was excluded from the current

review due to poor quality. Three cohort studies[127, 129, 135] assessed the effectiveness of primary ADT compared with conservative management. We did not identify any RCTs or cohort studies comparing high-intensity focused ultrasound (HIFU) or cryotherapy with conservative management. Median followup ranged from 2.0 years[114, 131] to 13.4 years[117] across all studies and of 10.0 years[121, 133] to 13.4 years[117] in the RCTs.

Although each of the three treatment-related RCTs received a good-quality rating, several differences are notable. First, patient recruitment occurred during different points in the period of PSA uptake, yielding important differences in the prognosis of enrolled men. All men in the ProtecT trial had cancer that were detected by PSA screening, and approximately 77 percent of men had low-grade cancers (Gleason score = 6) with favorable prognoses. Even so, some men randomized to AS in ProtecT had intermediate grade tumors (or other tumor characteristics) such that they would not have been considered sufficiently low-risk to receive AS at many centers.[32] In contrast to ProtecT, approximately half of men in the PIVOT trial had PSA-detected cancers, and most men in the SPCG-4 trial had palpable tumors that were diagnosed prior to the PSA screening era. Prognoses of men with clinically-detected prostate cancer would be expected to be poorer than men with screen-detected cancer.

Second, PIVOT and SPCG-4 included men up to age 75 years, while ProtecT limited recruitment to men aged 69 years or less. Third, only one of the three trials (PIVOT) included US men and was conducted exclusively among veterans which may limit generalizability to the general US screening population. Finally, the treatment protocol for men in the conservative management arm differed across trials. In the ProtecT trial, men in conservative management arm received "active monitoring," which consisted chiefly of periodic PSA testing to monitor disease progression with urological evaluation and potential biopsy if PSA rose beyond specified thresholds. In contrast, in the PIVOT and SPCG-4 trials, conservatively managed men received "watchful waiting," emphasizing palliative approaches when men experienced clinical progression.

Information on the interventions delivered was limited in most cohort studies. For example, of the 11 studies of radical prostatectomy, only one specified the type of prostatectomy performed (nerve-sparing versus non-nerve sparing).[75] Similarly, of the 9 studies of radiation therapy, five[75, 125, 129, 134, 135] specified the type of radiation therapy delivered (EBRT or brachytherapy, or a combination) but only one[135] stratified outcomes by the type of radiation therapy delivered. Most cohort studies compared active treatments to a group of men who did not receive immediate active treatment, and thus the conservative management may have included men undergoing a watchful waiting approach or active surveillance.

Findings

Radical Prostatectomy

We identified three RCTs[117, 121, 133] and eight cohort studies[75, 115, 125, 129-131, 134, 135] that evaluated risk of all-cause mortality and prostate cancer-specific mortality associated with radical prostatectomy (RP) as compared with conservative management for treatment of men with localized (stages T1 or T2) prostate cancer. One of the eight cohort studies only presented results

stratified by subgroups (e.g. age, comorbidities, etc.);[131] therefore this study will be discussed only in the subsequent section addressing effectiveness among patient subgroups.

RCTs

ProtecT. Conducted in the U.K., the recently published ProtecT study[121] randomized 1,643 men aged 50 to 69 years with PSA screen-detected localized prostate cancer to RP, RT, or active surveillance. ProtecT recruited men who were diagnosed with localized prostate cancer within practices participating in the CAP trial (Cluster randomized trial of PSA testing for Prostate cancer) in which participating U.K. primary care practices were randomized to PSA screening versus no screening. (Results of the CAP trial have not been reported and are expected in 2018.) The PSA threshold for diagnostic evaluation was 3.0 ng/dL. Among 2,896 men diagnosed with prostate cancer after screening, 270 (9.3%) were ineligible because they had advanced disease at diagnosis, 209 (7.2%) had localized disease but were excluded for other reasons (e.g., deemed unfit for radical treatment). Of the remaining men, 1,643 (62%) agreed to be randomized to RP (n=553), RT (n=545) or active surveillance (n=545).

At 10.0 years median followup, the hazard ratio (HR) for all-cause mortality with RP as compared to active surveillance was not statistically significant (0.93 [95% CI, 0.21 to 1.93]). The prostate cancer mortality rate for men randomized to RP was 0.9 per 1,000 person years (95% CI, 0.4 to 2.2) compared to 1.5 per 1,000 person years among men randomized to active surveillance (95% CI, 0.7 to 3.0), but this difference was not statistically significant. There were no differences in prostate cancer-specific mortality between treatment and non-treatment groups as cancer-specific survival remained above 98.8 percent in all study arms. Over half of men randomized to active surveillance eventually received radical treatment (54.8% [95% CI, 50.4 to 59.3%]); thus, nearly half the men in the monitoring arm remained stable without any curative treatment at 10 years.

A pre-specified secondary outcome of ProtecT[121] was clinical progression, defined as progression to metastases, clinical T3 or T4 disease, long-term androgen deprivation therapy, ureteric obstruction, rectal fistula, or need for a urinary catheter due to obstruction. At a median of 10 years followup, 8.4 percent of men who underwent RP experienced clinical progression as compared to 20.6 percent of men randomized to active surveillance (HR, 0.39 [95% CI, 0.27 to 0.54]). Men who received RP were less than half as likely to progress to metastatic disease (2.4 per 1,000 person years [95% CI, 1.4 to 4.2]) compared with men randomized to active surveillance (6.3 per 1,000 person years [95% CI, 4.5 to 8.8]). Over a ten year period, an estimated 27 men would need to be treated with RP rather than receiving active surveillance to avert one case of metastatic prostate cancer.

PIVOT. Conducted in U.S. Veterans Affairs medical centers, the PIVOT study (n=731)[133] randomized men with localized prostate cancer (approximately half of which were not palpable and were detected via PSA testing) to RP or observation. The first publication from PIVOT reported outcomes at a median followup of 10 years,[133] while a recent publication reported outcomes at a median of 12.7 years of followup.[133] After a median followup of 12.7 years, RP was not associated with statistically significant decrease in the trial's primary outcome of all-cause mortality compared with observation (HR, 0.84 [95% CI, 0.70 to 1.01]; absolute risk

reduction, 5.5% [95% CI, -1.5% to 12.4%]). RP was not associated with significant decrease in risk of prostate cancer-specific mortality compared to observation (HR, 0.63 [95% CI, 0.39 to 1.02]). After a median followup of 12.7 years, the percentage of men in the PIVOT trial who experienced systemic progression of their prostate cancer was significantly lower among men randomized to RP as compared to observation (HR 0.64 [95% CI, 0.42 to 0.97]; absolute risk reduction, 4.5% [95% CI, -0.3% to 9.4%]. Similarly, after a median followup of 10.0 years, the incidence of bone metastases was significantly lower for men randomized to RP as compared with men randomized to observation (4.7% vs. 10.6%; HR, 0.40 [95% CI, 0.22 to 0.70]).

SPCG-4. In the SPCG-4 trial (n=695),[117] men with localized prostate cancer identified in the pre-PSA era in several Scandinavian countries were randomized to RP or watchful waiting. After a median of 13.4 years of followup, RP was associated with a decrease in risk for all-cause mortality versus watchful waiting (RR, 0.71 [95% CI, 0.59 to 0.86]; absolute difference, 12.7% [95% CI, 5.1% to 20.3%]). Similarly, RP was associated with significantly reduced prostate cancer-specific mortality compared to watchful waiting (RR, 0.56 [95% CI, 0.41 to 0.77]; absolute difference, 11.0% [95% CI, 4.5% to 17.5%]) and reduced risk of progression to metastatic disease (RR, 0.57 [95% CI, 0.44 to 0.74]; absolute risk difference, 12.2% [95% CI, 5.1 to 19.3%]).

Cohort Studies

Seven cohort studies compared mortality or morbidity among men with localized prostate cancer treated with RP versus conservative management (median n=3,242; followup duration: 3-13 years). [75, 115, 125, 129, 130, 134, 135] In three of four cohort studies that compared prostate cancer-specific mortality among patients undergoing RP versus conservative management,[130, 134, 135] RP was associated with statistically significantly reduced prostate cancer mortality in three studies as compared to conservative management, while few prostate cancer deaths occurred in the fourth cohort study, which had a short median followup of three years.[75] All seven cohorts[75, 115, 125, 129, 130, 134, 135] reported on all-cause mortality; radical prostatectomy was associated with statistically significantly decreased risk of all-cause mortality compared to conservative management in all but two cohorts.[75, 115] No cohort studies assessed the impact of radical prostatectomy on cancer-related morbidity (i.e. metastatic disease).

Radiation Therapy

One RCT[121] and eight cohort studies[75, 114, 115, 125, 129, 130, 134, 135] evaluated mortality or morbidity outcomes associated with RT as compared with conservative management in men with localized prostate cancer. One of the eight cohort studies only presented results stratified by subgroups so it is discussed in a later subsection addressing subgroups.[114] Only the ProtecT trial (and none of the cohort studies) assessed the impact of radiation therapy on cancer-related morbidity (e.g., progression to metastatic disease).

RCTs

ProtecT. Within the good-quality ProtecT trial, approximately one-third of men with screen-detected prostate cancer (n=545) were randomized to EBRT, and outcomes were compared to a

group randomized to active surveillance (n=545). Patients receiving radiation therapy in ProtecT also received neoadjuvant ADT beginning 3 to 6 months prior to and during radiation therapy. At 10.0 years of median followup, randomization to EBRT was not associated with a statistically significant reduction in all-cause mortality compared with active surveillance (HR, 0.94 [95% CI, 0.65 to 1.36]). Prostate cancer mortality was also not significantly lower among men randomized to EBRT versus active surveillance (HR, 0.51 [95% CI, 0.15 to 1.69]). Furthermore, prostate cancer-specific survival remained above 98.8 percent in all study arms at a median followup of 10 years.

At 10.0 years median followup, 8.4 percent of men who were randomized to EBRT experienced clinical progression as compared to 20.6 percent of men randomized to active surveillance (HR, 0.39 [95% CI, 0.27 to 0.55]). Men who received radiation therapy were about half as likely to progress to metastatic disease (3.0 per 1,000 person years [95% CI, 1.9 to 4.9]) compared with men on active surveillance (6.3 per 1,000 person years [95% CI, 4.5 to 8.8]). Approximately 33 men with screen-detected localized prostate cancer would need to be treated with radiation therapy (with neoadjuvant androgen deprivation therapy) rather than active surveillance to avert one case of metastatic prostate cancer.

Cohort Studies

Seven cohort studies compared mortality outcomes among men with localized prostate cancer receiving RT vs conservative management (median n=3,450; followup duration, 3 to 13 years).[125, 130, 134, 135, 75, 115, 129] In four of seven studies,[125, 130, 134, 135] RT (EBRT, brachytherapy, or unspecified modality) was associated with a statistically significant reduction in all-cause mortality (median HR, 0.62 [range, 0.40 to 0.81]). Among the four cohort studies[115, 130, 135] that reported prostate cancer-specific mortality, RT was not associated with a statistically significant reduction in three studies,[75, 115, 130] while brachytherapy was associated with statistically significantly reduced prostate cancer-specific mortality in the fourth (HR, 0.45 [95% CI, 0.23 to 0.87]).[135] In the single study that presented separate hazard ratios for EBRT and brachytherapy,[135] there was no statistically significant difference in prostate cancer survival at 7.0 years of median followup between the two modalities, but all-cause mortality was significantly lower (compared to a referent of no treatment) among men who received brachytherapy (HR 0.40 [95% CI, 0.32 to 0.52]) compared to men who received EBRT (HR, 0.63 [95% CI, 0.53 to 0.75]).

We did not identify any cohort studies that assessed the impact of RT on cancer-related morbidity (i.e., metastatic disease).

ADT

We found no RCTs comparing ADT with conservative management for localized or screen-detected prostate cancer. Three cohort studies[129, 135, 189] evaluated risk of all-cause or prostate cancer-specific mortality among men with localized prostate cancer receiving ADT as compared to conservative management. We did not identify any studies that assessed the impact of ADT on cancer-related morbidity (i.e. bone pain from metastases or progression to advanced-stage cancer).

Cohort Studies

Three cohort studies[129, 135, 189] of men with localized prostate cancer and median followup durations ranging from 5.0 to 15.0 years examined the association between ADT with all-cause and prostate cancer-specific mortality outcomes as compared with conservative management strategies. The largest and most recent study[189] (n=66,717) was a fair-quality retrospective analysis of Medicare patients identified from SEER-Medicare linked records who received either ADT as primary therapy (n=25,125) or no therapy (n=41,592) during the first six months following diagnosis. In an instrumental variable analysis, ADT was not associated with any difference in prostate cancer-specific mortality (adjusted HR, 1.01 [95% CI, 0.90 to 1.14]) or all-cause mortality (adjusted HR, 1.04 [95% CI, 0.99-1.09]) compared to conservative management. Results from another fair-quality analysis of elderly men with localized prostate cancer[135] (n=4,316) were mixed; men who received primary ADT as monotherapy were more likely to die of prostate cancer compared with no treatment (HR, 1.32 [95% CI, 1.01 to 1.73]), but were less likely to die overall (HR, 0.89 [95% CI, 0.80 to 0.98]). A multivariable analysis of men recruited from seven state registries (n=3,297) yielded no significant differences in all-cause mortality between men who received primary ADT as compared to those on watchful waiting.[129]

Cryotherapy

We did not identify any RCTs or cohort studies that assessed the impact of cryotherapy on all-cause mortality, prostate cancer-specific mortality, or morbidity.

HIFU

We did not identify any RCTs or cohort studies that assessed the impact of HIFU on all-cause mortality, prostate cancer-specific mortality, or morbidity.

KQ3a. Does the Effectiveness of These Treatment Approaches Vary Between a Priori Subgroups: Age, Race/Ethnicity, Family History, or Clinical Risk?

Below we summarize evidence from included studies on the differential impact of alternative treatment approaches among a priori subgroups. In the ProtecT trial,[121] tests for significant interaction between patient and tumor characteristics (age, baseline PSA, Gleason score, and clinical stage T1c vs. T2) and treatment effects on prostate cancer mortality were all non-significant. Because prostate cancer survival exceeded 99 percent at 10 years followup in all patient and treatment strata, we do not discuss these ProtecT subgroup analyses further below.

Age

Radical Prostatectomy

Two studies evaluated the differential impact of RP, compared with conservative management,

on morbidity and mortality outcomes by age. In the PIVOT trial,[133] no significant age-related differences in the association between RP and all-cause mortality were observed among men greater or less than age 65 years at diagnosis after a median followup of 12.7 years (**Table 15**). However, after a median followup of 13.4 years in the SPCG-4 trial,[117] the risk of all-cause mortality for RP versus watchful waiting was significantly reduced among men younger than 65 years at diagnosis (RR, 0.50 [95% CI, 0.37 to 0.68]) but not significantly reduced among men aged 65 years and older at diagnosis (RR, 0.92 [95% CI, 0.73 to 1.18]). In both the PIVOT and SPCG-4 trials tests for interaction were not significant when assessing whether patient age at diagnosis modified the impact of prostatectomy on prostate cancer mortality or progression to metastatic disease.

Radiation Therapy

One good-quality, propensity-adjusted analysis of elderly men identified in the linked SEER-Medicare database (n=68,797) observed that RT (compared to observation) was associated with a statistically significant reduction in prostate cancer mortality among men aged 75 to 80 years (HR, 0.70 [95% CI, 0.59 to 0.80]) but not among men aged 65 to 69 years (HR, 0.93 [95% CI, 0.72 to 1.19]; p=0.60) or 70 to 74 years (HR, 0.80 [95% CI, 0.68 to 1.03]; p=0.08).[114]

ADT

We found no studies that compared differential outcomes of ADT by patient age relative to a conservative management referent group.

Race/Ethnicity

Radical Prostatectomy

In analyses for effect modification in the PIVOT trial, there was no evidence of differential impact of prostatectomy as compared to conservative management on study outcomes by race/ethnicity.[133]

Radiation Therapy and ADT

We found no studies assessing differential impact of radiation therapy or androgen deprivation therapy as compared with conservative management by racial/ethnic group.

Family History

We did not identify any studies that assessed the variation of treatment-associated mortality and morbidity by patient family history.

Clinical Risk Assessment

We assessed studies for evidence of differential impact of treatments by clinical risk assessment,

considering pre-treatment factors such as tumor characteristics, clinical stage, baseline PSA, or a combination of these factors.

Radical Prostatectomy

Two trials evaluated the differential impact of RP, compared with conservative management, on morbidity and mortality outcomes by clinical risk (**Table 15**). Tests for interaction in the PIVOT trial[133] by tumor risk category were not significant for the primary outcome of all-cause mortality (p=0.08), although men with intermediate risk tumors randomized to RP had significantly reduced all-cause mortality as compared to men randomized to observation (HR 0.68 [95% CI, 0.50 to 0.92]). However, tests for interaction between tumor risk category and prostate cancer mortality were not significant (p=0.89), and hazard ratios for prostate cancer mortality associated with RP did not differ significantly across tumor risk categories. A similar pattern was observed when comparing outcomes for men with baseline PSA ≤ 10 ng/mL versus PSA > 10 ng/mL, with all-cause mortality being statistically significantly reduced with RP only among men with baseline PSA > 10 ng/mL (HR, 0.73 [95% CI, 0.54 to 0.98]) but not among men with baseline PSA ≤ 10 ng/mL (HR, 0.91 [95% CI, 0.72 to 1.14]). Caution is warranted when interpreting these subgroup analyses due to the risk Type I error with multiple comparisons. In the SPCG-4 trial,[117] a statistical test for difference in RP impact on prostate cancer mortality by tumor risk was not significant (p=0.07). No tests of interaction were reported for all-cause mortality or progression to metastases.

Two fair-quality cohorts performed subgroup analyses by clinical risk category for RP versus conservative management. In a fair-quality Swedish cohort study comparing outcomes of localized prostate cancer among men treated with RP or surveillance (n=6,849), relative risk reductions in prostate cancer-specific mortality associated with RP were not statistically significantly different between men with low risk tumors (RR, 0.29 [95% CI, 0.09 to 0.87]) and men with intermediate risk tumors (RR, 0.53 [95% CI, 0.35 to 0.80]).[130] Similarly, a large, fair-quality SEER analysis (n=67,087) that stratified men by life expectancy of greater or less than ten years found that life expectancy did not seem to modify the association between RP and lower all-cause and prostate cancer mortality.[131]

Radiation Therapy

Two fair-quality cohort studies assessed whether prostate cancer mortality reductions associated with radiation therapy differed by either tumor risk or grade.[114, 130] In a stratified competing risks mortality analysis (n=68,797), RT was associated with significantly reduced prostate cancer mortality for men with high-risk tumors (HR, 0.59 [95% CI, 0.50 to 0.68]) but not for men with low or intermediate risk tumors.[114] A smaller population-based cohort analysis of Swedish men who received RT or watchful waiting did not detect a significant difference in outcomes based on tumor risk.[130]

ADT

In an instrumental variable analyses from a good-quality cohort study of older U.S. men in SEER regions (n=66,717), primary ADT was not associated with significant differences in prostate

cancer mortality or all-cause mortality either in men with moderately differentiated tumors (Gleason<7) or in men with poorly differentiated tumors (Gleason ≥7).[127]

No studies of ADT reported whether morbidity outcomes differed by tumor risk or grade.

KQ4. What Are the Harms of the Various Treatment Approaches for Early-Stage or Screen-Detected Prostate Cancer?

Four RCTs (3 good-quality and 1 fair-quality)[70, 71, 74, 126, 132, 133, 136, 147, 148, 166] and 14 cohort studies (2 good- and 12 fair-quality)[75, 76, 139, 145, 149-152, 154, 156, 158-161] compared the harms of various active treatments to conservative management for early-stage or screen-detected prostate cancer (**Figures 2-5; Tables 10, 11,** and **20-26**). These studies compared radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT), or cryotherapy with conservative management (active surveillance [AS] or watchful waiting [WW]) or no treatment. In addition, we identified six fair-quality uncontrolled observational studies of RP[137, 138, 140, 155, 164, 165], one of RT,[157] and seven of high-intensity focused ultrasound (HIFU)[141-143, 146, 153, 162, 163] meeting inclusion criteria (**Table 12**).

We included studies reporting on the physical harms associated with treatment (e.g., urinary, bowel, and sexual function), surgical complications (including mortality associated with surgery), and adverse impacts on quality of life. Gastrointestinal effects (e.g., diarrhea, leakage, urgency) were primarily reported in studies of RP or RT, and hormonal side effects (e.g., hot flashes, gynecomastia) were primarily reported in studies of ADT.

The studies used a variety of continuous scales (**Table 13**) to assess generic and disease-specific quality of life changes following prostate cancer treatments. Commonly used quality of life scales were the Short-Form 36-Item Health Survey (SF-36)[75, 139, 144, 150-152, 154, 156, 159-161] and the University of California, Los Angeles Prostate Cancer Index (UCLA-PCI).[139, 150, 152, 156, 159-161] The SF-36 scores range from 0 to 100, with higher scores representing better functioning or quality of life across eight areas (subscales). PCI scores also range from 0 to 100, across six areas of urinary, sexual and bowel function or bother (higher scores indicate less bother or better function). For both scales, differences of 5 to 10 points are generally thought to indicate clinically meaningful changes.[190]

Summary

The harms of active treatments for early-stage or screen-detected cancers vary by modality. After radical prostatectomy, many men will experience urinary incontinence and erectile dysfunction. Across three RCTs with followup duration ranging from one year to six years, pooled analyses indicate that RP approximately doubles the risk of urinary incontinence (RR, 2.27 [95% CI, 1.82 to 2.84]; I^2=0.0%);[133, 148, 166] approximately 7.9 men need to be treated with RP for one man to develop incontinence based on RCT data (95% CI, 5.4 to 12.2). Using pooled data from two RCTs, the risk of erectile dysfunction with RP was also nearly doubled as compared to

conservative management (RR, 1.82 [95% CI, 1.62 to 2.04]; I^2=0.0%);[133, 148, 166] we estimate that 2.7 men need to be treated with RP for one man to develop erectile dysfunction (95% CI, 2.2 to 3.6). Approximately 7 percent of patients undergoing prostatectomy will experience major medical or surgical complications, and the median perioperative mortality after RP in 2 RCTs and 6 cohorts was 0.29 percent.[121, 133, 137, 138, 140, 155, 164, 191]

While the association between radiation therapy and urinary incontinence varied widely across studies, pooled analyses of seven cohort studies demonstrate an increased risk of erectile dysfunction with RT as compared with conservative management (RR, 1.31 [95% CI, 1.20 to 1.42]; I^2=22.1%).[75, 76, 145, 150, 156, 158, 159, 161] We estimate that 6.9 men need to be treated with RT for one man to develop erectile dysfunction (95% CI, 5.1 to 10.7). Radiation therapy was also associated with statistically significant increases in the percentage of men experiencing bothersome bowel symptoms.[70, 75, 76, 145, 159, 166] Compared to conservative management, RP and RT do not seem to have clinically significant impacts on global quality of life or physical or mental health status aside from the adverse urinary, sexual, and bowel impacts specified above.

Although less commonly used for localized prostate cancer, androgen deprivation therapy (ADT) was associated with erectile dysfunction in 73.8 to 85.6 percent of men in three cohort studies,[145, 154, 159] and studies of men with advanced prostate cancer have shown that ADT can cause a range of systemic adverse effects, including osteoporosis, insulin resistance, gynecomastia, and cognitive impairment. Seven uncontrolled observational studies of patients with localized prostate cancer suggest that high-intensity focused ultrasound (HIFU) is commonly associated with erectile dysfunction (range, 37.3% to 52.7%) and local complications, such as bladder outlet obstruction or urethral stricture.[141-143, 146, 153, 162, 163]

The risk of medical complications and perioperative mortality after RP were significantly greater in older (age greater than 70 years) as compared to younger men;[137, 140, 164] however, evidence on whether other treatment harms differ by patient age, race/ethnicity, family history, or clinical risk assessment was limited or absent.

Study Characteristics

Overall, we identified four RCTs,[71, 133, 144, 148] 14 cohort studies,[75, 76, 139, 145, 149-152, 154, 156-161] and 14 uncontrolled observational studies[137, 138, 140-143, 146, 153, 155, 162-165] reporting urinary, sexual or bowel dysfunction, surgical complications, adverse quality of life impacts, or other harms for active prostate cancer treatment compared with conservative management strategies (i.e., active surveillance or watchful, waiting). We identified three RCTs[71, 133, 144] and eleven cohort studies[75, 76, 139, 145, 149-152, 156, 158-160] that compared RP with conservative management, as well as six uncontrolled studies of surgical harms related to RP.[137, 138, 140, 155, 164, 165] We also identified two RCTs[70, 71, 144] and 12 cohort studies[75, 76, 139, 145, 149-152, 156-161] that compared RT with conservative management, as well as one uncontrolled observational study of RT.[157] Four cohort studies of ADT[145, 154, 159, 160] and one cohort study of cryotherapy[160] compared harms of treatment versus conservative management. We identified no RCTs or cohort studies of HIFU, but we did identify seven uncontrolled observational studies reporting harms of HIFU.[141-143, 146, 153, 162, 163]

The design of three of the included RCTs – ProtecT, PIVOT, and the SPCG-4 – were presented

in the discussion of KQ3. In the ProtecT trial, 85 percent of the 1,643 men randomized to RP, RT or AS completed a battery of urinary, sexual and bowel function and quality of life assessments (Expanded Prostate Cancer Index Composite [EPIC]; International Consultation on Incontinence Questionnaire [ICIQ]; International Continence Society Male Short-Form [ICSmaleSF]; Hospital Anxiety and Depression Scale [HADS]; SF-12 (an abbreviated version of the SF-36); and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer [EORTC QLQ-C30]) (**Table 13**) before diagnosis, at six- and twelve-months after randomization, and annually therafter.[144] The PIVOT trial reported the incidence of 30-day perioperative complications after RP, as well as patient-reported urinary, bowel, and sexual function after two years of followup among men randomized to RP compared with watchful waiting.[133] In a recent publication with extended followup, the PIVOT trial reported patient-reported adverse events and quality of life up to 10 years post-randomization.[74] After a mean of 4.1 years, the SPCG-4 reported the incidence of urinary, sexual and bowel dysfunction among men 2 to 3 years, 4 to 5 years, and 6 to 8 years post-randomization to either RP or watchful waiting,[147] as well as on additional quality of life measures after a median of 12.2 years followup.[148] One additional, small RCT – the Swedish trial – randomized men to RT (n=59) or watchful waiting (n=49) and collected data using the Prostate Cancer Symptom Scale (PCSS) and the EORTC QLQ-C30 questionnaire after 30 to 41 months and 10.0 years followup.[70, 71]

The ProtecT and Swedish trials reported the incidence of physical harms or quality of life across multiple time points.[70, 71, 144] However, the ProtecT study only reported one overall measure of significance across all treatment arms and time points, and did not assess any between-arm or between-time point differences.[144] While the Swedish trial reported results from the same group of randomized men at 30 to 41 months' followup[70] and 10 years' followup,[71] there was 50 percent loss to followup at 10 years. In addition to varying timing of data collection, the methods for reporting harms (urinary incontinence, erectile dysfunction, and bowel dysfunction) varied across the trials, which may limit the ability to compare data across the different trials. Only the PIVOT study was set in the United States, which may limit the generalizability of results due to differences in treatment practice patterns.

Eleven of the fourteen cohort studies were set in the United States (median followup range, 0 to 15 years). Two studies identified distinct cohorts of men in the SEER registry as part of the Prostate Cancer Outcomes Study (PCOS), which identified 3,500 men diagnosed with prostate cancer between October 1994 and October 1995.[192] In one cohort, 24 months after diagnosis, men completed a survey that included general and disease-specific measures of health-related quality of life, including urinary, sexual, and bowel function, as well as treatment satisfaction and impacts on other aspects of daily life.[145] In the second cohort, men completed either a 6-month or 12-month post-diagnosis survey on health-related quality of life. Survey elements included the SF-36 generic health status questionnaire as well as a prostate-cancer-specific instrument designed specifically for the PCOS.[154] The other cohorts identified men from pathology laboratories[156] or registries;[75, 76, 139, 145, 149-152, 157-161] all of the men in all but one these cohorts[76] completed SF-36 or UCLA PCI measures, and eleven studies also reported the incidence of urinary, sexual, or bowel dysfunction.[75, 76, 145, 149, 154, 156-161]

As with the trials, the timing of data collection varied across the cohort studies, as did the methods for reporting and defining harms. Of the 14 cohort studies, five collected data cross-

sectionally and lacked baseline measures.[139, 145, 149, 150, 160, 161] Among the studies assessing harms longitudinally, there was variation in the data collection time points (for example, collecting data "pretreatment" and "posttreatment"[158] versus at baseline and three-years[159]), complicating comparison of outcomes across studies. Two recently published U.S. cohort studies examined the trajectory of reported harms across treatment groups from baseline (prior to treatment) over either two[76] or three years of followup.[75]

Three of the fourteen uncontrolled observational studies were set in the United States – two identified men from a single institution who received RP[155] or RT[157] and the other identified a large group of men (n=101,604) in Medicare claims who received RP.[165] The remaining studies were set in Europe,[138, 140-143, 153, 162] Canada,[137, 164] or Japan.[146, 163] None of the studies of HIFU were set in the U.S.

Findings

Radical Prostatectomy

We identified three RCTs,[133, 144, 147, 148] and 11 cohort studies[75, 76, 139, 145, 149-152, 156, 158-160] reporting on the harms and adverse quality of life impacts of men with early-stage prostate cancer who received RP compared with men who were conservatively managed. We also identified six uncontrolled observational studies with sample sizes exceeding 1,000 men reporting relevant outcomes.[137, 138, 140, 155, 164, 165] One cohort only reported data stratified by age; therefore, this will only be discussed in the subsequent section addressing harms among patient subgroups.[160]

Urinary, Sexual, and Bowel Function

All three trials found that urinary incontinence was more common among men who were randomized to RP compared with those were conservatively managed (**Table 20**).[133, 144, 147] Six cohort studies reported on the prevalence of urinary incontinence among men who received RP compared with men who were conservatively managed;[75, 76, 145, 149, 156, 159] at latest followup, all of the studies reported that incontinence was more common among men who received RP compared with men who were conservatively managed (**Table 20**). Across the three trials, the pooled relative risk of urinary incontinence was 2.27 (95% CI, 1.82 to 2.84; I^2=0.0%) and in the six cohort studies, the pooled relative risk was 2.75 (95% CI, 1.78 to 4.23; I^2=63.0%) (**Figure 2**). Based on estimated risk differences (computed from pooled relative risks and absolute urinary incontinence risk among conservatively managed men), we estimate that 7.9 men need to be treated with RP for one man to develop incontinence based on RCT data (95% CI, 5.4 to 12.2).

All three trials also found that erectile dysfunction was more common among men who underwent RP compared with men who were conservatively managed; in two trials, the prevalence of men who experienced erectile dysfunction after RP was approximately double that of men in the watchful waiting arms (81.1% vs. 44.1% in PIVOT and 80.5% vs. 44.9% in SPCG-4) (**Table 20**).[133, 147] Similarly, the seven studies reporting the prevalence of erectile dysfunction[75, 76, 145, 149, 156, 158, 159] found that it was more common among men who received RP compared with men who were conservatively managed (**Table 20**). In pooled meta-analyses of

the three RCTs, we observed marked heterogeneity (I^2=87.5%), which was attributable to disparate findings in ProtecT, in which many of the men randomized to active surveillance received radical treatments (either prostatectomy or radiation) during the comparatively long 6 years of median followup (**Figure 3**).[144] After excluding ProtecT from the meta-analysis of the RCT data, the pooled relative risk of erectile dysfunction associated with RP versus conservative management was 1.82 (95% CI, 1.62 to 2.04; I^2=0.0%). In the seven cohort studies, the pooled risk of erectile dysfunction was 1.49 (95% CI, 1.34 to 1.65; I^2=59.2%) (**Figure 3**). Using data from the RCTs other than ProtecT, we estimate that 2.7 men need to be treated with RP for one man to develop erectile dysfunction (95% CI, 2.2 to 3.6).

In two trials[144, 147] and five cohort studies, [75, 76, 145, 149, 159] RP was not associated with increased bowel symptoms or dysfunction compared conservative management (**Table 20**).

In five studies with longitudinal measures,[75, 76, 144, 159 74] mean urinary and sexual function scores decreased to a nadir during the six to twelve months after RP with some improvement during longer-term followup, although mean urinary and sexual function remained statistically significantly lower than at baseline up to 6 years of followup.

Surgical Complications

Two trials reported on surgical complications and mortality associated with radical prostatectomy. In the PIVOT trial, 21.4 percent of men undergoing RP experienced one or more complications within 30 days of surgery, with the most common complications being wound infection (4.3%), thromboembolic or cardiovascular events (2.9% overall, including myocardial infarction [1.1%], deep vein thrombosis [0.7%], stroke [0.4%], and pulmonary embolism [0.7%]), urinary tract infection (2.5%), the need for an additional surgical repair (2.5%), bleeding requiring transfusion (2.1%), or the presence of a urinary catheter more than 30 days post-surgery (2.1%).[133] The most common events reported for men undergoing RP in the ProtecT trial were bleeding requiring blood transfusion (2.5%), thromboembolic or cardiovascular events (1.6%), reintervention for anastomotic problems (1.6%), or rectal injury (0.2%) (**Table 25**).[121, 133]

Four uncontrolled observational studies reported on 30-day surgical complications associated with radical prostatectomy.[137, 138, 155, 165] Thromboembolic or cardiovascular events were the most common complications, affecting 0.4 percent[155] to 9.0 percent of patients[165] (with the latter incidence reported in a large, U.S. Medicare cohort). In a cohort study of 4,592 men undergoing prostatectomy, 1.7 percent experience major medical complications (most commonly cardiac or pulmonary) and 5.3 percent experienced major surgical complication (requiring re-intervention) within 30 days of surgery.[155] In a recent trial comparing short-term outcomes among men with localized prostate cancer randomized to open versus robot-assisted laparoscopic prostatectomy, men randomized to robot-assisted prostatectomy had statistically significantly lower estimated blood loss compared to men randomized to open prostatectomy (444 mL vs. 1338 mL; p<.001) and shorter hospital stays (1.6 vs. 3.3 days; p<.001). There were more post-operative complications in men randomized to open versus robot-assisted prostatectomy, although the difference was not statistically significant (4% vs. 9%; p=0.052).[193]

Eight studies reported on prostatectomy-associated mortality. In the PIVOT trial, 1 of 280 men

who underwent RP (0.4%) died within 30 days,[133] while there were no perioperative deaths in the ProtecT trial.[121] Four studies reported on 30-day perioperative mortality,[137, 138, 164, 165] with rates ranging from 0.0[138] to 0.54 percent in a large, U.S. Medicare cohort.[165] Two studies reported mortality after longer followup: 0.17 percent after 90-days [140] and 0.13 percent after 37-months[155] post-radical prostatectomy. Across all eight studies, the median perioperative mortality after RP was 0.29 percent (**Table 25**). In the single cohort study that compared 90-day mortality among men undergoing robot-assisted RP (n=7,524) versus open retropubic RP (n=14,820), no significant difference in 90-day mortality was found (adjusted OR, 1.14 [95% CI, 0.46 to 2.81]).[140]

Generic and Disease-Specific Quality of Life

Across all time points up to 72 months, men in the ProtecT trial who were randomized to RP or AS experienced similar levels of anxiety and depression (as measured by the HADS scale). After five years of followup, global health status scores, functional scale scores, and symptom scales were also similar between men randomized to RP or AS (as measured by the EORTC-QLQ-C30). Similarly, there were no clinically meaningful differences in scores on the SF-36 physical component or mental component summary scores (**Appendix E Table 6**).[144] Across 10 years of median followup in the PIVOT trial, there were no significant differences in the SF-12 Physical or Mental Component Scales among men randomized to RP versus observation.[74] After a median followup of 12.2 years in the SPCG-4 trial, there were no significant differences in anxiety, depression, sense of well-being, or self-assessed quality of life between men randomized to RP compared to watchful waiting.[148]

Results from cohort studies[75, 139, 150-152, 156, 159, 160] also suggest that measures of generic quality of life are similar among men with localized who receive RP and conservative management (**Table 26; Appendix E Table 6**). Six cohort studies (and no RCTs) evaluated urinary, sexual, and bowel function using the UCLA PCI (**Table 26; Appendix E Table 7**).[139, 150, 152, 156, 159, 160] Results based on the UCLA-PCI scores were consistent with pooled findings from the meta-analysis on urinary incontinence and erectile dysfunction; all of the cohort studies found worse urinary function and bother outcomes following RP compared with conservative management and five of the six cohort studies found worse sexual function and sexual/bowel bother outcomes. In these cohort studies, there were no clear differences in bowel function or bowel bother among men undergoing RP compared to those who were conservatively managed.

Radiation Therapy

We identified 15 studies (2 RCTs, 12 cohort studies, and one uncontrolled observational study)[70, 71, 75, 76, 139, 144, 145, 149-152, 156-161] reporting on the harms and quality of life impacts among men with localized prostate cancer who received RT compared with men who were conservatively managed. Two of the cohort studies only reported data stratified by either age or race/ethnicity and are only discussed in the subsequent section addressing harms among patient subgroups.[157, 160]

Urinary, Sexual, and Bowel Function

Because of marked variability in the incidence of urinary incontinence in eight studies comparing RT and conservative management (**Figure 4**), we did not perform pooled meta-analyses of these data. In the ProtecT trial, over the course of 6 years of median followup, urinary incontinence developed in 8.4 percent of men randomized to active monitoring compared to 3.5 percent of men randomized to RT.[144] One possible explanation for this difference was the crossover of many subjects in the AS group to active treatments, including RP which is associated with increased risk of urinary incontinence. In contrast, a small RCT (n=108) with 2.5 years of median followup, 17.5 percent of men randomized to RT regularly used urinary pads for incontinence as compared with 2.0 percent of men randomized to conservative management (RR, 8.3 [95% CI, 1.1 to 6.3]).[70] Six cohort studies found little or no difference in urinary incontinence.[75, 76, 145, 149, 156, 159] **Figure 4** illustrates the variability in urinary incontinence across all of the studies.

In the ProtecT trial, erectile dysfunction at baseline was similar among men randomized to RT and AS (15.9% and 16.3% respectively); after 72 months of followup, the difference in erectile dysfunction between the two groups was not significant (39.8% of men randomized to AS vs. 36.2% of men randomized to RT; RR, 0.91 [95% CI, 0.77 to 1.08]).[144] In contrast, in six of eight cohort studies, the prevalence of erectile dysfunction was statistically significantly more common in men treated with RT as compared to men who were conservatively managed (pooled RR, 1.31 (95% CI, 1.20 to 1.42; I^2=22.1%) (**Figure 5**).[75, 76, 145, 149, 156, 158, 159, 161] As with urinary incontinence, the similar incidence of erectile dysfunction among patient randomized to RT and active monitoring in the ProtecT trial may be attributable to the substantial use of active treatments during the six years of median followup among men randomized to AS. Using pooled relative risks from the cohort studies, we estimate that 6.9 men need to be treated with RT for one man to develop erectile dysfunction (95% CI, 5.1 to 10.7). Two recent U.S.-based longitudinal studies that average adverse impacts of RT on sexual function are most pronounced during the initial treatment with a tendency to moderate during longer term followup.[75, 76] However, in a longitudinal cohort study set in Australia,[159] initial decrements in sexual function associated EBRT persisted throughout the three year followup period.

In the ProtecT trial, fecal incontinence was more common among men randomized to AS at baseline (2.0% vs. 0.4% of men randomized to RT). However, over the course of followup men randomized to RT experienced an increase in the frequency of reporting fecal incontinence; after 72 months of followup, fecal incontinence was reported in 4.1 percent of men randomized to RT compared to 2.6 percent of men randomized to AS.[144] Three years after treatment, 14.5 percent of men in one cohort who were treated with EBRT characterized their bowel function as a moderate or big problem compared with 6.3 percent of men managed with AS and 6.3 percent of non-cancer controls (OR, 0.58 versus non-cancer controls).[159] In another cohort, men who were treated with RT reported frequent bowel urgency more often than men who were not treated (31.8% vs. 16.1%).[145] Two recent U.S. longitudinal cohort studies suggest that the average intensity of adverse bowel symptoms with RT peak in the first year of treatment with a tendency to diminish during longer term followup.[75, 76] In contrast, within an Australian cohort,[159] initial decrements in bowel function associated with RT persisted throughout a three-year followup period.

Generic and Disease-Specific Quality of Life

Across all time points up to 72 months, men in the ProtecT trial who were randomized to radiation or AS experienced similar levels of anxiety and depression (as measured by the HADS scale). After 5 years of followup, global health status scores, functional scale scores, and symptom scales were also similar between men randomized to both groups (as measured by the EORTC-QLQ-C30). Similarly, there were no clinically meaningful differences in scores on the SF-36 physical component or mental component summary scores (**Appendix E Table 8**).[144] In the small Swedish trial, no statistically significant differences in quality of life (as measured by the EORTC-QLQ-C30 scale) between 4 and 10 years of followup were observed between men randomized to radiation or watchful waiting. [71]

Nine cohort studies that compared SF-36 measures among men who underwent RT and men who underwent conservative management generally found small or unclear differences on component and subscales (**Table 26; Appendix E Table 8**).[75, 139, 149, 151, 152, 156, 159-161] Seven cohort studies evaluated urinary, sexual and bowel function using the UCLA PCI (**Table 26; Appendix E Table 9**).[139, 150, 152, 156, 159-161] Results based on the PCI found worse outcomes following radiation therapy compared with conservative management for sexual function and bother, as well as bowel function and bother; no clear differences were seen in urinary function or bother.

ADT

We identified five cohort studies reporting on the harms and quality of life impacts among men who received androgen deprivation therapy (ADT) compared with men who were conservatively managed or who did not receive any treatment.[139, 145, 154, 159, 160] One of the cohort studies only reported data stratified by age and is discussed only in the subsequent section addressing harms among patient subgroups.[160]

Urinary, Sexual, and Bowel Function

Two cohort studies reported on the prevalence of urinary incontinence among men who received ADT compared with men who were conservatively managed.[145, 159] Two to 3 years after treatment, both studies found no significant difference in urinary incontinence among men who received ADT compared with men who underwent either AS (RR, 1.1 [95% CI, 0.23 to 5.30])[159] or were not treated (RR, 1.40 [95% CI, 0.74 to 2.50]). [145] Three cohort studies found that the prevalence of erectile dysfunction was statistically significantly elevated among men who received ADT compared with men who were managed with AS or not treated (RR range, 1.6 to 2.9).[145, 154, 159] Prevalence of bowel dysfunction after ADT was reported in two studies with unclear effects as neither provided direct statistical comparisons with the group of men who were conservatively managed.[145, 159]

Generic and Disease-Specific Quality of Life

Three cohort studies found that physical role function, bodily pain, vitality, and emotional role function were generally worse among men who received ADT compared with those who were conservatively managed (**Table 26; Appendix E Table 10**).[139, 154, 160] However, these cross-

sectional analyses warrant careful interpretation, as they lack adjustment for baseline measures.

One study found that men who received ADT reported statistically significantly higher levels of physical discomfort compared to men who were not treated (p=0.02), yet more men receiving ADT reported satisfaction with their treatment choice (p=0.001).[154]

Three cohort studies evaluated urinary and sexual bother and function using the UCLA PCI; two of those studies reported on bowel function and bother (**Table 26; Appendix E Table 11**).[139, 159, 160] These studies generally found that urinary, sexual, and bowel function and bother scores were lower among men who received ADT compared with those who were conservatively managed. However, given the small number of studies reporting UCLA PCI outcomes, it is unclear whether the differences are clinically meaningful.

Other Harms

One study found that among men receiving ADT, a significantly higher proportion reported gynecomastia (20.0%) or hot flashes (58.0%) compared with men who did not receive treatment (3.8% and 11.1%, respectively).[154] In a recent longitudinal U.S. cohort study,[75] men with localized prostate cancer who received EBRT had statistically significantly worse hormone function during the year following treatment (i.e., higher rates of hot flashes, gynecomastia, asthenia, or weight change), and these adverse hormonal impacts were isolated to the 45 percent of men treated with ADT in addition to EBRT.[75] In men with advanced prostate cancer, ADT has been associated with osteoporosis and skeletal fractures, decreased lean body mass, insulin resistance, fatigue, decreased penile and testicular size, thinning of hair, depression, anemia, and cognitive impairment;[194] however, we did not find studies documenting these potential adverse effects among men treated with ADT for localized prostate cancer.

Cryotherapy

We identified one cohort study comparing cryotherapy with conservative management. This study included a small (n=28) sample of men receiving this treatment with a median of 3.8 years of followup after treatment. This study only reported urinary and sexual function stratified by age so is discussed in a subsequent section addressing harms among patient subgroups.[160]

HIFU

We identified one uncontrolled observational study with a sample size exceeding 1,000 men that reported the harms and quality of life impacts among men who received high-intensity focused ultrasound (HIFU).[143] Because only one study met sample size inclusion criteria, we included six smaller uncontrolled studies with sample sizes exceeding 100 men.[141, 142, 146, 153, 162, 163] None of the included studies reported SF-36 or UCLA PCI scores, or other measures of generic or disease-specific quality of life.

Urinary, Sexual, and Bowel Function

Seven uncontrolled observational studies reported the prevalence of urinary dysfunction

associated with HIFU;[141-143, 146, 153, 162, 163] five of those cohorts reported on erectile dysfunction. Our review did not identify any studies reporting on bowel dysfunction associated with HIFU. With followup ranging from 23 months to 6.4 years, between 0 percent and 7.3 percent of men undergoing HIFU for localized prostate cancer reported grade 2 urinary incontinence or worse (leakage with mild activity, such as walking or standing up).[141-143, 153, 162, 163] Three studies, with followup ranging from 6 months to 4.8 years, reported that erectile dysfunction occurred in 37.3 to 52.7 percent of men who were potent prior to HIFU treatment.[141, 142, 146] Other reported urinary harms included urinary tract infections (6 studies; median, 5.6%; range, 3.9% to 26.5%),[142, 143, 146, 153, 162, 163] urethral stricture (2 studies; range, 6.8% to 20.3%),[142, 143, 153, 162, 163] rectourethral fistulas (5 studies; median, 1.0%; range, 0.4% to 1.6%),[137, 142, 143, 153, 162, 163] and bladder outlet obstructions (3 studies; median, 16.6%; range, 11.7% to 24.5%).[141-143]

KQ4a. Do the Harms of These Treatment Approaches Vary Between a Priori Subgroups: Age, Race/Ethnicity, Family History, or Clinical Risk?

Age

Five studies (two cohort studies and three uncontrolled observational studies) stratified the treatment harms or quality of life impacts by patient age.[137, 140, 158, 160, 164]

Urinary Function

Comparing men younger than age 70 years with those age 70 years or older, one cohort study found no difference in urinary incontinence at 18-months post-treatment with RP, RT, ADT or cryotherapy compared with observation. Older men who had RP or RT rather than observation were more likely than younger men to consider their urinary function a moderate or big problem.[160]

Sexual Function

Comparing men younger than age 70 years with those age 70 years or older, one cohort found that at 18 months posttreatment, older men reported lack of erections more often regardless of the treatment received; however, the magnitude of the difference was largest among men receiving cryotherapy (30% erectile dysfunction in younger men versus 100% in older men). Across all treatment groups except ADT and cryotherapy, older men considered their sexual function a moderate or big problem more often than younger men.[160] Another cohort found statistically significant decreases in posttreatment potency across all age groups (<59 years, 60 to 70 years, ≥71 years) for men treated with radical prostatectomy and radiation therapy compared to conservative management or no treatment (p<0.0001).[158]

Bowel Function

We did not identify any studies reporting the differential impact of treatment on bowel function

by age.

Other Harms

An uncontrolled observational study of 30-day prostatectomy-associated complications found that the incidence increased with age, from 17.5 percent among men younger than 60 years of age to 26.9 percent among men aged 70 to 79 years. Regardless of age, the most common complications were genitourinary. After adjusting for comorbidity, age was found to be associated with statistically significantly higher risks of cardiac (p<0.001) and respiratory complications (p=0.01).[137]

One uncontrolled observational study of 30-day mortality after prostatectomy found that the mortality rate increases from 0.2 percent among men younger than 60 years of age to 0.7 percent among men aged 70 to 79 years;[137] another study found an increased risk in mortality among men aged 69 years or older compared with younger men (OR, 3.1; p<0.001).[164] An uncontrolled study of 90-day perioperative mortality after RP also found a borderline statistically significant increase in risk associated with age (OR, 1.07 [95% CI, 1.00 to 1.13] per one-year increase in age).[140]

Race/Ethnicity

2 studies (one cohort and one uncontrolled observational study) stratified the harms of prostate cancer treatment by race/ethnicity.[157, 158]

Urinary Function

One observational study found that white men who received EBRT were more likely to have urinary incontinence compared to African American men (8.9% vs. 6.7%, respectively; p<0.001), but there was no significant difference in incontinence by race among men who were treated with brachytherapy (p=0.82).[157]

Sexual Function

One U.S. cohort study evaluating pre- and post-treatment potency, found that African American and white men experienced similar decreases in potency after RP (65.2% and 67.2% absolute reduction for African-American and white men, respectively, p=0.74 pairwise comparison). In contrast, the decline in potency associated with radiation therapy was significantly less severe among African American men than white men (37.5% and 51.2% absolute reduction for African-American and white men respectively; p=0.04 for pairwise comparison).[158]

Bowel Function

One observational study found no significant differences in the frequency of diarrhea, rectal pain, or rectal bleeding associated with radiation therapy among white as compared to African American men.[157]

Other Harms

An uncontrolled U.S. observational study of radical prostatectomy found that non-white race was associated with higher risk of medical or surgical complications (African American vs. white, HR=1.4 [95% CI, 1.0 to 2.0]; p=0.027; other/unknown vs. white, HR=1.6 [95% CI, 1.1 to 2.6]; p=0.028).[155]

Family History

We did not identify any studies reporting the differential impact of the included treatment or monitoring approaches by family history.

Clinical Risk Assessment

We assessed studies for evidence of differentially greater or less treatment harms by clinical risk assessment, considering pre-treatment factors such as tumor characteristics, clinical stage, baseline PSA, or a combination of these factors. Five studies (one cohort and four uncontrolled observational studies) stratified the harms of treatments by one or more of these factors. [137, 140, 155, 158, 164]

Urinary, Sexual, and Bowel Function

We did not identify any studies reporting the differential impact of treatment on urinary, sexual or bowel function by clinical risk assessment.

Other Harms

An observational study of radical prostatectomy found that more comorbidities (and some specific conditions, such as diabetes and cardiovascular disease) and higher Gleason score were associated with higher risk of medical or surgical complications.[155] Another uncontrolled study of perioperative complications found that, after adjusting for age, increasing numbers of comorbidities was associated with increased risk of cardiac, respiratory, vascular, wound/bleeding, genitourinary and miscellaneous complications (p<0.001).[137]

One observational study of 30-day mortality after prostatectomy found an increased risk among men with comorbidities (defined as a Charlson comorbidity index score ≥1) compared with men without comorbidities (OR, 3.0; p=0.002).[164] In contrast, a more recent large study of 90-day perioperative mortality after prostatectomy in Sweden (n=22,344) found that the presence of comorbidities (defined as a Charlson comorbidity index score ≥1) was not significantly associated with perioperative mortality, although perioperative mortality was significantly greater among men with high-risk cancers (OR, 2.89 [95% CI, 1.18 to 7.06]), defined as T3, Gleason>7, or PSA>20 ng/mL.[140]

KQ4b. Do the Harms Differ by Treatment Approach?

Urinary, Sexual, and Bowel Function

Meta-analysis found that radical prostatectomy but not radiation therapy was associated with an increased risk of urinary incontinence (**Figure 2**) (RR, 2.9 [95% CI, 2.4 to 3.5]). Both radical prostatectomy and radiation therapy were found to be associated with an increased risk of erectile dysfunction (**Figures 4** and **8**) (RR, 1.6 [95% CI, 1.5 to 1.7] and RR, 1.2 [95% CI, 1.1 to 1.3]).

Generic and Health-Related Quality of Life

Based on assessment of SF-36 scales, neither RP nor RT were associated with significantly greater decrements in generic quality of life compared to conservative management, while ADT may be associated with a relative decline in generic quality of life compared to conservative management.

Cohort studies reporting median differences in PCI scores (**Table 26**) found that urinary function was lower in men undergoing radical prostatectomy compared with those treated with radiation (median difference, -3.3 points) or ADT; however, this was not true for urinary bother (men treated with ADT reported the lowest median PCI scores). Cohort studies also found that sexual function and bother was lower among men treated with either EBRT or brachytherapy as compared with men who were conservatively managed; however, median sexual function scores were lowest for men treated with ADT. Bowel function and bother scores on the UCLA PCI tended to be worse among men treated with radiation, while there was no clear difference among men treated with radical prostatectomy. Only two studies reported on bowel function and bother among men treated with ADT; while both studies reported mean scores in men treated with ADT as compared with those conservatively managed, the magnitude of the difference may not be clinically meaningful.

In a recent U.S. longitudinal cohort study,[76] adverse bowel symptoms were only associated with EBRT and not with brachytherapy (used by 30.4% of the men who received RT). Meanwhile, within this U.S. cohort and an Australian cohort, the incidence of adverse effects on sexual function was similar for EBRT and brachytherapy.[76, 159] However, within the Australian cohort, both EBRT and brachytherapy were associated with elevations in measures of bowel bother that persisted through the three year followup period.[159]

KQ5. 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 to PSA-Based Screening Alone?

Summary

The PCPT risk calculator has been externally validated for the identification of significant prostate cancer in 21 external cohorts.[78, 79, 167-177] While the calculator improves discrimination between patients with and without clinically significant prostate cancer, its predictive accuracy has varied substantially across samples. Calibration of the risk calculator has also been variable. Ankerst et al. (2014) did not identify clear sources of variability across the ten cohorts in their study (including differences in number of prostate cores, screening versus referral cohorts, and European versus United States settings),[171] so the heterogeneity in PCPT calculator performance remains unexplained.

Seven studies have externally validated the ERSPC risk calculator's ability to identify men with clinically significant prostate cancer,[77, 79, 167-169, 172, 175] in addition to the original ERSPC study which may more accurately be considered an internal validation. While the studies suggest that the calculator can improve discrimination of clinically significant cancer compared to PSA alone, calibration was mixed in the five cohorts in which it was assessed. The evidence base for use of the ERSPC calculator for the detection of clinically significant cancer is also limited by the use of TRUS to estimate prostate volume in all studies, while widespread use of the calculator for clinical decision-making would require use of digital rectal exam (DRE)-estimated prostate volume. The external validity of the calculator with strict use of DRE-based prostate volume estimates has not been established.

Risk Calculator Characteristics

Both the PCPT and ERSPC risk calculators were originally developed to predict the presence or absence of any prostate cancer with the potential clinical goals of minimizing the harm of biopsy among men without prostate cancer.[51, 195] In clinical use, both calculators estimate a probability of prostate cancer prior to biopsy and have been adapted to estimate the probability of clinically significant cancer. Men may vary in their risk threshold for undergoing biopsy based on how they value the benefits of cancer detection with the harms of negative biopsy, especially at intermediate levels of risk. Pre-biopsy discussion between patients and urologists conceivably could assist in defining patients' individual thresholds for undergoing biopsy. Men whose pre-biopsy risk falls below their personal threshold may elect to forego biopsy.

An adaptation of the PCPT calculator, termed "PCPT Calculator 2.0," was designed to predict the presence of high-grade (Gleason score ≥7) versus low-grade cancer with the potential clinical goal of minimizing the harms of overtreatment of low-grade prostate cancer.[170] The PCPT 2.0 calculator requires seven clinical variables: PSA level, DRE results, age, African American

race/ethnicity, prior biopsy, and family history. A further adaptation enables the addition of free PSA to these variables with the potential to further improve prediction.

The ERSPC risk calculator was also developed to predict the presence of high versus low-grade prostate cancer; the initial development was based on 3,616 men referred for biopsy during early screening rounds of the Rotterdam ERSPC.[172] The risk calculator uses four variables: PSA, DRE results, prior negative biopsy (if ever biopsied), and prostate volume as determined by TRUS. Because TRUS is an invasive procedure that is typically performed during biopsy, the authors converted TRUS volume measures to three categories that could be assigned by clinicians during office-based DRE. We discuss below a validation study of this risk calculator among men referred for biopsy for abnormal screening results whose prostate volume was estimated using DRE.

Findings

External Validation of the PCPT Risk Calculator

Including both versions, the PCPT risk calculator has been validated in 21 external biopsy cohorts. Earlier evaluations assessed the validity of the original PCPT calculator, while more recent studies assessed the validity of PCPT 2.0 for predicting clinically significant prostate cancer. The largest external evaluation was based on over 25,000 biopsies from 10 external biopsy cohorts from Europe and the United States.[170, 171] Across the cohorts, the risk calculator had a median AUC of 0.75 for the detection of clinically significant prostate cancer (range, 0.62 to 0.88).[170] However, calibration of the risk calculator was poor in some cohorts while adequate in others.[171] Decision curve analyses also yielded mixed results, suggesting net benefit in six cohorts but little or no benefit in four. In the decision curve analyses, expected benefits are the number of patients with significant prostate cancer who are detected (true-positives), while expected harms correlated with number of patients without significant prostate cancer who undergo biopsy. A decision curve analysis implies net benefit when the benefits of true-positives exceed the harms of false-positives across the range of pre-biopsy risk thresholds in which the risk calculator is likely to be applied (or net harm if the harms of false-positives exceed the benefits).

We identified 11 other studies reporting validation of the PCPT calculator within external cohorts (range, 322 to 4,515 biopsies).[78, 79, 167-169, 172-177] Cohorts were composed of men from North America, Europe, or South Korea, and most consisted of men referred to tertiary or academic centers for biopsy consideration. Across these 11 cohorts, the median AUC for the detection of significant cancer was 0.70 (range, 0.51 to 0.79). For comparison, the median AUC of PSA alone (reported in six studies) was 0.65 (range, 0.56 to 0.71).[167, 168, 172, 175-177]

Calibration was assessed in 8 of the 11 cohorts,[167-169, 173, 175, 176] yielding mixed results. Three of four studies that conducted decision curve analyses suggested small net benefits of risk calculator use,[168, 169, 173] but analyses suggested net harm of calculator use in one high-risk referral population.[167]

In a systematic review of the predictive validity of risk prediction models for prostate cancer,[196]

the authors analyzed the discrimination of the PCPT risk calculator for the prediction of clinically significant prostate cancer based on studies published through mid-2012 including 14 of the 21 cohort studies reviewed in this report.[51] In a meta-analysis of the AUCs from these 14 cohorts, the summary AUC for the detection of clinically significant cancer was 0.71 (95% CI, 0.67 to 0.75) with an I^2 statistic of 94.7 percent, consistent with marked heterogeneity.

External Validation of the ERSPC Risk Calculator

We identified seven validation studies of the ERSPC risk calculator for the identification of high-grade prostate cancer.[77, 79, 167-169, 172, 175] Roobol et al. (2012) described the development of the ERSPC calculator within a sample of 3,616 men referred for biopsy during early ERSPC screening rounds. Prostate volume in the development sample was estimated using TRUS rather than DRE. The calculator was validated among 322 men referred for biopsy during later screening rounds with prostate volume estimated during DRE conducted by urologists in training. Among these men, the ERSPC risk calculator had an AUC of 0.78 for the detection of clinically significant cancer (95% CI, 0.69 to 0.87) as compared to 0.68 for PSA alone (95% CI, 0.57 to 0.78). No data on calibration or clinical utility of the risk calculator were reported.[172] These results warrant cautious interpretation for various reasons. First, an optimal external validation is performed on a completely separate population than that from which the risk tool was derived; the validation study here was performed on ERSPC trial participants so may be considered an internal rather than an external validation and may be optimistically biased.[57] Second, the risk calculator was derived with TRUS-estimated prostate volume, while the prostate volume was estimated by DRE (prior to TRUS) in the validation phase. In the validation phase, DRE-estimated volume may not have been independent of TRUS, and accuracy may be less without TRUS volume estimates, which cannot be routinely obtained in ambulatory primary care or urology settings. Finally, while the authors provided evidence of correlation between urologist-estimated volume and TRUS-calculated prostate volume, [172] it is uncertain whether primary care physicians can accurately estimate prostate volume using DRE.

We identified six external validation studies of the ERSPC calculator.[77, 79, 167-169, 175] These biopsy cohorts originated in Europe, Canada, or South Korea with biopsy sample sizes ranging from 556 to 2,313. Within these cohorts, the AUC of the ERSPC calculator for the detection of clinically significant cancer ranged from 0.69 to 0.83, as compared to the AUC of PSA alone which ranged from 0.61 to 0.65 (reported in three cohorts[167, 168, 175]). The risk calculator was well-calibrated in four studies[168, 169] but underestimated actual risk across the entire risk range in another.[167] In four studies, decision curve analyses were conflicting, suggesting net benefit in two,[168] little impact in another,[169] and net harm in the third.[167] Notably, all of the external validation studies used TRUS-estimated volume, rather than DRE-estimated volume, since the study participants were undergoing TRUS-guided biopsy regardless of calculator results.

Chapter 4. Discussion

Summary of Evidence

The results of this synthesis are summarized in **Table 29**. We systematically reviewed the literature to assess the benefits and harms of PSA screening for prostate cancer. Recognizing that long-term impacts of screening are affected by treatment outcomes, we also systematically reviewed the literature on the benefits and harms of treatment for early-stage or screen-detected prostate cancer. We further synthesized evidence on whether screening or treatment benefits and harms may be greater or lesser among patient subgroups. Finally, we summarized the literature on the utility of prostate cancer risk calculators in distinguishing men with and without clinically significant prostate cancers prior to biopsy.

PSA-Based Screening

Of randomized trials of PSA screening, only the PLCO and ERSPC trials were of sufficient quality to inform key questions regarding screening effectiveness. Direct evidence from the two trials demonstrates that PSA screening substantially increases the detection of prostate cancer, particularly of early-stage, localized disease. Evidence from four ERSPC sites also suggests that screening can reduce the long-term incidence of metastatic disease. While the PLCO (at a median of 14.8 years of followup) found no association between randomization to annual screening and reduced prostate cancer mortality, the overall ERSPC results (at a median of 13.0 years of followup) suggest a 21 percent relative reduction in prostate cancer mortality with screening. Prostate cancer mortality was statistically significantly reduced at the Swedish and Netherlands ERSPC sites (each with comparatively high rates of biopsy), although point estimates favored screening at all sites except Switzerland. All-cause mortality was not reduced in either trial, and the number needed to diagnose (and potentially treat) to prevent one prostate cancer death in the ERSPC trial was 27 (95% CI, 17 to 66). Evidence is lacking on the differential benefit of screening among African-American men or men with a family history of prostate cancer.

Our review documented several harms stemming from prostate cancer screening. PSA screening is non-specific, and over one quarter of men randomized to screening in the PLCO had at least one positive screening PSA during up to six annual screening rounds. Most men with positive screening results who undergo biopsy will not have prostate cancer. The harms of biopsy include the pain, bleeding, and infectious complications. Perhaps the most serious harm of prostate cancer screening is overdiagnosis, because overdiagnosis burdens men with the harms of diagnosis and treatment without any benefit in terms of life expectancy or quality of life. We estimated that during the 13.0 years of median followup in the PLCO and ERSPC trials, approximately one-third to one-half of screen-detected cancers were overdiagnosed. Our estimates are largely consistent with estimates based on ecological or modeling studies based on U.S. and European data.[197-201] We recognize that an ideal estimate of overdiagnosis would account for cancer incidence across a patient's lifespan. However, followup duration in the trials does not allow such long-term projection, and post-trial use of PSA screening among participants

in both screening and control arms will affect long-term incidence rates in both trial arms, obscuring future attempts to estimate overdiagnosis rates from the PLCO and ERSPC trials. Our results nevertheless suggest that, over a median time horizon of 13.0 years in each trial, a substantial fraction of cancers diagnosed by PSA screening are overdiagnosed.

Prostate Cancer Treatments

Because prostate cancer screening markedly increases the rate of diagnosis of prostate cancer (especially of early-stage disease), a full picture of the benefits and harms of screening must incorporate the downstream impacts of early-stage prostate cancer treatments, particularly evidence regarding the comparative effectiveness and harms of active, potentially more harmful treatment modalities (e.g., surgery, radiation) versus conservative approaches, such as active surveillance. Evidence shows that the harms of active treatments for prostate cancer are common and long-lasting. A majority of men undergoing radical prostatectomy will have long-term erectile or sexual difficulties and one-third will have urinary difficulties, while one in seven men receiving radiation therapy experience erectile problems in addition to common bowel symptoms. Nevertheless, except for men treated with ADT, men with localized prostate cancers who underwent active and conservative treatments rated their overall quality of life and global health status similarly during extended followup, despite long-term differences in sexual and urinary function.

While earlier randomized trials comparing radical prostatectomy and watchful waiting included many men who were not diagnosed via PSA testing, the recent ProtecT trial compared prostatectomy, radiation therapy, and active surveillance (AS) among men with early-stage prostate cancer detected by screening PSA. Overall, survival at median followup of ten years was over 98.8 percent in each treatment arm, and no statistically significant differences in prostate cancer or all-cause mortality were detected. While power for these outcomes was low because of higher overall and prostate cancer-specific survival compared to earlier trials, nearly half of men assigned to AS were stable without receiving active treatment at 10 year followup, although a small absolute increase in the incidence of metastatic disease was observed in the AS arm as compared to the active treatment arms (approximately 6% with AS vs. 2 to 3% with active treatment). In contemporary case-series of men with low-risk prostate cancer, AS has been associated with cancer-specific survival rates exceeding 99 percent at 10 years of followup.[32] Nevertheless, the low event rate in ProtecT, the short median followup, and the small numbers of men with extended followup in AS case series leads to uncertainty regarding long-term differences in prostate cancer mortality among men with screen-detected cancer managed with active treatments versus AS.

To integrate synthesized data on screening and treatment benefits and harms, we compared the absolute number of men experiencing various outcomes of screening under alternative assumptions regarding the impact of PSA screening on prostate cancer mortality (**Table 28**). Estimates for the three scenarios were derived from trial data for: 1) participants in the PLCO trial; [70] 2) the ERSPC core-age group; [76] and 3) participants in the Goteborg (Sweden) site,[82] where the largest mortality reductions were observed among ERSPC sites. Under conditions of the ERSPC core-age group, we estimated that if 1,000 men were invited to undergo multiple PSA screening rounds, 1.3 men would avert prostate cancer death and 2.9 men would avert

metastatic cancer during a median followup of 13 years. During this period, 243 men would have positive screening tests, and 220 men would undergo prostate biopsy, resulting in 34.8 additional men being diagnosed with prostate cancer (3.5% of total). If these 34.8 men were treated as men were treated in the ERSPC screening arm, 23.9 would receive radical treatments without benefit, and 6.9 and 1.8 men would develop erectile dysfunction or urinary incontinence, respectively, as a consequence of radical treatments. If 1,000 men were invited to be screened under conditions of the Goteborg site, 3.4 prostate cancer deaths and 3.5 metastatic cases would be averted but with proportionally greater harms related to screening and treatment, while no benefit would derive from screening under conditions of the PLCO. If many of the men diagnosed with localized prostate cancer received active surveillance rather than radical treatment, ProtecT trial data suggest that the number of men developing erectile dysfunction or incontinence could be reduced but with potential increases in the number of men with prostate cancer metastases.[121]

Mitigating the Harms of Prostate Cancer Screening

Our review synthesized evidence on the potential for risk calculators to identify men with clinically significant prostate cancer, defined has higher-grade cancer or clinically aggressive cancer that is more likely to progress to locally advanced or metastatic disease. While we identified multiple external validation studies of two risk calculators, results were mixed regarding risk calculator discrimination, calibration, and clinical utility. The literature also does not address the practical challenges of implementing the calculators for screening or followup decisions in clinical practice, including the difficulty of communicating the numerical risk information to patients and caregivers. Additionally, no randomized trials have evaluated the impact of risk calculator use versus non-use on clinical decision-making, biopsy accuracy, or long-term incidence of advanced prostate cancer.

Greater use of AS for men with low-risk cancers may mitigate the harms stemming from PSA screening. As discussed in an accompanying review, recent modeling studies suggest that greater use of AS for low-risk cancer may tilt the balance of benefits and harms in PSA screening in favor screening.[202] Longer term followup of men managed with AS is needed to understand whether differences in prostate cancer mortality emerge between actively and conservatively treated men with screen-detected cancer. Observational studies further suggest that screening may be deferred or screening intervals lengthened in men with lower PSAs on baseline screening.[187, 203]

Efforts are ongoing to reduce the harms of PSA screening by improving the specificity of the screening process, reducing biopsies among cancer-free men, and decreasing overdiagnosis and overtreatment. Several strategies have been developed with the goal of improving the detection of men with aggressive cancer, including serum or urine tests, multivariable risk models, and multiparametric magnetic resonance imaging (mpMRI). In **Appendix F**, we focus on tests that are currently available in the U.S., and in the case of laboratory tests, that are Food and Drug Administration approved or included in National Comprehensive Cancer Network (NCCN) guidelines.[46] For selected men with mild elevations of screening PSA, NCCN guidelines suggest consideration of one of several biomarker tests to assist in decision-making about whether to proceed to biopsy or whether to repeat biopsy if initial biopsy is negative. Although several tests have been shown to predict the presence of any prostate cancer or higher-grade prostate on

biopsy, none of the biomarker tests or testing strategies described in **Appendix F** have been evaluated in completed randomized controlled trials, and few rigorous comparative effectiveness studies examining clinical outcomes have been reported. Research has also evaluated the use of multi-parametric magnetic resonance imaging (mpMRI) to improve biopsy accuracy, to evaluate men with negative biopsies, and to monitor men receiving active surveillance. Some studies suggest that mpMRI-targeted biopsy can increase the detection of higher-risk cancers,[204-207] although other studies have yielded null or mixed results.[208, 209] Few studies have been conducted evaluating the role of mpMRI in active surveillance.[210] Further research is needed to elucidate whether the use of adjunctive tests would improve the balance of benefits and harms of PSA-based prostate cancer screening in community settings.

Shared Decisionmaking

Compared with traditional health education materials, decision aids are designed to personalize the selection of a care pathway by eliciting patient preferences and values through a structured discussion about the benefits, limitations, and uncertainties associated with medical interventions.[211, 212] In a 2015 systematic review of 13 randomized trials, decision aids about prostate cancer screening were associated with improved patient knowledge, reduced decisional conflict and uncertainty, and improved decisional satisfaction.[211] With regard to screening behavior, a 2014 Cochrane review found a 13 percent pooled reduction in PSA screening with use of a decision aid (9 trials; RR, 0.87 [95% CI, 0.77 to 0.98]).[212] In a single RCT evaluating a decision aid among men making treatment decisions for early-stage prostate cancer, a multi-media decision aid reduced decisional conflict but did not significantly modify treatment decisions.[213] However, in the context of treatment, the adoption and use of decision aids may also be hindered by concerns among urologists and radiation oncologists that decision aids may not accurately estimate or communicate risk information to patients.[214]

Limitations of the Evidence

Length of Followup

Because the lead time for prostate cancer may be very long, it is conceivable that current trial reports (with 14.8 and 13.0 years of median followup in the PLCO and ERSPC, respectively) may underestimate prostate cancer mortality benefits. However, post-trial screening among men randomized to screening and control arms may obscure any potential mortality benefits of within-trial screening exposure.[81, 183] Meanwhile, in the ERSPC, there was no change in the relative risk of prostate cancer mortality in the screening vs. control arms when followup was extended from 11 to 13 years. Several modeling studies, summarized in separate reports that were submitted to the USPSTF, have assessed the lifetime impacts of prostate cancer screening. The 10 year median length of followup in the ProtecT trial may also be insufficient to delineate whether higher rates of metastatic disease in the AS arm will affect long-term prostate cancer mortality.

Screening Trial Limitations

The two screening trials each had significant limitations. The principal limitation of the PLCO was the high-rate of use of PSA screening among men randomized to the control group. The large amount of screening conducted among control arm subjects would be expected to bias all PLCO study results toward the null. Meanwhile the ERSPC trial was limited by unexplained differences in treatments received by men diagnosed with prostate cancer in screening and control arms even after adjustment for clinical stage; subjects diagnosed with intermediate- or high-risk prostate cancer in the screening arm were more likely to be treated with radical prostatectomy and less likely to be treated with hormonal therapy than men diagnosed with similar cancers in the control arm. As these analyses are stratified by tumor risk, the treatment differences are not attributable to a screening effect. Thus, the apparent benefit of screening in the ERSPC trial may be at least partly explained by post-randomization treatment differences. Across ERSPC sites, there was also substantial variation in methods of recruitment, screening intervals, use of ancillary testing, and PSA thresholds for biopsy referral.

Impact of Screening on High-Risk Populations

Some screening guidelines advocate an approach that accounts for risk factors for prostate cancer mortality (e.g., family history, African American descent). However, we found little direct evidence about whether tailoring screening approaches based on race/ethnicity or family history will reduce prostate cancer mortality risk in higher-risk men or alter the balance of screening benefits and harms. In observational studies, men with a low baseline PSA had a very low-risk of prostate cancer metastasis and death, implying that among men who initiate PSA screening, recommendations for ongoing testing could potentially be individualized based on baseline PSA.[187, 203]

Generalizability of Treatment Studies

The evidence on the comparative effectiveness of treatments for early-stage or screen-detected prostate cancer has grown considerably since the previous review,[50] but is limited to four randomized trials and multiple cohort studies. Only one of the randomized trials exclusively enrolled men with screen-detected cancer (ProtecT), and prostate cancer-specific and all-cause mortality were extremely low in this study.[121] Other treatment RCTs have enrolled many or mostly men with clinically detected prostate cancer.[117, 133] Thus, it remains uncertain whether treatment trial results are generalizable to U.S. populations of men with early-stage prostate cancer diagnosed by PSA screening. Meanwhile, when evaluating treatment effectiveness, cohort studies are subject to potential confounding by indication, as patients pursuing active treatments in cohort studies may be healthier in unmeasured ways that may exaggerate the benefits of active prostate cancer treatments.

Evidence on treatment harms predominately pertains to more traditional treatment techniques, such as retropubic radical prostatectomy and external beam radiotherapy; evidence is limited regarding more recently developed techniques, such as nerve-sparing or robotic prostatectomy, brachytherapy, and conformal radiotherapy. Evidence was limited regarding the effectiveness of

cryotherapy or HIFU.

Limitations of the Review

In addition to limitations discussed above, this review may be limited by language or publication biases. We also found limited evidence on some potential harms of ADT among men with early-stage prostate cancer and no long-term evidence on the carcinogenic potential of radiation therapy. Aside from uncontrolled studies of treatment harms, we found few or no studies on comparative effectiveness of new or novel treatment modalities, such as alternative surgical approaches to prostatectomy (e.g., nerve-sparing or robotic surgery), cryotherapy, or HIFU. Due to the limited use and variable definitions of active surveillance during the time periods of most included studies, we grouped active surveillance and watchful waiting in our analyses, although outcomes may differ between these two conservative approaches to prostate cancer treatment.

Future Research Needs

Additional long term randomized trials of screening would be useful to confirm the effectiveness of prostate cancer screening and to more precisely quantify the impact of screening on prostate cancer mortality. An extension of the ProtecT trial, the CAP trial (Cluster randomized trial of PSA testing for Prostate Cancer) randomized U.K. practices to screening or usual care without screening and is expected to report results in 2017 or 2018.[126] However, the low rate of prostate cancer death within the ProtecT trial suggests that statistical power may be low for mortality outcomes in the CAP trial. Randomized trials or comparative cohort studies would also be useful in evaluating alternate PSA screening protocols, adjunctive testing, or the differential impact among men at higher risk of prostate cancer, such as African-American men or men with a family history of prostate cancer.

There is a continuing need for evidence on comparative effectiveness of new or novel treatment approaches and their harms. To date, the ProtecT trial provides the only randomized evidence regarding the comparative effectiveness of active surveillance versus active treatments,[121] yet the AS protocol in ProtecT consisted principally of serial PSA testing. It is conceivable that alternative AS protocols may be associated with lower risk of disease progression and metastasis than was observed with AS in ProtecT. Long-term prostate cancer survival has been very high in several case series of men with low-risk cancers treated initially with AS,[32, 215, 216] but relatively few men in these series have been followed for more than 10 years, leading to uncertainty in long-term survival estimates. Ongoing followup of men in these series will be helpful in obtaining more precise estimates of the long-term prognosis of men managed with AS.

Research is also needed to assess the clinical impact of prostate cancer risk calculators when implemented in real practice prior to biopsy decisions. Ideally, such studies would use a randomized design to assess the long-term impact of communicating risk information derived from calculators on patient decisions and clinical outcomes (e.g., accurate detection of high-risk cancers). Research is also needed on outcomes from the use of risk calculators that incorporate newer modalities for pre-biopsy risk assessment, such as multiparametric MRI or tests based on

novel biomarkers.

Conclusion

PSA screening likely reduces the risk of prostate cancer mortality but screening benefits may require a high-rate of biopsy among screen-positive men. In the overall ERSPC trial during a 13.0 years median followup, approximately 27 men needed to be diagnosed with prostate cancer to prevent one prostate cancer death. In current practice, most men with screen-detected prostate cancer undergo active treatments, which are associated with risk of long-term urinary, sexual and bowel complications. Active surveillance of low-risk, screen-detected prostate cancer may mitigate treatment harms, although active surveillance in the ProtecT trial was associated with a higher risk of progression to metastatic disease compared to active treatments during 10 years of followup. Longer term followup is needed to delineate whether the higher rate of metastatic disease among men randomized to active surveillance will increase prostate cancer mortality compared to men randomized to active treatment.

References

1. Mazhar D, Waxman J. Prostate cancer. Postgraduate medical journal. 2002;78(924):590-5.
2. American Joint Committee on Cancer. Genitourinary Sites: Prostate AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
3. Edge S, Byrd D, Compton C, et al. AJCC Cancer Staging Manuel (7th ed). New York, NY: Spring; 2010.
4. National Cancer Institute. SEER Cancer Statistics Factsheets: Prostate Cancer. http://seer.cancer.gov/statfacts/html/prost.html Accessed: Accessed July 24, 2017.
5. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA-Cancer J Clin. 2017;67(1):7-30. 10.3322/caac.21387
6. Stern MC, Fejerman L, Das R, et al. Variability in Cancer Risk and Outcomes Within US Latinos by National Origin and Genetic Ancestry. Current epidemiology reports. 2016;3:181-90. 10.1007/s40471-016-0083-7
7. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2011 Incidence and Mortality Web-based Report. http://www.cdc.gov/uscs. Accessed: Accessed March 26, 2015.
8. Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5alpha-reductase-2 deficiency. Molecular and cellular endocrinology. 2002;198(1-2):51-9.
9. Bell KJ, Del Mar C, Wright G, et al. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. International journal of cancer Journal international du cancer. 2015;137(7):1749-57. 10.1002/ijc.29538
10. Kirschner-Hermanns R, Jakse G. Quality of life following radical prostatectomy. Critical reviews in oncology/hematology. 2002;43(2):141-51.
11. Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. International journal of cancer Journal international du cancer. 2003;107(5):797-803. 10.1002/ijc.11466
12. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. The New England journal of medicine. 2000;343(2):78-85. 10.1056/nejm200007133430201
13. Sinha R, Park Y, Graubard BI, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. American journal of epidemiology. 2009;170(9):1165-77. 10.1093/aje/kwp280
14. Allen NE, Key TJ, Appleby PN, et al. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. British journal of cancer. 2008;98(9):1574-81. 10.1038/sj.bjc.6604331
15. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. Journal of the National Cancer Institute. 2000;92(1):61-8.
16. Islami F, Moreira DM, Boffetta P, et al. A Systematic Review and Meta-analysis of Tobacco Use and Prostate Cancer Mortality and Incidence in Prospective Cohort Studies. European urology. 2014;66(6):1054-64. 10.1016/j.eururo.2014.08.059
17. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190(2):419-26. 10.1016/j.juro.2013.04.119

18. Fleshner K, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol. 2017;14(1):26-37. 10.1038/nrurol.2016.251

19. Parker PM, Rice KR, Sterbis JR, et al. Prostate cancer in men less than the age of 50: a comparison of race and outcomes. Urology. 2011;78(1):110-5. 10.1016/j.urology.2010.12.046

20. Hoffman RM, Gilliland FD, Eley JW, et al. Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study. Journal of the National Cancer Institute. 2001;93(5):388-95.

21. Powell IJ, Banerjee M, Sakr W, et al. Should African-American men be tested for prostate carcinoma at an earlier age than white men? Cancer. 1999;85(2):472-7.

22. Cross CK, Shultz D, Malkowicz SB, et al. Impact of race on prostate-specific antigen outcome after radical prostatectomy for clinically localized adenocarcinoma of the prostate. J Clin Oncol. 2002;20(12):2863-8.

23. Barocas DA, Grubb R, Black A, et al. Association between race and follow-up diagnostic care after a positive prostate cancer screening test in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer [serial on the Internet]. 2013 [cited Search 2 Database 20160304; 119(12): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/484/CN-00964484/frame.html http://onlinelibrary.wiley.com/store/10.1002/cncr.28042/asset/cncr28042.pdf?v=1&t=ilel7j 4n&s=c16f5e4f9eb423babb11d926b64b51d4f7744b47.

24. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. Jama. 1993;270(7):860-4.

25. Vickers AJ, Savage C, O'Brien MF, et al. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. J Clin Oncol. 2009;27(3):398-403. 10.1200/jco.2008.18.1685

26. Hoffman R. Screening for prostate cancer. In: Rind D, editor. UpToDate 2015.

27. Moul JW, Sesterhenn IA, Connelly RR, et al. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. Jama. 1995;274(16):1277-81.

28. Morgan TO, Jacobsen SJ, McCarthy WF, et al. Age-specific reference ranges for prostate-specific antigen in black men. The New England journal of medicine. 1996;335(5):304-10. 10.1056/nejm199608013350502

29. Klein E. Initial approach to low- and very low-risk clinically localized prostate cancer In: Ross M, editor. UpToDate 2015.

30. American Cancer Society. Hormone (androgen deprivation) therapy for prostate cancer. http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy. Accessed: Accessed February 11, 2015.

31. Dahabreh IJ, Chung M, Balk EM, et al. Active surveillance in men with localized prostate cancer: a systematic review. Annals of internal medicine. 2012;156(8):582-90. 10.7326/0003-4819-156-8-201204170-00397

32. Tosoian JJ, Carter HB, Lepor A, et al. Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nat Rev Urol. 2016;13(4):205-15. 10.1038/nrurol.2016.45

33. Walter LC, Fung KZ, Kirby KA, et al. Five-year downstream outcomes following prostate-specific antigen screening in older men. JAMA internal medicine. 2013;173(10):866-73. 10.1001/jamainternmed.2013.323

34. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010;28(7):1117-23. 10.1200/jco.2009.26.0133

35. Filson CP, Shelton JB, Tan HJ, et al. Expectant management of veterans with early-stage prostate cancer. Cancer. 2016;122(4):626-33. 10.1002/cncr.29785

36. Filson CP, Schroeck FR, Ye Z, et al. Variation in use of active surveillance among men undergoing expectant treatment for early stage prostate cancer. J Urol. 2014;192(1):75-80. 10.1016/j.juro.2014.01.105

37. Womble PR, Montie JE, Ye Z, et al. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. European urology. 2015;67(1):44-50. 10.1016/j.eururo.2014.08.024

38. Ritch CR, Graves AJ, Keegan KA, et al. Increasing use of observation among men at low risk for prostate cancer mortality. J Urol. 2015;193(3):801-6. 10.1016/j.juro.2014.08.102

39. Weiner AB, Patel SG, Etzioni R, et al. National trends in the management of low and intermediate risk prostate cancer in the United States. Journal of Urology. 2015;193(1):95-102. http://dx.doi.org/10.1016/j.juro.2014.07.111

40. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. Jama. 2015;314(1):80-2. 10.1001/jama.2015.6036

41. American Academy of Family Physicians. Prostate Cancer Screening. http://www.aafp.org/patient-care/clinical-recommendations/all/prostate-cancer.html. Accessed: Accessed September 12, 2016.

42. Lim LS, Sherin K. Screening for prostate cancer in U.S. men ACPM position statement on preventive practice. American journal of preventive medicine. 2008;34(2):164-70. 10.1016/j.amepre.2007.10.003

43. Bell N, Connor Gorber S, Shane A, et al. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2014;186(16):1225-34. 10.1503/cmaj.140703

44. Mottet N, Bellmunt J, Briers E, et al. EAU Guidelines on Prostate Cancer. http://uroweb.org/guideline/prostate-cancer/. Accessed: February 27, 2017.

45. American Cancer Society. American Cancer Society recommendations for prostate cancer early detection. http://www.cancer.org/cancer/prostatecancer/moreinformation/prostatecancerearlydetection/prostate-cancer-early-detection-acs-recommendations. Accessed: Accessed September 12, 2016.

46. Carroll PR, Parsons JK, Andriole G, et al. NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw. 2016;14(5):509-19.

47. Moyer VA, Force USPST. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. 2012;157(2):120-34. http://dx.doi.org/10.7326/0003-4819-157-2-201207170-00459

48. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual, AHRQ Publication No. 08-05118-EF.

http://www.uspreventiveservicestaskforce.org/Home/GetFile/6/7/procedure-manual_2015/pdf. Accessed: May 24, 2016.

49. Lin K, Croswell JM, Koenig H, et al. Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force. 12-05160-EF-1. Rockville, MD: Agency for Healthcare Resaerch and Quality October 2011.

50. Chou R, Dana T, Bougatsos C, et al. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. 12-05161-EF-1. Rockville, MD: Agency for Healthcare Research and Quality October 2011.

51. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. Journal of the National Cancer Institute. 2006;98(8):529-34. 10.1093/jnci/djj131

52. United Nations Development Programme. Human Develoment Data (1980-2015). http://hdr.undp.org/en/data. Accessed: August 16, 2016.

53. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. The New England journal of medicine. 2009;360(13):1310-9. 10.1056/NEJMoa0810696

54. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. The New England journal of medicine. 2009;360(13):1320-8. 10.1056/NEJMoa0810084

55. National Cancer Institute. SEER Training Module: Summary Staging. https://training.seer.cancer.gov/staging/systems/summary/. Accessed: September 12, 2016.

56. D'Amico AV, Whittington R, Malkowicz SB, et al. Predicting prostate specific antigen outcome preoperatively in the prostate specific antigen era. J Urol. 2001;166(6):2185-8.

57. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS medicine. 2014;11(10):e1001744. 10.1371/journal.pmed.1001744

58. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. European urology. 2015;68(3):464-70. 10.1016/j.eururo.2014.10.021

59. Nordstrom T, Vickers A, Assel M, et al. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. European urology. 2015;68(1):139-46. http://dx.doi.org/10.1016/j.eururo.2014.08.010

60. Salami SS, Vira MA, Turkbey B, et al. Multiparametric magnetic resonance imaging outperforms the Prostate Cancer Prevention Trial risk calculator in predicting clinically significant prostate cancer. Cancer. 2014;120(18):2876-82. http://dx.doi.org/10.1002/cncr.28790

61. Wells GA, Shea B, O'Connell D ea. The Newcastle-Ottowa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed: August 16, 2016.

62. National Institute for Health and Care Excellence. The Guidelines Manual. London: National Institute for Health and Care Excellence; 2006.

63. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Annals of internal medicine. 2015;162(1):55-63. 10.7326/m14-0697

64. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81. 10.1016/j.jbi.2008.08.010

65. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. Bmj. 2015;350:g7773. 10.1136/bmj.g7773

66. Miller AB, Wall C, Baines CJ, et al. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. Bmj. 2014;348:g366. 10.1136/bmj.g366

67. Zackrisson S, Andersson I, Janzon L, et al. Rate of over-diagnosis of breast cancer 15 years after end of Malmo mammographic screening trial: follow-up study. Bmj. 2006;332(7543):689-92. 10.1136/bmj.38764.572569.7C

68. Patz EF, Jr., Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA internal medicine. 2014;174(2):269-74. 10.1001/jamainternmed.2013.12738

69. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making. 2006;26(6):565-74. 10.1177/0272989x06295361

70. Fransson P, Damber JE, Tomic R, et al. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. Cancer. 2001;92(12):3111-9.

71. Fransson P, Damber JE, Widmark A. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer. Scand J Urol Nephrol. 2009;43(2):119-26. 10.1080/00365590802519396

72. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015;68(11):1312-24. 10.1016/j.jclinepi.2014.11.023

73. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. 2004;4(1):38. 10.1186/1472-6963-4-38

74. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. The New England journal of medicine. 2017;377(2):132-42. 10.1056/NEJMoa1615869

75. Barocas DA, Alvarez J, Resnick MJ, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. Jama. 2017;317(11):1126-40. 10.1001/jama.2017.1704

76. Chen RC, Basak R, Meyer AM, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. Jama. 2017;317(11):1141-50. 10.1001/jama.2017.1652

77. Gomez-Gomez E, Carrasco-Valiente J, Blanca-Pedregosa A, et al. European Randomized Study of Screening for Prostate Cancer Risk Calculator: External Validation, Variability, and Clinical Significance. Urology. 2017;102:85-91. 10.1016/j.urology.2016.11.004

78. Maruf M, Fascelli M, George AK, et al. The prostate cancer prevention trial risk calculator 2.0 performs equally for standard biopsy and MRI/US fusion- guided biopsy. Prostate Cancer and Prostatic Diseases. 2017;20(2):179-85. 10.1038/pcan.2016.46

79. Park JY, Yoon S, Park MS, et al. Development and external validation of the Korean prostate cancer risk calculator for high-grade prostate cancer: Comparison with two western risk calculators in an asian cohort. PLoS ONE. 2017;12(1). 10.1371/journal.pone.0168917

80. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. Journal of the National Cancer Institute. 2012;104(2):125-32. 10.1093/jnci/djr500

81. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic Testing Versus Organized Prostate-specific Antigen Screening: Outcome After 18 Years in the Göteborg Randomized Population-based Prostate Cancer Screening Trial. European urology. 2015;68(3):354-60.

82. Bokhorst LP, Bangma CH, van Leenders GJ, et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. European urology. 2014;65(2):329-36. http://dx.doi.org/10.1016/j.eururo.2013.08.005

83. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: New insights from the European Randomized Study of Screening for Prostate Cancer. European urology. 2015;68(5):885-90.

84. Ciatto S, Zappa M, Villers A, et al. Contamination by opportunistic screening in the European Randomized Study of Prostate Cancer Screening. BJU international. 2003;92 Suppl 2:97-100.

85. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. The Lancet Oncology. 2010;11(8):725-32. 10.1016/s1470-2045(10)70146-7

86. Kilpeläinen TP, Pogodin-Hannolainen D, Kemppainen K, et al. Estimate of opportunistic prostate-specific antigen testing in the Finnish Randomized Study of Screening for Prostate Cancer. The Journal of Urology. 2017. http://dx.doi.org/10.1016/j.juro.2017.01.048

87. Kilpelainen TP, Tammela TL, Malila N, et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute. 2013;105(10):719-25. 10.1093/jnci/djt038

88. Liss MA, Chen H, Hemal S, et al. Impact of family history on prostate cancer mortality in white men undergoing prostate specific antigen based screening. Journal of Urology. 2015;193(1):75-9. http://dx.doi.org/10.1016/j.juro.2014.07.085

89. Lujan M, Paez A, Angulo JC, et al. Prostate cancer incidence and mortality in the Spanish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate Cancer Prostatic Dis. 2014;17(2):187-91. http://dx.doi.org/10.1038/pcan.2014.7

90. Pinsky P, Prorok P, Yu K, et al. Extended Mortality Results for Prostate Cancer Screening in the PLCO Trial with Median 15 Years Follow-up. Cancer. 2017;123(4):592-9.

91. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000;21(6 Suppl):273s-309s.

92. Roobol MJ, Kranse R, Bangma CH, et al. Screening for prostate cancer: results of the Rotterdam section of the European randomized study of screening for prostate cancer. European urology. 2013;64(4):530-9. http://dx.doi.org/10.1016/j.eururo.2013.05.030

93. Saarimaki L, Tammela TL, Maattanen L, et al. Family history in the Finnish Prostate Cancer Screening Trial. International Journal of Cancer. 2015;136(9):2172-7. http://dx.doi.org/10.1002/ijc.29243

94. Schroder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). European urology. 2012;62(5):745-52. http://dx.doi.org/10.1016/j.eururo.2012.05.068

95. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. The New England journal of medicine. 2012;366(11):981-90. 10.1056/NEJMoa1113135

96. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet (London, England). 2014;384(9959):2027-35. 10.1016/s0140-6736(14)60525-0

97. Wolters T, Roobol MJ, Steyerberg EW, et al. The effect of study arm on prostate cancer treatment in the large screening trial ERSPC. International journal of cancer Journal international du cancer. 2010;126(10):2387-93. 10.1002/ijc.24870

98. ERSPC. Study Book: European Randomized Study of Screening for Prostate Cancer (ERSPC). http://www.erspc.org/wp-content/uploads/Study-protocol-ERSPC.pdf Accessed: April 11, 2016.

99. Pinsky PF, Blacka A, Kramer BS, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clinical trials (London, England). 2010;7(4):303-11. 10.1177/1740774510374091

100. Sandblom G, Varenhorst E, Lofman O, et al. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. European urology. 2004;46(6):717-23; discussion 24. 10.1016/j.eururo.2004.08.011

101. Kilpelainen TP, Tammela TL, Roobol M, et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer. 2011;47(18):2698-705. 10.1016/j.ejca.2011.06.055

102. Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. Bmj. 2012;344:d7894. 10.1136/bmj.d7894

103. Pinsky PF, Parnes HL, Andriole G. Mortality and complications after prostate biopsy in the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial. BJU international. 2014;113(2):254-9. 10.1111/bju.12368

104. Carlsson SV, Holmberg E, Moss SM, et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU international. 2011;107(12):1912-7. 10.1111/j.1464-410X.2010.09712.x

105. Vasarainen H, Malmi H, Määttänen L, et al. Effects of prostate cancer screening on health-related quality of life: results of the Finnish arm of the European randomized screening trial (ERSPC). Acta oncologica (Stockholm, Sweden) [serial on the Internet]. 2013 [cited Search 2 Database 20160304; 52(8): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/782/CN-00913782/frame.html http://www.tandfonline.com/doi/pdf/10.3109/0284186X.2013.802837.

106. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2016. 10.1002/cncr.30474

107. Croswell JM, Kramer BS, Kreimer AR, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. Annals of family medicine. 2009;7(3):212-22. 10.1370/afm.942

108. Raaijmakers R, Kirkels WJ, Roobol MJ, et al. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology. 2002;60(5):826-30.

109. Bokhorst LP, Zhu X, Bul M, et al. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial. BJU international. 2012;110(11):1654-60. http://dx.doi.org/10.1111/j.1464-410X.2012.11481.x

110. Fowler FJ, Jr., Barry MJ, Walker-Corkery B, et al. The impact of a suspicious prostate biopsy on patients' psychological, socio-behavioral, and medical care outcomes. J Gen Intern Med. 2006;21(7):715-21. 10.1111/j.1525-1497.2006.00464.x

111. McNaughton-Collins M, Fowler FJ, Jr., Caubet JF, et al. Psychological effects of a suspicious prostate cancer screening test followed by a benign biopsy result. Am J Med. 2004;117(10):719-25. 10.1016/j.amjmed.2004.06.036

112. Katz DA, Jarrard DF, McHorney CA, et al. Health perceptions in patients who undergo screening and workup for prostate cancer. Urology. 2007;69(2):215-20. 10.1016/j.urology.2006.09.059

113. Brindle LA, Oliver SE, Dedman D, et al. Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK. BJU international. 2006;98(4):777-82. 10.1111/j.1464-410X.2006.06401.x

114. Abdollah F, Sun M, Schmitges J, et al. Competing-risks mortality after radiotherapy vs. observation for localized prostate cancer: a population-based study. International Journal of Radiation Oncology, Biology, Physics. 2012;84(1):95-103. http://dx.doi.org/10.1016/j.ijrobp.2011.11.034

115. Albertsen PC, Hanley JA, Penson DF, et al. 13-year outcomes following treatment for clinically localized prostate cancer in a population based cohort. J Urol. 2007;177(3):932-6. 10.1016/j.juro.2006.10.051

116. Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. Journal of the National Cancer Institute. 2008;100(16):1144-54. 10.1093/jnci/djn255

117. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. The New England journal of medicine. 2014;370(10):932-42. 10.1056/NEJMoa1311593

118. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. The New England journal of medicine. 2011;364(18):1708-17. 10.1056/NEJMoa1011967

119. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. The New England journal of medicine. 2005;352(19):1977-84. 10.1056/NEJMoa043739

120. Godtman RA, Holmberg E, Khatami A, et al. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised

population-based prostate cancer screening trial. European urology. 2013;63(1):101-7. http://dx.doi.org/10.1016/j.eururo.2012.08.066

121. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. The New England journal of medicine. 2016;375(15):1415-24. 10.1056/NEJMoa1606220

122. Holmberg L, Bill-Axelson A, Garmo H, et al. Prognostic markers under watchful waiting and radical prostatectomy. Hematol Oncol Clin North Am. 2006;20(4):845-55. 10.1016/j.hoc.2006.03.007

123. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. The New England journal of medicine. 2002;347(11):781-9. 10.1056/NEJMoa012794

124. Holmberg L, Bill-Axelson A, Steineck G, et al. Results from the Scandinavian Prostate Cancer Group Trial Number 4: a randomized controlled trial of radical prostatectomy versus watchful waiting. Journal of the National Cancer Institute Monographs. 2012;2012(45):230-3. http://dx.doi.org/10.1093/jncimonographs/lgs025

125. Ladjevardi S, Sandblom G, Berglund A, et al. Tumour grade, treatment, and relative survival in a population-based cohort of men with potentially curable prostate cancer. European urology. 2010;57(4):631-8. 10.1016/j.eururo.2009.03.007

126. Lane JA, Donovan JL, Davis M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. The Lancet Oncology. 2014;15(10):1109-18. 10.1016/S1470-2045(14)70361-4

127. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. JAMA internal medicine. 2014;174(9):1460-7. http://dx.doi.org/10.1001/jamainternmed.2014.3028

128. Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. Jama. 2008;300(2):173-81. 10.1001/jama.300.2.173

129. Schymura MJ, Kahn AR, German RR, et al. Factors associated with initial treatment and survival for clinically localized prostate cancer: results from the CDC-NPCR Patterns of Care Study (PoC1). BMC Cancer. 2010;10:152. 10.1186/1471-2407-10-152

130. Stattin P, Holmberg E, Johansson JE, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. Journal of the National Cancer Institute. 2010;102(13):950-8. 10.1093/jnci/djq154

131. Sun M, Sammon JD, Becker A, et al. Radical prostatectomy vs radiotherapy vs observation among older patients with clinically localized prostate cancer: a comparative effectiveness evaluation. BJU international. 2014;113(2):200-8. http://dx.doi.org/10.1111/bju.12321

132. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. Journal of the National Cancer Institute Monographs. 2012;2012(45):184-90. http://dx.doi.org/10.1093/jncimonographs/lgs041

133. Wilt TJ, Brawer MK, Jones KM, et al. Radical Prostatectomy versus Observation for Localized Prostate Cancer. New England Journal of Medicine. 2012;367(3):203-13. doi:10.1056/NEJMoa1113162

134. Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs observation of localized prostate cancer in elderly men. Jama. 2006;296(22):2683-93. 10.1001/jama.296.22.2683

135. Zhou EH, Ellis RJ, Cherullo E, et al. Radiotherapy and survival in prostate cancer patients: a population-based study. Int J Radiat Oncol Biol Phys. 2009;73(1):15-23. 10.1016/j.ijrobp.2008.04.001

136. Hamdy F, Donovan J, Lane J, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England Journal of Medicine. 2016;375(15):1415-24.

137. Alibhai SM, Leach M, Tomlinson G, et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. Journal of the National Cancer Institute. 2005;97(20):1525-32. 10.1093/jnci/dji313

138. Augustin H, Hammerer P, Graefen M, et al. Intraoperative and perioperative morbidity of contemporary radical retropubic prostatectomy in a consecutive series of 1243 patients: results of a single center between 1999 and 2002. European urology. 2003;43(2):113-8.

139. Bacon CG, Giovannucci E, Testa M, et al. The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. J Urol. 2001;166(5):1804-10.

140. Bjorklund J, Folkvaljon Y, Cole A, et al. Postoperative mortality 90 days after robot-assisted laparoscopic prostatectomy and retropubic radical prostatectomy: a nationwide population-based study. BJU international. 2016. 10.1111/bju.13404

141. Blana A, Rogenhofer S, Ganzer R, et al. Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology. 2008;72(6):1329-33; discussion 33-4. 10.1016/j.urology.2008.06.062

142. Blana A, Walter B, Rogenhofer S, et al. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. Urology. 2004;63(2):297-300. 10.1016/j.urology.2003.09.020

143. Crouzet S, Chapelon JY, Rouviere O, et al. Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. European urology. 2014;65(5):907-14. http://dx.doi.org/10.1016/j.eururo.2013.04.039

144. Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. The New England journal of medicine. 2016;375(15):1425-37. 10.1056/NEJMoa1606221

145. Hoffman RM, Hunt WC, Gilliland FD, et al. Patient satisfaction with treatment decisions for clinically localized prostate carcinoma. Results from the Prostate Cancer Outcomes Study. Cancer. 2003;97(7):1653-62. 10.1002/cncr.11233

146. Inoue Y, Goto K, Hayashi T, et al. Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer. International Journal of Urology. 2011;18(5):358-62. http://dx.doi.org/10.1111/j.1442-2042.2011.02739.x

147. Johansson E, Bill-Axelson A, Holmberg L, et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. European urology. 2009;55(2):422-30. 10.1016/j.eururo.2008.08.054

148. Johansson E, Steineck G, Holmberg L, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4

randomised trial. The Lancet Oncology. 2011;12(9):891-9. 10.1016/s1470-2045(11)70162-0

149. Litwin MS. Health-related quality of life after treatment for localized prostate cancer. Cancer. 1995;75(S7):2000-3. 10.1002/1097-0142(19950401)75:7+<2000::AID-CNCR2820751641>3.0.CO;2-4

150. Litwin MS, Hays RD, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. Jama. 1995;273(2):129-35.

151. Litwin MS, Lubeck DP, Spitalny GM, et al. Mental health in men treated for early stage prostate carcinoma: a posttreatment, longitudinal quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. Cancer. 2002;95(1):54-60. 10.1002/cncr.10651

152. Lubeck DP, Litwin MS, Henning JM, et al. Changes in health-related quality of life in the first year after treatment for prostate cancer: results from CaPSURE. Urology. 1999;53(1):180-6.

153. Pfeiffer D, Berger J, Gross AJ. Single application of high-intensity focused ultrasound as a first-line therapy for clinically localized prostate cancer: 5-year outcomes. BJU international. 2012;110(11):1702-7. http://dx.doi.org/10.1111/j.1464-410X.2012.11375.x

154. Potosky AL, Reeve BB, Clegg LX, et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. Journal of the National Cancer Institute. 2002;94(6):430-7.

155. Rabbani F, Yunis LH, Pinochet R, et al. Comprehensive standardized report of complications of retropubic and laparoscopic radical prostatectomy. European urology. 2010;57(3):371-86. 10.1016/j.eururo.2009.11.034

156. Schapira MM, Lawrence WF, Katz DA, et al. Effect of treatment on quality of life among men with clinically localized prostate cancer. Med Care. 2001;39(3):243-53.

157. Shah C, Jones PM, Wallace M, et al. Differences in disease presentation, treatment outcomes, and toxicities in African American patients treated with radiation therapy for prostate cancer. Am J Clin Oncol. 2012;35(6):566-71. http://dx.doi.org/10.1097/COC.0b013e3182208262

158. Siegel T, Moul JW, Spevak M, et al. The development of erectile dysfunction in men treated for prostate cancer. J Urol. 2001;165(2):430-5. 10.1097/00005392-200102000-00019

159. Smith DP, King MT, Egger S, et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. Bmj. 2009;339:b4817. 10.1136/bmj.b4817

160. Smith DS, Carvalhal GF, Schneider K, et al. Quality-of-life outcomes for men with prostate carcinoma detected by screening. Cancer. 2000;88(6):1454-63.

161. Thong MS, Mols F, Kil PJ, et al. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden. BJU international. 2010;105(5):652-8. 10.1111/j.1464-410X.2009.08815.x

162. Thuroff S, Chaussy C, Vallancien G, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol. 2003;17(8):673-7. 10.1089/089277903322518699

163. Uchida T, Tomonaga T, Kim H, et al. Improved outcomes with advancements in high intensity focused ultrasound devices for the treatment of localized prostate cancer. Journal of Urology. 2015;193(1):103-10. http://dx.doi.org/10.1016/j.juro.2014.07.096

164. Walz J, Montorsi F, Jeldres C, et al. The effect of surgical volume, age and comorbidities on 30-day mortality after radical prostatectomy: a population-based analysis of 9208 consecutive cases. BJU international. 2008;101(7):826-32. 10.1111/j.1464-410X.2007.07373.x

165. Yao SL, Lu-Yao G. Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay. Journal of the National Cancer Institute. 1999;91(22):1950-6.

166. Donovan J, Hamdy F, Lane J, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. New England Journal of Medicine. 2016;375(15):1425-37.

167. Foley RW, Maweni RM, Gorman L, et al. The ERSPC Risk Calculators Significantly Outperform The PCPT 2.0 In The Prediction Of Prostate Cancer; A Multi-Institutional Study. BJU international. 2016. 10.1111/bju.13437

168. Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: independent validation and comparison in a contemporary European cohort. BJU international. 2016;117(3):401-8. 10.1111/bju.13314

169. Lundon DJ, Kelly BD, Foley R, et al. Prostate cancer risk assessment tools in an unscreened population. World journal of urology. 2015;33(6):827-32. http://dx.doi.org/10.1007/s00345-014-1365-7

170. Ankerst DP, Hoefler J, Bock S, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology. 2014;83(6):1362-7. http://dx.doi.org/10.1016/j.urology.2014.02.035

171. Ankerst DP, Boeck A, Freedland SJ, et al. Evaluating the Prostate Cancer Prevention Trial High Grade prostate cancer risk calculator in 10 international biopsy cohorts: Results from the prostate biopsy collaborative group. World journal of urology. 2014;32(1):185-91.

172. Roobol MJ, van Vugt HA, Loeb S, et al. Prediction of Prostate Cancer Risk: The Role of Prostate Volume and Digital Rectal Examination in the ERSPC Risk Calculators. European urology. 2012;61(3):577-83. 10.1016/j.eururo.2011.11.012

173. Nam RK, Kattan MW, Chin JL, et al. Prospective multi-institutional study evaluating the performance of prostate cancer risk calculators. Journal of Clinical Oncology. 2011;29(22):2959-64. http://dx.doi.org/10.1200/JCO.2010.32.6371

174. Ngo TC, Turnbull BB, Lavori PW, et al. The prostate cancer risk calculator from the Prostate Cancer Prevention Trial underestimates the risk of high grade cancer in contemporary referral patients. Journal of Urology. 2011;185(2):483-7. http://dx.doi.org/10.1016/j.juro.2010.09.101

175. Trottier G, Roobol MJ, Lawrentschuk N, et al. Comparison of risk calculators from the Prostate Cancer Prevention Trial and the European Randomized Study of Screening for Prostate Cancer in a contemporary Canadian cohort. BJU international. 2011;108(8 Pt 2):E237-44. http://dx.doi.org/10.1111/j.1464-410X.2011.10207.x

176. Nguyen CT, Yu C, Moussa A, et al. Performance of prostate cancer prevention trial risk calculator in a contemporary cohort screened for prostate cancer and diagnosed by extended prostate biopsy. J Urol. 2010;183(2):529-33. 10.1016/j.juro.2009.10.007

177. Hernandez DJ, Han M, Humphreys EB, et al. Predicting the outcome of prostate biopsy: comparison of a novel logistic regression-based model, the prostate cancer risk calculator,

and prostate-specific antigen level alone. BJU international. 2009;103(5):609-14. 10.1111/j.1464-410X.2008.08127.x

178. Sandblom G, Varenhorst E, Rosell J, et al. Randomised prostate cancer screening trial: 20 year follow-up. BMJ. 2011;342:d1539. 10.1136/bmj.d1539

179. Kjellman A, Akre O, Norming U, et al. 15-year followup of a population based prostate cancer screening study. J Urol. 2009;181(4):1615-21; discussion 21. 10.1016/j.juro.2008.11.115

180. Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ. 2010;341:c4543. 10.1136/bmj.c4543

181. Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer: an updated Cochrane systematic review. BJU international. 2011;107(6):882-91. 10.1111/j.1464-410X.2010.10032.x

182. Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. The Lancet Oncology. 2014;15(11):e484-92. 10.1016/s1470-2045(14)70211-6

183. Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. The New England journal of medicine. 2016;374(18):1795-6. 10.1056/NEJMc1515131

184. Otto SJ, van der Cruijsen IW, Liem MK, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. International journal of cancer Journal international du cancer. 2003;105(3):394-9. 10.1002/ijc.11074

185. Wolters T, Roobol MJ, Van Leeuwen PJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. Journal of Urology. 2011;185(1):121-5.

186. Powell IJ, Vigneau FD, Bock CH, et al. Reducing prostate cancer racial disparity: evidence for aggressive early prostate cancer PSA testing of African American men. Cancer Epidemiol Biomarkers Prev. 2014;23(8):1505-11. http://dx.doi.org/10.1158/1055-9965.EPI-13-1328

187. van Leeuwen PJ, Connolly D, Tammela TL, et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer. 2010;116(20):4857-65. 10.1002/cncr.25474

188. Gulati R, Feuer EJ, Etzioni R. Conditions for Valid Empirical Estimates of Cancer Overdiagnosis in Randomized Trials and Population Studies. American journal of epidemiology. 2016;184(2):140-7. 10.1093/aje/kwv342

189. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer. European urology. 2015;68(5):805-11. 10.1016/j.eururo.2015.03.021

190. Litwin MS, Hays RD, Fink A, et al. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998;36(7):1002-12.

191. Yao A, Iwamoto H, Masago T, et al. The role of staging MRI in predicting apical margin positivity for robot-assisted laparoscopic radical prostatectomy. Urologia Internationalis. 2014;93(2):182-8. http://dx.doi.org/10.1159/000358175

192. National Cancer Institute, Surveillance Epidemiology and End Results Program (SEER). Prostate Cancer Outcomes Study - Landmark Studies. http://seer.cancer.gov/archive/studies/endresults/study24.html. Accessed: September 13, 2016.

193. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet (London, England). 2016;388(10049):1057-66. 10.1016/s0140-6736(16)30592-x

194. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. European urology. 2015;67(5):825-36. 10.1016/j.eururo.2014.07.010

195. Roobol MJ, Schroder FH, Hugosson J, et al. Importance of prostate volume in the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators: results from the prostate biopsy collaborative group. World journal of urology. 2012;30(2):149-55. http://dx.doi.org/10.1007/s00345-011-0804-y

196. Louie KS, Seigneurin A, Cathcart P, et al. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of Oncology. 2015;26(5):848-64.

197. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. Journal of the National Cancer Institute. 2009;101(19):1325-9. 10.1093/jnci/djp278

198. Zappa M, Ciatto S, Bonardi R, et al. Overdiagnosis of prostate carcinoma by screening: an estimate based on the results of the Florence Screening Pilot Study. Ann Oncol. 1998;9(12):1297-300.

199. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. Journal of the National Cancer Institute. 2003;95(12):868-78.

200. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. Journal of the National Cancer Institute. 2009;101(6):374-83. 10.1093/jnci/djp001

201. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. Journal of the National Cancer Institute. 2002;94(13):981-90.

202. Roth JA, Gulati R, Gore JL, et al. Improving the value of PSA prostate cancer screening with "smarter" strategies and increased use of active surveillance. Journal of Clinical Oncology. 2015;33(15).

203. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ. 2014;348:g2296. 10.1136/bmj.g2296

204. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. Jama. 2015;313(4):390-7. 10.1001/jama.2014.17942

205. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet (London, England). 2017. 10.1016/s0140-6736(16)32401-1

206. Panebianco V, Barchetti F, Sciarra A, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol. 2015;33(1):17.e1-7. 10.1016/j.urolonc.2014.09.013

207. Pokorny MR, De Rooij M, Duncan E, et al. Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound-Guided Biopsy Versus

Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies. European urology. 2014;66(1):22-9. 10.1016/j.eururo.2014.03.002

208. Tonttila PP, Lantto J, Paakko E, et al. Prebiopsy Multiparametric Magnetic Resonance Imaging for Prostate Cancer Diagnosis in Biopsy-naive Men with Suspected Prostate Cancer Based on Elevated Prostate-specific Antigen Values: Results from a Randomized Prospective Blinded Controlled Trial. European urology. 2016;69(3):419-25. 10.1016/j.eururo.2015.05.024

209. Radtke JP, Kuru TH, Boxler S, et al. Comparative analysis of transperineal template saturation prostate biopsy versus magnetic resonance imaging targeted biopsy with magnetic resonance imaging-ultrasound fusion guidance. J Urol. 2015;193(1):87-94. 10.1016/j.juro.2014.07.098

210. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. European urology. 2015;67(4):627-36. 10.1016/j.eururo.2014.10.050

211. Ilic D, Jammal W, Chiarelli P, et al. Assessing the effectiveness of decision aids for decision making in prostate cancer testing: a systematic review. Psycho-Oncol. 2015;24(10):1303-15. 10.1002/pon.3815

212. Stacey D, Legare F, Col NF, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews. 2014(1):335. 10.1002/14651858.CD001431.pub4

213. Berry DL, Halpenny B, Hong F, et al. The Personal Patient Profile-Prostate decision support for men with localized prostate cancer: a multi-center randomized trial. Urol Oncol. 2013;31(7):1012-21. 10.1016/j.urolonc.2011.10.004

214. Wang EH, Gross CP, Tilburt JC, et al. Shared decision making and use of decision AIDS for localized prostate cancer : perceptions from radiation oncologists and urologists. JAMA internal medicine. 2015;175(5):792-9. 10.1001/jamainternmed.2015.63

215. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J Clin Oncol. 2015;33(30):3379-85. 10.1200/jco.2015.62.5764

216. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33(3):272-7. 10.1200/jco.2014.55.1192

217. Qaseem A, Barry MJ, Denberg TD, et al. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. Annals of internal medicine. 2013;158(10):761-9. 10.7326/0003-4819-158-10-201305210-00633

218. Carroll PR, Parsons JK, Andriole G, et al. Prostate cancer early detection, version 1.2014. Featured updates to the NCCN Guidelines. J Natl Compr Cancer Netw. 2014;12(9):1211-9; quiz 9.

219. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20. 10.1016/j.jclinepi.2008.10.009

220. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. The Prostate. 2004;59(3):311-8. 10.1002/pros.20017

221. Wang W, Wang M, Wang L, et al. Diagnostic ability of %p2PSA and prostate health index for aggressive prostate cancer: a meta-analysis. Sci. 2014;4:5012. http://dx.doi.org/10.1038/srep05012

222. Foley RW, Gorman L, Sharifi N, et al. Improving multivariable prostate cancer risk assessment using the Prostate Health Index. BJU international. 2016;117(3):409-17. 10.1111/bju.13143

223. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw. 2016;14(1):19-30.

224. Bostrom PJ, Bjartell AS, Catto JW, et al. Genomic Predictors of Outcome in Prostate Cancer. European urology. 2015;68(6):1033-44. 10.1016/j.eururo.2015.04.008

225. Moore CM, Ridout A, Emberton M. The role of MRI in active surveillance of prostate cancer. Current Opinion in Urology. 2013;23(3):261-7. http://dx.doi.org/10.1097/MOU.0b013e32835f899f

226. PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance or Not? (PRECISION). [database on the Internet]. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT02380027.

Figure 1. Analytic Framework
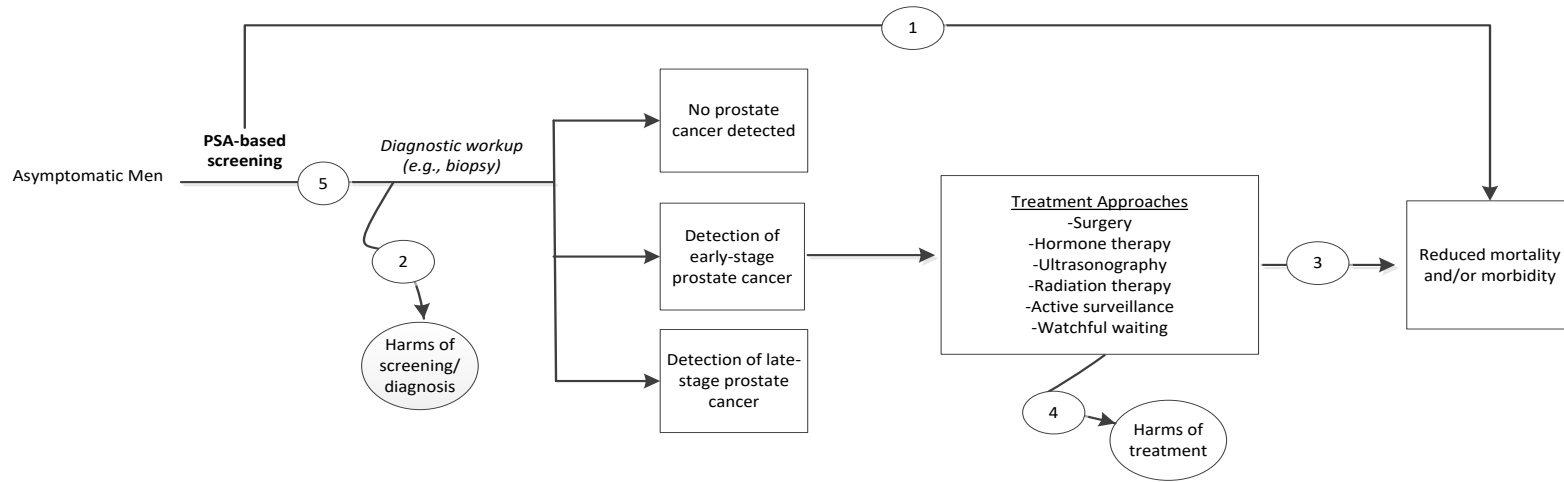
Key Questions

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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., cancer that is more likely to cause symptoms or lead to advanced disease) compared to PSA-based screening alone?

Figure 2. Relative Risk of Urinary Incontinence After Radical Prostatectomy vs. Conservative Management* for Treatment of Localized Prostate Cancer

Author	Year	Design	Followup		RR (95% CI)	Events, Treatment	Events, Control
RCT							
Donovan	2016	RCT	6 years		2.07 (1.44, 2.98)	79/455	38/453
Wilt	2012	RCT	2 years		2.69 (1.61, 4.51)	49/287	18/284
Johansson	2009	RCT	1-8 years		2.29 (1.63, 3.22)	79/162	33/155
Subtotal (I-squared = 0.0%, p = 0.714)					2.27 (1.82, 2.84)	207/904	89/892
.							
Cohort							
Barocas	2017	Cohort	3 years		2.34 (1.49, 3.65)	175/1307	20/349
Chen	2017	Cohort	2 years		1.58 (0.99, 2.53)	58/360	21/206
Smith	2009	Cohort	3 years		3.77 (1.68, 8.46)	111/981	6/200
Hoffman	2003	Cohort	2 years		4.27 (2.76, 6.60)	484/1373	19/230
Schapira	2001	Cohort	1 year		11.11 (1.57, 78.47)	16/36	1/25
Litwin	1995	Cohort	6 years		1.94 (0.82, 4.58)	19/98	6/60
Subtotal (I-squared = 63.0%, p = 0.019)					2.75 (1.78, 4.23)	863/4155	73/1070

.5   1   2   78.5

Favors RP   Favors CM

Note: Measurement of followup varied across studies; some studies reported mean/median followup, while others reported ranges or longest followup point.
*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: CM=conservative management; RCT=randomized controlled trial; RR=relative risk

Figure 3. Relative Risk of Erectile Dysfunction After Radical Prostatectomy vs. Conservative Management* for Treatment of Localized Prostate Cancer†

Author	Year	Design	Followup (years)		RR (95% CI)	Events, Treatment	Events, Control
RCT							
Donovan	2016	RCT	6		1.25 (1.08, 1.45)	227/457	174/437
Wilt	2012	RCT	2		1.84 (1.59, 2.12)	231/285	124/281
Johansson	2009	RCT	4.1		1.79 (1.48, 2.16)	128/159	71/158
Subtotal (I-squared = 87.5%, p = 0.000)					1.60 (1.23, 2.07)	586/901	369/876
.							
Cohort							
Barocas	2017	Cohort	3		1.42 (1.27, 1.59)	893/1307	168/349
Chen	2017	Cohort	2		1.33 (1.18, 1.51)	285/373	130/227
Smith	2009	Cohort	3		1.51 (1.29, 1.76)	695/981	94/200
Hoffman	2003	Cohort	2		2.11 (1.69, 2.64)	757/1373	60/230
Schapira	2001	Cohort	2.5 - 3.4		1.31 (0.98, 1.76)	33/37	17/25
Siegel	2001	Cohort	4.3		1.44 (1.19, 1.75)	353/392	40/64
Litwin	1995	Cohort	6		1.50 (1.15, 1.96)	76/98	31/60
Subtotal (I-squared = 59.2%, p = 0.023)					1.49 (1.34, 1.65)	3092/4561	540/1155

.4   1   2   2.7

Favors RP   Favors CM

Note: Measurement of followup varied across studies; some studies reported mean/median followup, while others reported ranges or longest followup point.

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

†Data from Donovan et al. (in press) are the source of marked heterogeneity, potentially because of the crossover of many active surveillance patients to radical treatments during the six years of median followup. Excluding those data and pooling only data from Wilt (2012) and Johansson (2009) results in a RR=1.82 (95% CI, 1.62 to 2.04; I^2=0.0%)

Abbreviations: CM=conservative management; RCT=randomized controlled trial; RR=relative risk

Figure 4. Relative Risk of Urinary Incontinence After Radiation Therapy vs. Conservative Management* for Treatment of Localized Prostate Cancer

Author	Year	Design	Followup	RR (95% CI)	Events, Treatment	Events, Control
Barocas	2017	Cohort	3 years	0.87 (0.49, 1.55)	24/482	20/349
Chen	2017	Cohort	2 years	0.88 (0.47, 1.65)	15/168	21/206
Smith	2009	Cohort	3 years	0.81 (0.21, 3.19)	3/123	6/200
Hoffman	2003	Cohort	2 years	1.47 (0.91, 2.39)	71/583	19/230
Schapira	2001	Cohort	1 year	1.97 (0.22, 17.92)	3/38	1/25
Litwin	1995	Cohort	6 years	0.71 (0.21, 2.40)	4/56	6/60
Donovan	2016	RCT	6 years	0.42 (0.24, 0.75)	16/452	38/453
Fransson	2001	RCT	2.5 to 3.8 years	8.31 (1.10, 62.63)	10/59	1/49

.07   1   2   63

Favors RT   Favors CM

Note: Measurement of followup varied across studies; some studies reported mean/median followup, while others reported ranges or longest followup point.

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: CM=conservative management; RCT=randomized controlled trial; RR=relative risk

Figure 5. Relative Risk of Erectile Dysfunction After Radiation Therapy vs. Conservative Management for Treatment of Localized Prostate Cancer

Author	Year	Design	Followup (years)	RR (95% CI)	Events, Treatment	Events, Control
RCT						
Donovan	2016	RCT	6	0.91 (0.77, 1.08)	162/447	174/437
Subtotal (I-squared = .%, p = .)				0.91 (0.77, 1.08)	162/447	174/437
.						
Cohort						
Barocas	2017	Cohort	3	1.41 (1.24, 1.59)	326/482	168/349
Chen	2017	Cohort	2	1.11 (0.95, 1.30)	120/189	130/227
Smith	2009	Cohort	3	1.25 (1.01, 1.54)	72/123	94/200
Thong	2009	Cohort	5.0 - 10.0	1.46 (1.06, 2.01)	43/63	28/60
Hoffman	2003	Cohort	2	1.50 (1.18, 1.91)	228/583	60/230
Schapira	2001	Cohort	2.5 - 3.4	1.10 (0.80, 1.52)	30/40	17/25
Siegel	2001	Cohort	4.3	1.37 (1.12, 1.66)	269/315	40/64
Litwin	1995	Cohort	6	1.35 (1.00, 1.82)	39/56	31/60
Subtotal (I-squared = 22.1%, p = 0.253)				1.31 (1.20, 1.42)	1127/1851	568/1215

.4   1   1.5   2.1

Favors RT   Favors CM

Note: Measurement of followup varied across studies; some studies reported mean/median followup, while others reported ranges or longest followup point.

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: CM=conservative management; RCT=randomized controlled trial; RR=relative risk

Table 1. Prostate Cancer Tumor Staging

Stage	T*	N†	M‡	PSA§	Gleason‖	Description
I	T1a-c	N0	M0	<10	≤6	Clinically unapparent tumor, not palpable or visible by imaging. No regional node involvement and no distant metastasis
	T2a	N0	M0	<10	≤6	
IIa	T1a-c	N0	M0	<20	7	Tumor confined within the prostate. No regional node involvement and no distant metastasis
	T1a-c	N0	M0	≥10<20	≤6	
	T2a	N0	M0	≥10<20	≤6	
	T2a	N0	M0	<20	7	
	T2b	N0	M0	<20	≤7	
IIb	T2c	N0	M0	Any	Any	
	T1-2	N0	M0	≥20	Any	
	T1-2	N0	M0	Any	≥8	
III	T3a-b	N0	M0	Any	Any	Tumor extends through the prostate capsule. No regional node involvement and no distant metastasis
IV	T4	N0	M0	Any	Any	Tumor is fixed or invades adjacent structures other than seminal vesicles (bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall)
	Any	N1	M0	Any	Any	
	Any	Any	M1	Any	Any	

Source: American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition

*Primary Tumor (T)
 T1a: Tumor incidental histologic finding in ≤5% of tissue resected
 T1b: Tumor incidental histologic finding in >5% of tissue resected
 T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
 T2a: Tumor involves one-half of one lobe or less
 T2b: Tumor involves more than one-half of one lobe but not both lobes
 T2c: Tumor involves both lobes
 T3a: Extracapsular extension (unilateral or bilateral)
 T3b: Tumor invades seminal vesicle(s)
 T4: Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder,
  levator muscles, and/or pelvic wall
† Regional lymph nodes (N)
 N0: No regional lymph node metastasis
 N1: Metastasis in regional lymph node(s)
‡ Distant metastasis (M)
 M0: No distant metastasis
 M1: Distant metastasis
§PSA serum levels
 PSA < 10 ng/nL: low risk
 PSA 10-20 ng/nL: intermediate risk
 PSA > 20 ng/nL: high risk
‖ Gleason score (tumor grading)
 Gleason ≤6: Well differentiated
 Gleason 7: Moderately differentiated
 Gleason 8-10: Poorly differentiated

Table 2. Recommendations From Other Groups

Organization, year	Population	Recommendation
American Academy of Family Physicians, 2012[41]	Asymptomatic men	Adopts the U.S. Preventive Services Task Force 2012 recommendation, which recommended against prostate-specific antigen (PSA)-based screening for prostate cancer
American Cancer Society, 2016[45]	Asymptomatic men	Recommends that men make an informed decision with their doctor about whether to be tested for prostate cancer. Recommends that men should not be tested without learning about the uncertainties, risks and potential benefits of screening. Starting at age 50 years, men with a life expectancy of more than 10 years should talk to their doctor about the pros and cons of testing so they can decide if testing is the right choice for them. African American men or men with a father or brother who had prostate cancer before age 65 years should have this talk with their doctor starting at age 45 years. Men with more than one first-degree relative (father, brother) who had prostate cancer before age 65 should have this talk with their doctor starting at age 40 years. Men who choose to be screened should be tested with the PSA blood test (a DRE may also be performed as part of screening). Men whose PSA test result is less than 2.5 ng/mL may only need to be retested every 2 years; screening should be done on an annual basis for men whose PSA levels is 2.5 ng/mL or higher.
American College of Physicians, 2013[217]	Asymptomatic men	For men ages 50 to 69 years, the decision to be screened for prostate cancer should be made after discussions with their physicians about the benefits and harms of screening, the patient's preferences, and their general health and life expectancy. Only recommends screening for men between the ages of 50 and 69 years with a life expectancy greater than 10 to 15 years.
American College of Preventive Medicine, 2008[42]	Asymptomatic men	Insufficient evidence to recommend routine population screening with DRE or PSA. Clinicians caring for men, especially African American men and those with positive family histories should provide information about potential benefits and risks of prostate cancer screening, and the limitations of current evidence for screening, in order to maximize informed decision making.
American Urological Association, 2013[17]	Asymptomatic men	Recommends that men ages 55 to 69 years should discuss the benefits and harms of screening with their physician and that the decision to screen be reached through shared decision-making, taking into account men's values and preferences. For African American men or those with a positive family history who are also younger than 55 years of age, decisions about screening should be individualized.
Canadian Task Force on Preventive Health Care, 2014[43]	Asymptomatic men	Recommends against screening for prostate cancer with the PSA test at any age.
European Association of Urology, 2017[44]	Asymptomatic men	Recommends individualized screening strategy based on patient risk and shared decision making for men with at least 10 to 15 years life expectancy.
National Comprehensive Cancer Network, 2016[218]	Asymptomatic men	Recommends discussing risks and benefits of baseline PSA and DRE in previously unscreened men aged 45 and older with subsequent screening or diagnostic evaluation based on the results of these tests. For men over age 75 years, screening can be cautiously considered among men with little or no comorbidity.,

Table 3. Study Characteristics of Randomized, Controlled Trials of PSA-Based Prostate Cancer Screening

Study Reference Quality Rating	Location Study population (age and N)	PSA Screening Protocol			Enrollment Method	Compliance With Screening	Contamination in Control Arm	Followup
		PSA Threshold (ng/mL)	Screening Interval	Additional Screening Tests (If Any)				
PLCO Pinsky, 2016[106] Andriole, 2009[53] Fair	United States Multi-center randomized trial (N=76,683)‡ Age (range): 55 to 74 years	4.0	Annual for up to 6 screening rounds	Annual DRE for first 4 years of the study	Volunteer	85% (average compliance per screening round)[53]	46% overall had routine PSA testing during the screening phase (40% in year 1 and 52% by year 6)[53]	14.8 years (median)
ERSPC* Schroder, 2014[96] Ciatto, 2003[84] Fair ERSPC Site-Specific Reports *Sweden (Göteborg):* Arnsrud Godtman, 2015[81] *Spain:* Lujan, 2014[89] *Netherlands (Rotterdam):* Roobol, 2013[92] Bokhorst, 2014[82]	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, France)† Men identified from population-based registries (N=162,388; core age group)§ Age (median): 60.2 years	Netherlands: 1993–1997: 4.0 1997 and on: 3.0 Belgium: 1991–1994: 10.0 1995 to 1997: 4.0 Sweden: 1995–1998: 3.0 1999 and on: 2.5 Finland: 4.0 Spain: 3.0 Switzerland: 3.0 Italy: 4.0	Netherlands: 4 years Belgium: 4-7 years Sweden: 2 years Finland: 4 years Spain: 4 years Switzerland: 4 years Italy: 4 years	Netherlands: From 1991 to 1997, PSA combined PSA with DRE and TRUS Belgium: From 1991 to 1997, PSA combined with DRE and TRUS. Finland: PSA of 3.0 to 3.9 prompted DRE, and after 1999, calculation of free PSA: total PSA ratio led to biopsy, if either was positive Italy: PSA of 2.5 to 3.9 prompted DRE and TRUS	Mixed (some sites population, some volunteer)	83% (percent of men in screening arm who were screened at least once)	No report on contamination overall.[84] Site-specific estimates for Spain, Finland, and Netherlands given below. PSA use in prior year among control arms subjects in Italy: 28.9% (1997), 36.6% (2001)	13.0 years (median)
Finland: Kilpelainen, 2013[87] Kilpelainen, in press[86]	Sweden (Göteborg) N=20,000 Age (median): 56.0 years	1995–1998: 3.0 1999 and on: 2.5	2 years	None	Population	NR	NR	18.0 years
	Spain Men identified from population registry lists	3.0	4 years	None	Volunteer	NR	Ever use of PSA in control arm: 6.7%	15.2 years (median)

Table 3. Study Characteristics of Randomized, Controlled Trials of PSA-Based Prostate Cancer Screening

Study Reference Quality Rating	Location Study population (age and N)	PSA Screening Protocol			Enrollment Method	Compliance With Screening	Contamination in Control Arm	Followup
		PSA Threshold (ng/mL)	Screening Interval	Additional Screening Tests (If Any)				
	(N=4,276) Age (range): 45 to 70 years							
	Netherlands (Rotterdam) Men selected from a population-based registry (N=42,376) Age (range): 54 to 74 years	1993–1997: 4.0 1997 and on: 3.0	4 years	PSA of 3.0–3.9 prompted DRE; after 1999, calculation of free PSA: total PSA ratio led to biopsy, if either was positive	Volunteer	94.5% at first screening; 85%–88% at repeat screenings	Use of screening PSA during screening phase of trial: 19.4%[82]	12.8 years (median)
	Finland Men identified from the Finnish Population Registry (N=80,144) Age (median): 58.7 years	4.0	4 years	1996–1999: PSA of 3.0-3.9 received DRE	Population	74.6%	Baseline contamination among screening arms subjects (range): 6.7% (1996) to 13.8% (1999)[84] Contamination in control arm at 12.0 years of followup: 62.7%[86]	12.0 years (median)

*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports
†Core age group only; excluded France due to incomplete followup
‡Population sample sizes in the PLCO differ between the 13-year followup publication (Andriole, 2012; n=76,685) and the 11.5-year and 14.8-year followup (Andriole, 2009 and Pinsky, 2016; n=76,683)
§Population sample sizes in the ERSPC differ between the 9-year followup publication (Schroder, 2009; n=162,387) and the 11-year and 13-year followup (Schroder, 2012 and Schroder, 2014; n=162,388)

Abbreviations: DRE=digital rectal exam; ERSPC=European Randomized Study of Screening for Prostate Cancer; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; TRUS=transrectal ultrasound

Table 4. Study Characteristics of Cohort Studies of Physical or Psychological Harms of Prostate Cancer Screening

| Study Reference Quality Rating | Location Study Population | PSA Screening Protocol | | | Diagnostic Procedures | Followup |
		PSA Threshold (ng/mL)	Screening Interval	Additional Screening Tests (If Any)		
Walter, 2013[33] Fair	United States VA health care cohort (N=295,645) Age (mean): 73 years	4.0	NR	NR	Prostate biopsy	5 years (planned)
ProBE cohort Rosario, 2012[102] Good	United Kingdom Men attending PSA screening at 8 medical practices in the UK (N=1,147); cohort was embedded in the ProtecT trial Age (mean): 62.1 years	3.0	NR	NR	TRUS-guided biopsy	35 days (planned)
Fowler, 2006[110] McNaughton-Collins, 2004[111] Good	United States Men attending primary care at single academic medical center, including men with recent benign biopsy after abnormal PSA screening (n=163) and men with normal PSA screening (n=237)	2.5	NA	NA	Prostate biopsy	6 weeks, 6 months, 12 months
Katz, 2007[112] Fair	United States Men receiving care at university-affiliated hospitals or primary care practices who either had an abnormal PSA or DRE result but negative biopsy findings (n=109), or who had a normal PSA result (n-101)	4.0	NA	NA	Prostate biopsy	5 weeks
Brindle, 2006[113] Fair	United Kingdom Men attending general practice centers who had an abnormal PSA result and received a prostate biopsy (n=569); cohort was identified during case-finding for the ProtecT trial Age (mean): 61.9 years	3.0	NR	NR	TRUS-guided biopsy	NR

Abbreviations: ProBE=Prostate Biopsy Effects; ProtecT=Prostate testing for cancer and Treatment; TRUS=transrectal ultrasound

Table 5. The Effect of PSA-Based Screening on Prostate Cancer Incidence

Study Reference Quality Rating	Location	N	Followup	Prostate Cancer Incidence	Stage or Risk Distribution at Diagnosis
PLCO Andriole, 2012[80] Fair	United States	76,683[‡]	13.0 years (median)	IG: 11.1% (4250/38,340 men) 108.4 per 10,000 PY CG: 9.9% (3815/38,345 men) 97.1 per 10,000 PY RR=1.12 (95% CI, 1.07 to 1.17)	Stage 1: IG: 0.5% (19/4250 men) CG: 0.5% (17/3815 men) Stage 2: IG: 95.4% (4056/4250 men) CG: 94.0% (3584/3815 men) Stage 3: IG: 1.4% (58/4250 men) CG: 1.7% (65/3815 men) Stage 4: IG: 2.3% (96/4250 men) CG: 2.9% (111/3815 men)
ERSPC* Schroder, 2014[96] Buzzoni, 2015[83] Fair ERSPC Site-Specific Reports Sweden (Göteborg): Arnsrud Godtman, 2015[81] Spain: Lujan, 2014[89] Netherlands (Rotterdam): Roobol, 2013[92]	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France)[†]	162,388 (core age group) [§]	13.0 years (median)	IG: 10.2% (7408/72,891 men) 95.5 per 10,000 PY CG: 6.8% (6107/89,352 men) 62.3 per 10,000 PY RR=1.57 (95% CI, 1.51 to 1.62)	Low Risk: IG: 60% (4442/7408 men) CG: 42% (2543/6107 men) RR=2.14 (95% CI, 2.03 to 2.25) Intermediate Risk: IG: 22% (1625/7408 men) CG: 28% (1711/6107 men) RR=1.24 (95% CI, 1.16 to 1.34) High Risk: IG: 7% (519/7408 men) CG: 11% (667/6107 men) RR=1.00 (95% CI, 0.89 to 1.13) Metastatic: IG: 3% (252/7408 men) CG: 10% (586/6107 men) RR=0.60 (95% CI, 0.52 to 0.70)
Finland: Kilpelainen, 2013[87]	Sweden (Göteborg)	20,000	18.0 years	IG: 14.0% (1396/10,000 men) CG: 9.6% (962/10,000 men)	Low Risk: IG: 50.0% (697/1396) CG: 26.3% (253/962) Intermediate Risk: IG: 33.6% (469/1396) CG: 37.4% (360/962)

Table 5. The Effect of PSA-Based Screening on Prostate Cancer Incidence

Study Reference Quality Rating	Location	N	Followup	Prostate Cancer Incidence	Stage or Risk Distribution at Diagnosis
					High Risk: IG: 9.7% (136/1396) CG: 17.6% (169/962) Advanced: IG: 2.7% (67/1396) CG: 12.2% (117/962)
	Spain	4,276	15.2 years (median)	IG: 6.7% (161/2415 men) 47.8 per 10,000 PY CG: 4.3% (80/1861 men) 30.5 per 10,000 PY RR=1.57 (95% CI, 1.20 to 2.05)	NR
	Netherlands (Rotterdam)	42,376	12.8 years (median)	IG: 12.7% (2674/20,985 men) CG: 6.8% (1430/20,917 men)	Low Risk: IG: 68.3% (1444/2113 men) CG: 42.3% (605/1430 men) Intermediate Risk: IG: 25.1% (531/2113 men) CG: 27.9% (399/1430 men) High Risk: IG: 5.5% (116/2113 men) CG: 13.0% (183/1430 men) Metastatic: IG: 0.8% (16/2113 men) CG: 12.8% (183/1430 men)
	Finland	80,144	12.0 years (median)	IG: 9.0% (2883/31,866 men) 88.0 per 10,000 PY CG: 6.9% (3337/48,278 men) 66.0 per 10,000 PY HR= 1.34 (95% CI 1.27 to 1.40; p<0.001)	Low risk: IG: 61.5% (1774/2883 men) CG: 46.9% (1565/3337 men) HR=1.75 (95% CI 1.64 to 1.87; p<0.001) Moderate risk: IG: 25.0% (719/2883 men) CG: 32.2% (1076/3337 men) HR=1.03 (95% CI 0.94 to 1.14; p=0.48) High risk: IG: 13.2% (380/2883 men)

Table 5. The Effect of PSA-Based Screening on Prostate Cancer Incidence

Study Reference Quality Rating	Location	N	Followup	Prostate Cancer Incidence	Stage or Risk Distribution at Diagnosis
					CG: 20.5% (684/3337 men) HR=0.86 (95% CI 0.76 to 0.97; p=0.02) Advanced: HR=0.73 (95% CI, 0.64 to 0.82; p<0.001)

*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports

†Results for core age group only; excluded France due to incomplete followup

‡Population sample sizes in the PLCO differ between the 13-year followup publication (Andriole, 2012; n=76,685) and the 11.5-year and 14.8-year followup (Andriole, 2009 and Pinsky, 2016; n=76,683)

§Population sample sizes in the ERSPC differ between the 9-year followup publication (Schroder, 2009; n=162,387) and the 11-year and 13-year followup (Schroder, 2012 and Schroder, 2014; n=162,388)

Abbreviations: CI=confidence interval; CG=control group; ERSPC=European Randomized Study of Screening for Prostate Cancer; HR=hazard ratio; IG=intervention group assigned to screening; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RR=relative risk

Table 6. The Effect of PSA-Based Screening on Prostate Cancer-Specific and All-Cause Mortality

Study Reference Quality Rating	Location	N	Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality[‡]
PLCO Pinsky, 2016[106] Fair	United States	76,683	14.8 years (median)	IG: 0.67% (255/38,340 men) 4.8 per 10,000 PY CG: 0.64% (244/38,345 men) 4.6 per 10,000 PY RR=1.04 (95% CI, 0.87 to 1.24; p=0.67) HR=1.03 (95% CI, 0.87 to 1.23; p=0.72)	IG: 24.0% (9212/38,340 men) 172.8 per 10,000 PY CG: 24.5% (9375/38,345 men) 176.9 per 10,000 PY RR=0.98 (95% CI, 0.95 to 1.00; p=0.11) HR=0.97 (95% CI, 0.95 to 1.00; p=0.06)
ERSPC* Schroder, 2014[96] Fair ERSPC Site-Specific Reports Sweden (Göteborg): Arnsrud Godtman, 2015[81] Hugosson, 2010[85] Spain: Lujan, 2014[89] Netherlands (Rotterdam): Roobol, 2013[92] Finland: Kilpelainen, 2013[87]	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France)[†]	162,388 (core age group)	13.0 years (median)	IG: 0.5% (355/72,891 men) 4.3 per 10,000 PY CG: 0.6% (545/89,353 men) 5.4 per 10,000 PY RR=0.79 (95% CI, 0.69 to 0.91; p=0.001)	IG: 21.1% (15,369/72,891 men) 186.0 per 10,000 PY CG: 21.4% (19,108/89,353 men) 189.0 per 10,000 PY RR=1.00 (95% CI, 0.98 to 1.02; p=0.82)
	Sweden (Göteborg)	20,000	18.0 years (median)	IG: 0.79% (79/10,000 men) CG: 1.22% (122/10,000 men) RR=0.58 (95% CI, 0.46 to 0.72) Absolute risk reduction=0.72% (95% CI, 0.50 to 0.94)	14-year followup IG: 19.8% (1,981/10,000) CG: 19.8% (1,982/10,000)
	Spain	4,276	15.2 years (median)	IG: 0.21% (5/2415 men) 1.4 per 10,000 PY CG: 0.27% (5/1861 men) 1.9 per 10,000 PY RR=0.76 (95% CI, 0.22 to 2.62)	IG: 12.5% (303/2415 men) 86.0 per 10,000 PY CG: 13.5% (251/1861 men) 93.8 per 10,000 PY RR=0.92 (95% CI, 0.78 to 1.08)
	Netherlands (Rotterdam)	42,376	12.8 years (median)	IG: 0.43% (91/20,985 men) CG: 0.90% (188/20,917 men) RR=0.80 (95% CI, 0.65 to 0.99; p=0.042)	IG: 2.8% (578/20,985 men) CG: 2.3% (483/20,917 men)
	Finland	80,144	12.0 years (median)	IG: 0.5% (149/31,866 men) CG: 0.6% (266/48,278 men) HR=0.85 (95% CI, 0.69 to 1.04; p=0.10)	IG: 20.8% (6618/31,866 men) CG: 20.9% (10,079/48,278 men)

Table 6. The Effect of PSA-Based Screening on Prostate Cancer-Specific and All-Cause Mortality

Study Reference Quality Rating	Location	N	Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality[‡]
					HR=0.99 (95% CI, 0.96 to 1.02; p=0.69)

*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports
†Results for core age group only; excluded France due to incomplete followup
‡The PLCO trial excluded lung and colorectal cancers from their analysis of all-cause mortality

Abbreviations: ARR=absolute risk reduction; CI=confidence interval; CG=control group; ERSPC=European Randomized Study of Screening for Prostate Cancer; HR=hazard ratio; IG=intervention group assigned to screening; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RR=relative risk

Table 7. The Effect of PSA-Based Screening on Prostate Cancer-Specific Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Location	Age	Gleason Score	Family History	Comorbid Conditions
PLCO Andriole, 2012[80] Liss, 2015[88] Fair	United States	13.0-years followup *55 to 64 years:* IG: 2.35 per 10,000 PY CG: 1.97 per 10,000 PY RR=1.19 (95% CI, 0.83 to 1.72) *65 to 74 years:* IG: 6.17 per 10,00 PY CG: 6.02 per 10,000 PY RR=1.02 (95% CI, 0.77 to 1.37) p (interaction)=0.81	NR	11.6-years followup *Among men with positive FH:* IG: 0.36% (18/2,350) CG: 0.77% (9/2,483) HR=0.49 (95% CI, 0.22 to 1.00; p=0.08) *Negative FH:* 0.37% (216/58,767) *Positive FH:* 0.56% (27/4,833) HR=1.47 (95% CI, 0.98 to 2.21; p=0.06)	13.0-years followup *No comorbidity* IG: 3.47 per 10,000 PY CG: 3.48 per 10,000 PY RR=1.00 (95% CI, 0.76 to 1.31) *At least one comorbidity (CCI≥1)* IG: 3.78 per 10,000 PY CG: 3.41 per 10,000 PY RR=1.11 (95% CI, 0.72 to 1.71) p (interaction)=0.68
Schroder, 2014[96] ERSPC* ERSPC site-specific reports Netherlands (Rotterdam): Roobol, 2013[92]	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France)†	13.0-years followup *≤54 years* IG: 0.9 per 10,000 PY CG: 1.1 per 10,000 PY RR=0.84 (95% CI, 0.28 to 2.49; p=0.75) *55-59 years:* IG: 2.8 per 10,000 PY CG: 3.3 per 10,000 PY RR=0.81 (95% CI, 0.93 to 1.03; p=0.09) *60-64 years:* IG: 5.0 per 10,000 PY) CG: 5.7 per 10,000 PY RR=0.90 (95% CI, 0.71 to 1.15; p=0.41) *65-69 years:* IG: 7.0 per 10,000 PY CG: 10.3 per 10,000 PY RR=0.69 (95% CI, 0.55 to 0.87; p=0.002) *70+ years:* IG: 14.4 per 10,000 PY) CG: 12.4 per 10,000 PY RR=1.17 (95% CI, 0.82 to 1.66; p=0.40)	NR	NR	NR
	Sweden (Göteborg)	NR	NR	NR	NR
	Spain	NR	NR	NR	NR

Table 7. The Effect of PSA-Based Screening on Prostate Cancer-Specific Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Location	Age	Gleason Score	Family History	Comorbid Conditions
	Netherlands (Rotterdam)	12.8-years followup *55-69 years:* RR=0.68 (95% CI, 0.53 to 0.89; p=0.004) *70-74 years:* RR=1.14 (95% CI, 0.0.78 to 1.68; p=0.50)	NR	NR	NR
	Finland	NR	NR	NR	NR

*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports
†Results for core age group only; excluded France due to incomplete followup

Abbreviations: CCI=Charlson Comorbidity Index; CI=confidence interval; CG=control group; ERSPC=European Randomized Study of Screening for Prostate Cancer; FH=family history; HR=hazard ratio; IG=intervention group assigned to screening; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RR=relative risk

Table 8. False-Positives, Complications, and Biopsy-Related Mortality Associated With PSA-Based Screening

Study Reference Quality Rating	Location Study Design	False Positives	Screening and Biopsy-Related Complications	Biopsy-Related Mortality
PLCO Andriole, 2009[53] Pinsky, 2014[103] Croswell, 2009[107] Fair	United States RCT	Any FP* with PSA after 36.0-months followup 10.4% (3388/32,576) Cumulative risk of receiving ≥1 FP result, by number of screening tests: 1 test: 5.4% (95% CI, 5.2-5.7) 2 tests: 7.9% (95% CI, 7.5-8.3) 3 tests: 10.4% (95% CI, 9.8-11.0) 4 tests: 12.9% (95% CI, 12.1-3.8) Moderately invasive procedure as a result of a FP: 4.6% (1491/32413) Cumulative risk of receiving at least 1 biopsy as a result of a FP, by number of screening tests: 1 test: 1.7% (95% CI, 1.5 to 1.8) 2 tests: 3.0% (95% CI, 2.5 to 3.4) 3 tests: 4.2% (95% CI, 3.5 to 4.9) 4 tests: 5.5% (95% CI, 4.6 to 6.5)	Screening & biopsy-related complications: All complications: 26.2 per 10,000 screenings (primarily dizziness, bruising, and hematoma) Medical complications: 68 per 10,000 diagnostic evaluations (primarily infection, bleeding, clot formation, urinary difficulties) Biopsy-related complications All complications: 20.2 per 1000 biopsies Infectious complications: 7.8 per 1000 biopsies Non-infectious complications: 13.0 per 1000 biopsies *Age <70 years vs. ≥70 years* All complications: OR=1.4 (95% CI, 0.9 to 2.4; p=0.06) Infectious complications: OR=1.8 (95% CI, 0.8 to 4.0; p=0.09) Non-infectious complications: OR=1.3 (95% CI, 0.7 to 2.4; p=0.23) *Non-black race vs. black race* All complications: OR=2.6 (95% CI, 1.2 to 5.9; p=0.05) Infectious complications: OR=7.1 (95% CI, 2.7 to 18.0; p<0.001) Non-infectious complications: OR=0.5 (95% CI, 0.1 to 3.6; p=0.53) *No comorbidity vs. one or more comorbidities* All complications: OR=1.4 (95% CI, 0.9 to 2.3; p=0.08) Infectious complications: OR=0.9 (95% CI, 0.4 to 2.1; p=0.82) Non-infectious complications: OR=1.7 (95% CI, 0.9 to 3.0; p=0.06)	4.0-months followup IG: 6/6295 (0.95 per 1,000 biopsies) CG: 255/139931 negative screens (1.8 per 1,000 negative screens) RR=0.49 (95% CI, 0.2 to 1.1) 6.0-months followup IG: 14/6295 (2.2 per 1000 biopsies) CG: 411/139931 negative screens (4.9 per 1000 negative screens) RR=0.70 (95% CI, 0.4 to 1.2)
ERSPC Carlsson, 2011[104] Kilpelainen, 2011[101] Raaijmakers, 2002[108] Fair	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France)†	Any FP: 17.8% (10972/61604) 1 FP: 74.7% (7752/10972) 2 FPs: 20.1% (2089/10972) 3 FPs: 5.2% (538/10972)	Minor complications of biopsy Hematuria >3 days: 22.6% (1280/5676) Hematospermia: 50.4% (2858/5676) Rectal bleeding: 1.3% (75/5676) Voiding problems: 0.8% (48/5676) Major complications of biopsy Pain after biopsy: 7.5% (286/5676) Fever: 3.5% (200/5676)	Mortality at 12.0-month followup Screen-negative 0.89% (330/37235) Screen-positive, biopsied: 0.62% (72/11721)

Table 8. False-Positives, Complications, and Biopsy-Related Mortality Associated With PSA-Based Screening

Study Reference Quality Rating	Location Study Design	False Positives	Screening and Biopsy-Related Complications	Biopsy-Related Mortality
	RCT		Hospitalization: 0.5% (27/5676) Urinary retention: 0.4% (20/5676) Nausea/sickness: 0.3% (17/5676)	RR=0.54 vs. screen-negative men (95% CI, 0.42 to 0.70; p<0.001)
ProBE cohort Rosario, 2012[102] Good	United Kingdom Cohort	NR	<u>Self-reported symptoms rated as moderate or severe within 7-days of biopsy</u> Pain: 5.7% (95% CI, 4.4 to 7.3%) Fever: 4.0% (95% CI, 3.0 to 5.4%) Shivers: 3.2% (95% CI, 2.3 to 4.5) Hematuria: 4.8 (95% CI, 3.6 to 6.3) Hematochezia: 1.7% (95% CI, 1.0 to 2.7%) Hematoejaculate: 20.0% (95% CI, 17.2 to 23.1%) <u>Self-reported symptoms rated as moderate or severe within 35-days of biopsy</u> Pain: 7.3% (95% CI, 5.7 to 9.1%) Fever: 5.5% (95% CI, 4.2 to 7.1) Shivers: 5.0% (95% CI, 3.7 to 6.6) Hematuria: 6.2% (95% CI, 4.7 to 7.9) Hematochezia: 2.5% (95% CI, 1.6 to 3.7) Hematoejaculate: 26.6% (95% CI, 23.3 to 30.2) Hospitalization within 35 days: 1.3% (15/1147; 95% CI, 0.8% to 2.1%), including 0.6% (7/1147) admitted for sepsis within 3 days of biopsy Outpatient healthcare contact due to biopsy symptoms: 10.4% (95% CI, 8.7% to 12.3%)	<u>35-days followup</u> 0% (0/1147; 95% CI, 0.0 to 0.4%)
Walter, 2013[33] Fair	United States Cohort	NR	Biopsy-related 7-day complications: 5.6% (468/8313) of men who underwent biopsy Biopsy-related 7-day hospitalizations: 1.6% (131/8313) of men who underwent biopsy	<u>7-days followup</u> 0.12% (9/8313) of men who underwent biopsy

* Authors define false positives as any PSA test score >4 ng/mL without a resulting cancer after three years of followup
*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports
†Results for core age group only; excluded France due to incomplete followup
‡Denominator includes biopsy procedures confirmed by completion of survey
‡Excludes 339 men who reported no sexual activity at either the 7-day or 35-day assessment

Abbreviations: CG=control group; ERSPC=European Randomized Study of Screening for Prostate Cancer; FP=false positive; IG=intervention group assigned to screening; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; OR=odds ratio; RR=relative risk

Table 9. Estimates of Overdiagnosis of Prostate Cancer Based on Excess Incidence in the Screening Arms of Randomized, Controlled Trials

Study Reference Quality Rating	Location	Followup (median) Sample Size (n) Randomization Method	Numerator (Excess Cases With Long-Term Followup)	Denominator #1 (Prostate Cancer Diagnosed in Screening Arm During Screening Phase)	Denominator #2 (Screen-Detected Prostate Cancer During Screening Phase)	Overdiagnosis Estimates, Method #1 (%)	Overdiagnosis Estimates, Method #2 (%)
PLCO Andriole, 2012[80] Fair	United States	13.0 years N=76,693 1:1 randomization	425	2,577	2,049	16.4	20.7
ERSPC* Schroder, 2014[96] Fair	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France)[†]	13.0 years N=162,388 1:1.23 randomization	2,461[‡]	7,408	4,883	33.2	50.4
ERSPC site-specific reports Sweden (Göteborg): Hugosson, 2010[85]	Sweden (Göteborg)	14.0 years N=20,000 1:1 randomization	420	896	NR	46.8	NA
Spain: Lujan, 2014[89]	Spain	15.2 years N=4276, 1:1 randomization (at end, was1.29:1)	58[‡]	161	NR	36.0	NA
Netherlands (Rotterdam): Roobol, 2013[92]	Netherlands (Rotterdam)	12.8 years N=42,376 1:1 randomization	1,244	2,597	2,113	47.9	58.9
Finland: Kilpelainen, 2013[87]	Finland	12.0 years N=80,144 1:1.52 randomization	680[‡]	2,883	2,661	23.6	25.6

*Main ERPSC trial includes most patients that are included in site-specific ERSPC reports
†Results for core age group only; excluded France due to incomplete followup
‡Prostate cancer cases in control arm were weighted according to the randomization ration
§Overdiagnosis method 1: percentage of all cancer diagnosed during the screening phase that are overdiagnosed
∥ Overdiagnosis method 2: percentage of screen-detected cancers that are overdiagnosed

Abbreviations: ERSPC=European Randomized Study of Screening for Prostate Cancer; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Table 10. Study Characteristics of Randomized, Controlled Trials of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
ProtecT Hamdy, 2016[121] Lane, 2014[126] Good	United Kingdom Men were recruited from 337 primary care centers in nine cities	10.0 years (median)	Radical prostatectomy (n=553) Radiation therapy (n=545, EBRT; included neoadjuvant ADT concurrently and for 3 to 6 months prior to radiation) Active monitoring (n=545) Active monitoring: serum PSA every 2 months in the first year and 6 to 12 monthly thereafter. A rise of at least 50% during the previous 12-months triggered a review. Management options included continued monitoring or further tests, and radical or palliative treatments as required.	Age (median): 62 years Age (range): 49 to 69 years Race/Ethnicity: White: 98% (1606/1643) African-Caribbean: <1% (10/1643) Other: 2% (37/1643) Family history of prostate cancer: 7% (119/1643) PSA (median): 4.6 ng/mL PSA (range): 3.0-19.9 ng/mL	Mortality; morbidity; harms
SPCG-4 Bill-Axelson, 2014[117] Good	Sweden, Finland, Iceland Men were recruited from clinical treatment centers	13.4 years (median) 3 weeks to 23.2 years (range)	Radical prostatectomy (n=347) Watchful waiting (n=348) Watchful waiting: men assigned to observation who did not receive any immediate treatment Men who experienced local progression were offered transurethral resection of the prostate.	Age (mean): 65 years Tumor Risk: Low: 36% (249/695) Intermediate: 40% (281/695) High: 24% (165/695) Tumor Stage: T1b: 12% (83/695) T1c: 11.7% (81/695) T2: 76% (529/695) Unknown: 0.3% (2/695) Gleason Score: 2 to 4: 13% (90/695) 5 to 6: 47% (331/695) 7: 23% (159/695) 8 to 10: 5% (35/695) Unknown: 11.5% (80/695)	Mortality; morbidity; harms

Table 10. Study Characteristics of Randomized, Controlled Trials of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
PIVOT Wilt, 2017[74] Wilt, 2012[133] Good	United States Men recruited from 44 VA and 8 NCI sites	12.7 years (median)	Radical prostatectomy (n=364) Observation (n=367) Observation: men were offered palliative (non-curative) therapies (e.g., transurethral resection of the prostate for local progression causing urinary obstruction, ADT and/or targeted radiation therapy for evidence of distant spread).	Age (mean): 67 years Tumor Risk: Intermediate/high: 66% Tumor Stage: T1c: 50% Gleason Score: >7: 48%	Mortality; morbidity; harms
Fransson, 2009[71] Fransson, 2001[70] Fair	Sweden Men were recruited from treatment centers	10.0 years (median)	Radiotherapy (n=59) Watchful waiting (n=49) Watchful waiting: regular monitoring and deferred treatment until time of disease progression	Age (mean): 77.5 years Age (range): 54 to 88 years Tumor stage: T1: 25% (14/57) T2: 75% (43/57)	Harms

Abbreviations: ADT=androgen deprivation therapy; PIVOT=Prostate Cancer Intervention versus Observation Trial; ProtecT=Prostate testing for cancer and Treatment; SPCG-4=Scandinavian Prostate Cancer Group Study Number 4

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Barocas, 2017 Good	United States Men were identified in 5 SEER registries (Atlanta, Los Angeles, Louisiana, New Jersey, and Utah) and the CaPSURE database	3.3 years	Radical Prostatectomy (n=1,523) Radiation Therapy (n=598, EBRT) Active Surveillance (n=429) Active Surveillance: absence of treatment or no treatment administered within 1 year of diagnosis	Age (mean): 63.8 years Race/ethnicity White: 73% (1874/2550) Black: 14% (358/2550) Hispanic: 7% (186/2550) Asian: 3% (80/2550) Other: 1% (37/2550) Comorbidity 0-2: 28% (687/2550) 3-4: 42% (1024/2550) $\geq$5: 30% (728/2550) Tumor Stage T1c: 76% (1933/2550) T2: 24% (606/2550) Gleason Score $\leq$7: 90% (2298/2550) >7: 10% (252/2550)	Mortality (survival) Harms
Chen, 2017 Good	United States Men were identified in the North Carolina Central Cancer Registry	2 years	Radical Prostatectomy (n=469) Radiation Therapy (n=358, including EBRT [n=249] and brachytherapy [n=109]) Active Surveillance (n=314) Active surveillance: medical records indicating that active surveillance was the selected treatment strategy	Race/ethnicity White: 72% (825/1141) African American: 25% (290/1141) Other: 3% (26/1141)	Harms
Lu-Yao, 2014[70] Good	United States Men were identified in the SEER-Medicare database	9.2 years (median)	ADT (n=25,125) Conservative management (n=41,592) Conservative management: no evidence of receiving surgery, radiotherapy, or ADT during the first 180 days following diagnosis	NR	Mortality
Sun, 2014[131] Fair	United States Men were identified in the SEER-Medicare database	2 to 15 years (range)	Radical prostatectomy (n=15,532) Radiation therapy (n=33,613) Observation (n=17,942) Observation: absence of active treatment within 6 months of prostate cancer diagnosis	NR	Mortality

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Abdollah, 2012[114] Fair	United States Men were identified in the SEER-Medicare database	2 to 15 years (range)	Radiation therapy (n=20,986) Observation (n=20,986) Observation: absence of active treatment within 6 months of prostate cancer diagnosis	Age: 65 to 69 years: 22.8% 70 to 74 years: 35.8% 75 to 80 years: 41.4% Comorbidity 0: 42.3% 1: 27.5% $\geq$2: 30.2%	Mortality
Thong, 2010[161] Fair	Netherlands Men were identified in the Eindhoven Cancer Registry (ECR)	5 to 10 years (range)	Radiation therapy (n=71; EBRT) Active surveillance (n=71) Active surveillance: stage and tumor grade $\leq$2 at time of diagnosis who received no active treatment	Age (mean): 76 years Tumor stage: T1: 80% (114/142) T2: 20% (28/142)	Harms
Ladjevardi, 2010[125] Fair	Sweden Men were identified in Sweden's National Prostate Cancer Register (NPCR)	4.4 years (median) 0 to 12 years (range)	Radical prostatectomy (n=12,950) Radiation therapy (n=6,308, including EBRT [n=4443] and brachytherapy [n=1865]) Conservative management (n=12,645; watchful waiting, n=9,435, palliative treatment [included ADT], n=3,210) Conservative management: not clearly defined, but includes both watchful waiting and men on palliative treatment	Age (mean): 65.2 years Tumor stage: T0: <1% (220/31903) T1: 54.5% (17438/31903) T2: 34.3% (10933/31903) T3: 9.6% (3071/31903) TX: <1% (241/31903)	Mortality

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
CDC-NPCR Breast, Colon, and Prostate Cancer Data Quality and Patterns of Care Study (PoC1) Schymura, 2010[129] Fair	United States Random samples of prostate cancer patients were selected from the databases of participating cancer registries in seven states	5 years	Radical prostatectomy (n=1310) Radiation therapy (n=1037, including EBRT or brachytherapy) ADT (n=339) Watchful waiting (n=614) Watchful waiting: no therapy within six months of diagnosis	Age: <60 years: 18% (601/3300) 60 to 64 years: 17% (565/3300) 65 to 69 years: 22% (730/3300) 70 to 74 years: 21% (703/3300) 75 to 79 years: 14% (453/3300) $\geq$80 years: 8% (248/3300) Race/ethnicity: Non-Hispanic white: 80% (2649/3300) Non-Hispanic black: 14% (460/3300) Non-Hispanic other: 2% (56/3300) Hispanic: 3% (113/3300) Unknown: 1% (22/3300)	Mortality (survival)
National Prostate Cancer Register of Sweden Follow-Up Study Stattin, 2010[130] Fair	Sweden Men identified in the Swedish Cancer Registry	8.2 years (median)	Radical prostatectomy (n=3399) Radiation therapy (n=1429) Surveillance (n=2021) Surveillance: combined active surveillance and watchful waiting (no further definition provided)	Age: <60 years: 26.8% (1836/6849) 60 to 64 years: 29.7% (2036/6849) 65 to 69 years: 43.5% (2977/6849) Tumor stage: T1: 58.6% (4015/6849) T2: 41.4% (2834/6849) Gleason score: 2 to 6: 85.8% (5875/6849) 7: 14.2% (974/6849) Comorbidity: 0 to 1: 92.7% (6347/6849) $\geq$2: 7.3% (502/6849)	Mortality

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Smith, 2009[159] Fair	Australia Men were identified in the New South Wales central cancer registry.	3.8 years (mean)	Radical prostatectomy (n=981) Radiation therapy (n=394, including EBRT [n=123], low-dose brachytherapy [n=58], high-dose brachytherapy [n=47], EBRT/ADT [n=166]) ADT (n=61) Active surveillance (n=200) Active surveillance: no further definition provided	Age (mean): 61.2 years Age (range): 37 to 69 years Tumor stage: T1: 54.4% (889/1636) T2: 45.7% (747/2636) Gleason score: 2 to 6: 55.0% (894/1636) 7: 34.3% (557/1636) 8 to 10: 10.7% (173/1636) Comorbidity: 0: 37.9% (623/1636) 1: 32.1% (529/1636) >2: 30.1% (484/1636)	Harms
Zhuo, 2009[135] Fair	United States Men were identified in the Ohio Cancer-Aging Linked Database (CALD), which combines data from the Ohio Cancer Incidence Surveillance System (OCISS) and Medicare	7 years	Monotherapy: Radical prostatectomy (n=936) Radiation therapy (n=1520, including EBRT [n=876] and brachytherapy [n=644]) ADT (n=2947) No treatment (n=2306) No treatment: no definitive therapy within 6 months of diagnosis)	Age: 65 to 69 years: 21.5% (2186/10179) 70 to 74 years: 32.1% (3263/10179) >75 years: 46.8% (4760/10179) Race/ethnicity: Non-African American: 91.0% (9265/10179) African American: 9.0% (914/10179) Gleason score: <7: 66.4% (6761/10179) 7 to 10: 23.8% (2418/10179) Unknown: 9.8% (1000/10179)	Mortality
Albertsen, 2007[115] Fair	United States Men identified in the Connecticut Tumor Registry (CTR)	13.3 years (median)	Radical prostatectomy (n=802) Radiation therapy (n=702) No initial therapy (n=114) No initial therapy: observation (not further defined)	Gleason score: 2 to 4: 4% 5: 6% 6: 47% 7: 26% 8 to 10: 17%	Mortality

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Wong, 2006[134] Good	United States Men were identified in the SEER-Medicare database	12.0 years	Active treatment (n=32,022, including radical prostatectomy [n=13,292] and EBRT or brachytherapy [n=18,249], alone or in combination) Observation (n=12,608) Observation: no Medicare data indicating prostatectomy, radiation therapy or hormonal therapy	Age (mean): 72 years Tumor stage: $\leq$T2a: 55% T2b-T2c: 45%	Mortality
Hoffman, 2003[145] Fair	United States Men identified in the SEER registry as part of the Prostate Cancer Outcomes Study (PCOS)	2.0 years	Radical prostatectomy (n=1373) Radiation therapy (n=583) ADT (n=179) No treatment (n=230) No treatment: no active treatment	Age (mean): 66 years Age (range): 39 to 88 years Race/ethnicity: Non-Hispanic white: 74.0% (1751/2365) Non-Hispanic black: 13.2% (311/2365) Hispanic: 12.8% (303/2365)	Harms
Litwin, 2002[151] Fair	United States Men were drawn from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database	1.6 years (mean)	Radical prostatectomy (n=282) Radiation therapy (n=104) Watchful waiting (n=66) Watchful waiting = no further definition provided	Age (mean): 65.5 years Race/ethnicity: White: 89.2% (403/ 452) African American: 8.2% (37/452) Other: 2.4% (11/452)	Harms
Potosky, 2002[154] Fair	United States Men identified in the SEER registry as part of the Prostate Cancer Outcomes Study (PCOS)	1.0 year	ADT (n=245) No treatment (n=416) No treatment: no active treatment	Age: 40 to 59 years: 4% (27/661) 60 to 69 years: 22% (145/661) 70 to 79 years: 53% (350/661) $\geq$80 years: 21% (139/661) Tumor stage: T1: 33% (221/661) T2: 51% (338/661) Unknown: 15% (101/661)	Harms

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Bacon, 2001[139] Fair	United States Men who participated in the Health Professionals Followup Study (HPFS)	5.0 years	Radical prostatectomy (n=421) Radiation therapy (n=290, including EBRT [n=221] and brachytherapy [n=69]) Hormonal therapy (n=33) Other (n=67; not otherwise defined) Watchful waiting (n=31) Watchful waiting: no further definition provided	Age (mean): 71 years Tumor stage: T1: 3% (23/842) T2: 86% (726/842) Other: 11% (93/842)	Harms
Schapira, 2001[156] Fair	United States Men were identified through surveillance of the pathology laboratories at participating hospitals	1.0 year	Radical prostatectomy (n=42) Radiation therapy (n=51) Expectant management (n=29) Expectant management: no further definition provided	Age (median): 69 years Tumor stage: T1: 50% (61/122) T2: 50% (61/122)	Harms
Siegal, 2001[158] Fair	United States Men registered at the Center for Prostate Disease Research	4.3 years (median)	Radical prostatectomy (n=419) Radiation therapy (n=319; EBRT) Watchful waiting (n=64) Watchful waiting: no further definition provided	Age: $\leq$70 years: 62% (500/802) >70 years: 33% (268/802) Unknown: 5% (34/802) Race/ethnicity: White: 70% (563/802) Black: 24% (190/802) Other/unknown: 6% (49/802) Gleason score: 2 to 4: 42% (340/802) 5 to 7: 44% (349/802) 8 to 10: 5% (41/802) Unknown: 9% (72/802)	Harms
Smith, 2000[160] Fair	United States Men enrolled in a serial prostate cancer screening study at a university center	3.8 years	Radical prostatectomy (n=1247) Radiation therapy (n=189) Hormone therapy (n=67) Cryotherapy (n=28) Observation (n=120) Observation: no further definition provided	Age (mean): 67 years Race/ethnicity: African American: 4.0% (66/1651) White/other: 96.0% (1585/1651)	Harms

Table 11. Study Characteristics of Cohort Studies of Prostate Cancer Treatment Benefits and Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Treatment Approaches (n) Conservative Management Definition	Participant and Tumor Characteristics	Outcomes Reported
Lubeck, 1999[152] Fair	United States Men were drawn from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database	2.0 years	Radical prostatectomy (n=351) Radiation therapy (n=75) Hormone therapy (*results not abstracted, as 32% [51/179] had stage T3 or higher at baseline*) Observation (n=87) Observation: no surgery, radiation or medical therapy within the first year following diagnosis	Age (mean): 66.0 years Tumor stage: T1: 25% (174/692) T2: 62% (427/692) T3/T4: 5% (33/6692) Other: 8% (52/692)	Harms
Litwin, 1995a&b[149, 150] Fair	United States Men were identified from the tumor registry of a large managed care population	6.0 years	Radical prostatectomy (n=98) Radiation therapy (n=56) Observation (n=60) Observation: no further definition provided	Age (mean): 73 years	Harms

Abbreviations: ADT=androgen deprivation therapy; EBRT=external beam radiation therapy

Table 12. Study Characteristics of Uncontrolled Observational Studies of Prostate Cancer Treatment Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Interventions (n)	Participant and Tumor Characteristics
Bjorklund, 2016[140] Fair	Sweden Men were identified in the National Prostate Cancer Register of Sweden	3-months	Radical prostatectomy (n=22,344; [RRP=14820; RARP=7524])	Age (median): 63.6 years Tumor Risk Low: 43% (9598/22344) Intermediate: 44% (9793/22344) High: 13% (2953/22344)
Uchida, 2015[163] Fair	Japan Men were recruited from a clinical cohort of patients receiving HIFU at a single institution	3.9 to 9.0 years (range)	HIFU (n=918)	Age (median): 68 years
Crouzet, 2014[143] Fair	France Men were recruited from a single site	6.4 years (median)	HIFU (n=1,002)	Age (median): 71 years Age (range): 48 to 87 years Tumor Risk: Low: 35.6% (357/1002) Intermediate: 45.1% (452/1002) High: 17.4% (174/1002) Undefined: 1.9% (19/1002) Tumor Stage T1: 51.7% (518/1002) T2: 44.8% (449/1002) T3: 2.8% (28/1002) Undefined: 0.7% (7/1002) Gleason Score: $\leq$6: 55.4% (555/1002) 7: 34.7% (348/1002) $\geq$8: 8.4% (84/1002) Undefined: 1.5% (15/1002)
Pfeiffer, 2012[153] Fair	Germany Men were recruited at a single clinical institution among those who received HIFU as a first-line curative therapy	4.4 years (median)	HIFU (n=191)	Age (median): 69.7 years Age (range): 51 to 82 years Tumor Risk: Low: 37.7% (72/191) Intermediate: 34.6% (66/191) High: 27.7% (53/191) Tumor Stage: T1a/b: 19.4% (37/191)

Table 12. Study Characteristics of Uncontrolled Observational Studies of Prostate Cancer Treatment Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Interventions (n)	Participant and Tumor Characteristics
				T1c: 35.6% (68/191) T2a: 18.9% (36/191) T2b: 13.1% (25/191) T2c: 7.8% (15/191) cT3a - cT3b: 5.2% (10/191)
Shah, 2012[157] Fair	United States Men treated at a single institution	6.6 years (median)	Radiation therapy (n=3180 [EBRT=1154; ART=1036; brachytherapy=540; combined EBRT/HDR=450])	Age (median): 71 years Age (range): 40 to 92 years Race/Ethnicity White: 91.6% (2912/3180) African American: 8.4% (268/3180) Tumor Stage: T1a to T1c: 46% (1461/3180) T2a to T2c: 50% (1568/3180) T3a to T3c: 4% (141/3180) Gleason Score <7: 60% (1898/3180) >7: 40% (1266/3180)
Inoeu, 2011[146] Fair	Japan Men were recruited from population of patients undergoing HIFU at Takanobashi Central Hospital	3.0 years (mean)	HIFU (n=137)	Age (median): 70 years Age range: 50 to 82 years Tumor risk: Low: 21% (29/137) Intermediate: 50% (68/137) High: 29% (40/137) Tumor stage: T1b: 6% (8/137) T1c: 42% (58/137) T2a: 38% (52/137) T2b: 10% (14/137) T2c: 4% (5/137) Gleason score: ≤6: 30% (41/137) 7: 47% (64/137) >7: 23% (32/137)

Table 12. Study Characteristics of Uncontrolled Observational Studies of Prostate Cancer Treatment Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Interventions (n)	Participant and Tumor Characteristics
Rabbani, 2010[155] Fair	United States Men were identified from a single institution	37 months	Radical prostatectomy (n=4592)	Age (mean): 60 years Age (range): 55 to 64 years Race/ethnicity: White: 89% (4067/4592) Black: 7% (317/4592) Other/unknown: 4% (208/4592) Tumor stage: T1: 62% (2864/4592) T2: 34% (1571/4592) T3: 3% (150/4592) Tx: <1% (7/4592)
Blana, 2008[141] Fair	Germany Men were identified from a single institution	4.8 years (mean) 3.0 to 8.6 years (range)	HIFU (n=163)	Age (mean): 66 years Tumor stage: T1: 24% (39/163) T2: 76% (124/163)
Walz, 2008[164] Fair	Canada Men were identified in the Quebec Health Plan database	1.0 month	Radical prostatectomy (n=9208)	Age (mean): 65 years Age (range): 45 to 89 years
Alibhai, 2005[137] Fair	Canada Men were identified in the Ontario Cancer Registry	1.0 month	Radical prostatectomy (n=11,010)	Age (mean): 63 years
Blana, 2004[142] Fair	Germany Men were identified from a single institution	22.5 months (mean) 4 to 62 months (range)	HIFU (n=146)	Age (mean): 67 years
Augustin, 2003[138] Fair	Germany Men were identified from a single institution	1.0 month	Radical prostatectomy (n=1243)	Age (mean): 62 years Age (range): 40 to 76 years Tumor stage: T1: 65% (806/1243) T2: 34% (422/1243) T3: 1% (15/1243)
Thuroff ,2003[162] Fair	Germany, France and the Netherlands Participant selection not described	1.2 years	HIFU (n=402)	Age (mean): 69 years Age (range): 51 to 80 years

Table 12. Study Characteristics of Uncontrolled Observational Studies of Prostate Cancer Treatment Harms

Study Reference Quality Rating	Study Location Recruitment	Followup	Interventions (n)	Participant and Tumor Characteristics
Yao, 1999[165] Fair	United States Medicare claims data	1.0 month	Radical prostatectomy (n=101,604)	Age (median): 69 years Race/ethnicity: White: 89.5% (90936/101604) Black: 5.1% (5181/101604) Other: 5.4% (5487/101604)

Abbreviations: HIFU=high-intensity focused ultrasound; RARP=robot-assisted laparoscopic radical prostatectomy; RRP=retropubic radical prostatectomy

Table 13. Quality of Life Measures

Measure	Type	Description	Scales
SF-36 Short-form 36-item Health Survey (also known as Medical Outcomes Study General Health Survey; RAND 36-item Health Survey; UCLA 36-item Health Survey)	General QOL	36-item self-administered general quality of life measure used to evaluate physical function, social function, bodily pain, emotional wellbeing, energy/fatigue, general health perceptions, role limitations due to physical problems, and role limitations due to emotional problems.	5-point Likert scales
CARES-SF Cancer Rehabilitation Evaluation System–Short Form	Cancer-specific QOL	59-item self-administered cancer-specific quality of life measure; one global score and five higher-order factors representing physical, psychosocial, medical interaction, marital, and sexual quality of life.	5-point Likert scales
BSFI Brief Sexual Function Inventory	Cancer-specific QOL	11-item self-administered sexual function measure, divided into five domains: sexual drive (2 questions, pooled scores 0-8); erectile function (3 questions, pooled scores 0-12); ejaculation (2 questions, pooled scores 0-8); problem assessment (3 questions, pooled scores 0-12); and overall satisfaction (1 question, score 0-4).	5-point Likert scales
EROTC-QLQ-C30 European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer	Cancer-specific QOL	30-item self-administered quality of life measure for cancer patients, with disease-specific modules available.	4-and 7-point Likert scales
EPIC Expanded Prostate Cancer Index Composite	Cancer-specific QOL	32-item self-administered prostate cancer treatment-related quality of life measure assessing urinary, bowel, sexual, and hormone function, as well as overall satisfaction.	5-point Likert scales
FACT-G Functional Assessment of Cancer Therapy–General	Cancer-specific QOL	27-item self-administered general quality of life measure with physical, social/family, emotional, and functional well-being subscales.	5-point Likert scales
HADS Hospital Anxiety and Depression Scale	General QOL	14-item scale to assess patient anxiety and depression	0 (not at all) to 3-point linear scale
PCSI Prostate Cancer Symptom Indices	Cancer-specific QOL	19-item scale measuring treatment-related urinary (8 items), sexual (5 items) and bowel (6 items) problems	0-100 (higher score indicating more or worse dysfunction)
PCSS Prostate Cancer Symptom Scale	Cancer-specific QOL	18-item self-administered quality of life measure specific to prostate cancer.	0-(no problems/ very good function) to 10-point linear analogue scale
PTSS Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure	Cancer-specific QOL	19-item quality of life measure of bowel, bladder, and sexual function specific to prostate cancer.	5-point Likert scale

Table 13. Quality of Life Measures

Measure	Type	Description	Scales
QOL-CS scale Quality of Life – Cancer Survivors	Cancer-specific QOL	41-item self-administered quality of life measure specific to cancer	11-point Likert scales
QUF94W	Cancer-specific QOL	43-item self-administered quality of life measure for prostate cancer patients, designed to evaluate side effects after pelvic radiotherapy.	0-(no problems/ very good function) to 10-point linear analogue scale
UCLA-PCI University of California, Los Angeles Prostate Cancer Index	Cancer-specific QOL	17-item scale measuring treatment-related sexual (8 items), urinary (5 items), and bowel symptoms (4 items) and bother.	Various-point Likert scales

Table 14. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

Study Name Author, Year Related Publications	Study Design Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality	Morbidity
ProtecT Hamdy, 2016[121] Good	RCT 10.0 years (median)	RP: 0.9% (5/553) AS: 1.5% (8/545) HR=0.63 (95% CI, 0.21 to 1.93)	RP: 9.9% (55/553) AS: 10.8% (59/545) HR=0.93 (95% CI, 0.65 to 1.35)	Progression to Metastatic Disease RP: 2.5% (13/553) AS: 6.0% (33/545) HR not reported
SPCG-4 Bill-Axelson, 2014[117] Good	RCT 13.4 years (median)	RP: 17.7% (63/347; 95% CI, 14.0 to 22.4) WW: 28.7% (99/348; 95% CI, 24.2 to 34.2) RR=0.56 (95% CI, 0.41 to 0.77; p=0.001)	RP: 56.1% (200/347; 95% CI, 50.9 to 62.0) WW: 68.9% (247/348; 95% CI, 63.8 to 74.3) RR=0.71 (95% CI, 0.59 to 0.86; p<0.001)	Progression to Metastatic Disease RP: 26.1% (89/347; 95% CI, 12.7 to 31.4) WW: 38.3% (138/348; 95% CI, 33.4 to 44.0) RR=0.57 (95% CI, 0.44 to 0.75; p<0.001)
PIVOT Wilt, 2017[74] Wilt, 2012[133] Good	RCT 12.7 years (median)	RP: 7.4% (27/364; 95% CI 5.2 to 10.6) WW: 11.4% (42/367; 95% CI 8.6 to 15.1) RR=0.65 (95% CI, 0.41 to 1.03) HR=0.63 (95% CI, 0.39-1.02; p=0.06)	RP: 61.3% (223/364; 95% CI, 56.2 to 66.1) WW: 66.8% (245/367; 95% CI, 61.8 to 71.4) RR=0.92 (95% CI, 0.82 to 1.02) HR=0.84 (95% CI, 0.70 to 1.01; p=0.06)	Systemic Disease Progression RP: 10.2% (37/364) WW: 14.7% (54/367) HR=0.64 (95% CI, 0.42 to 0.97) Bone Metastases (10 y median followup) RP: 4.7% (17/364; 95% CI 2.9 to 7.4) WW: 10.6% (39/367; 95% CI 7.9-14.2) RR=0.44 (95% CI, 0.25 to 0.76; p=0.001) HR=0.40 (95% CI, 0.22 to 0.70; p<0.001)
Barocas, 2017[75] Good	Cohort 3.3 years (median)	RP: 0.1% (1/1523) AS: 0% (0/429)	RP: 1.3% (18/1523; 95% CI, 0.7 to 1.8%) AS: 2.9% (12/429; 95% CI, 1.3 to 4.6%)	NR
Ladjevardi, 2010[125] Fair	Cohort 4.4 years (median)	NR	Adjusted HR= 0.36 (95% CI, 0.32 to 0.40)	NR
Schymura, 2010[129] Fair	Cohort 5.0 years	NR	5-Year Survival (unadjusted) RP: 93.7% WW: 75.4% *In multivariate survival analysis with radical prostatectomy the reference category:*	NR

Table 14. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

Study Name Author, Year Related Publications	Study Design Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality	Morbidity
			HR (death with WW)=2.30 (95% CI: 1.70 to 3.12)	
Stattin, 2010[130] Fair	Cohort 8.2 years (median)	<u>Overall</u> RP: 1.7% (56/3399) WW: 2.9% (58/2021) <u>10-year cumulative mortality rate:</u> RP: 2.4% (95% CI, 1.8 to 3.3) WW: 3.6% (95% CI, 2.7 to 4.8) RR=0.49 (95% CI, 0.34 to 0.71)	<u>Overall</u> RP: 8.4% (286/3399) WW: 20.4% (413/2021) <u>10-year cumulative mortality rate</u> RP: 11.3% (95% CI, 10.0 to 12.9) WW: 23.4% (95% CI, 21.3 to 25.8) RR=0.49 (95% CI, 0.41 to 0.57)	NR
Zhuo, 2009[135] Fair	Cohort 7.0 years	Adjusted HR=0.25 (95% CI, 0.13 to 0.48; p<0.0001)	Adjusted HR=0.32 (95% CI, 0.25 to 0.41; p<0.0001)	NR
Albertsen, 2007[115] Fair	Cohort 13.3 years (median)	RP: 1.0% WW: 16.0% RR=3.4 (95% CI, 1.9 to 5.9)	RP: 25% WW: 57% RR=NR	NR
Wong, 2006[134] Good	Cohort 12.0 years	NR	Adjusted HR=0.50 (95% CI, 0.47 to 0.53)	NR

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: AS=active surveillance; HR=hazard ratio; RP=radical prostatectomy; RR=relative risk; WW=watchful waiting

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
PIVOT Wilt, 2017[74] Wilt, 2012[133] Good	RCT 12.7 years (median)	All-cause mortality	*Age <65 years* RP: 47.5% (58/122; 95% CI, 38.9 to56.3) WW: 59.5% (78/131; 95% CI, 51.0 to 67.6) RR=0.80 (95% CI, 0.63 to 1.01) HR=0.84 (95% CI, 0.70 to 1.01) *Age ≥65 years* RP: 68.2% (165/242; 95% CI, 62.1 to 73.7) WW: 70.8% (167/236; 95% CI, 64.7 to 76.2) RR=0.96 (95% CI, 0.86 to 1.09) HR=0.88 (95% CI, 0.71 to 1.09) P=0.56 for test of interaction by age	*Low risk* RP: 55.4% (82/148; 95% CI, 47.4 to 63.2) WW: 56.1% (83/148; 95% CI, 48.0 to 63.8) RR=0.99 (95% CI, 0.81 to 1.21) HR=0.98 (95% CI, 0.72 to 1.33) *Intermediate risk* RP: 59.7% (77/129; 95% CI, 47.4 to 63.2) WW: 74.2% (89/120; 95% CI, 65.7 to 81.2) RR=0.80 (95% CI, 0.67 to 0.96) HR=0.68 (95% CI, 0.50 to 0.92) *High risk* RP: 71.4% (55/77; 95% CI, 60.5 to 80.3) WW: 73.8% (59/80; 95% CI, 63.2 to 82.1) RR=0.97 (95% CI, 0.80 to 1.17) HR=0.78 (95% CI, 0.54 to 1.13) P=0.08 for test of interaction by tumor risk category	*Gleason score <7* RP: 57.1% (145/254; 95% CI, 50.9 to 63.0) WW: 64.0% (167/261; 95% CI, 58.0 to 69.6) RR=0.95 (95% CI, 0.78 to 1.03) HR=0.0.82 (95% CI, 0.65 to 1.02) *Gleason score ≥7* RP: 69.4% (68/98; 95% CI, 59.7 to 77.6 WW: 73.3% (63/86; 95% CI, 63.1 to 81.5) RR=0.95 (95% CI, 0.79 to 1.14) HR=0.83 (95% CI, 0.59 to 1.17) P=0.84for test of interaction by Gleason score	<u>Baseline PSA</u> *≤10 ng/mL* RP: 58.8% (140/238; 95% CI, 52.5 to 64.9) WW: 62.7% (151.241; 95% CI, 56.4 to 68.5) RR=0.94 (95% CI, 0.81 to 1.08) *>10 ng/mL* RP: 65.9% (83/126; 95% CI, 57.2 to 73.6) WW: 74.4% (93/125; 95% CI, 66.1 to 81.2) RR=0.89 (95% CI, 0.75 to 1.04) P=0.06 for test of interaction by race/ethnicity <u>Race</u> *White* RP: 64.7% (150/232; 95% CI, 58.3 to 70.5) WW: 70.5% (155/220; 95% CI, 64.1 to 76.1) RR=0.92 (95% CI, 0.81 to 1.04) *Black* RP: 57.7% (64/111; 95% CI, 48.4 to 66.4) WW: 62.0% (75/121; 95% CI, 53.1 to 70.1) RR=0.93 (95% CI, 0.75 to 1.15) *Other* RP: 42.9% (9/21; 95% CI, 24.5 to 63.5) WW: 57.7% (15/26; 95% CI, 39.0 to 74.5)

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
						RR=0.74 (95% CI, 0.41 to 1.34) P=0.87for test of interaction by race/ethnicity Comorbidities *None (Charlson score=0)* RP: 52.2% (117/206; 95% CI, 45.7 to 58.7) WW: 58.2% (128/206; 95% CI, 51.6 to 64.5) RR=0.90 (95% CI, 0.76 to 1.06) HR=0.84 (95% CI, 0.65-1.07) *One or more (Charlson Score≥1)* RP: 75.7% (106/155; 95% CI, 68.0 to 82.1) WW: 79.6% (117/158; 95% CI, 72.4 to 85.3) RR=0.95 (95% CI, 0.84 to 1.03) HR=0.85 (95% CI, 0.65-1.10) P=0.79 for test of interaction by comorbidity status
		Prostate cancer-specific mortality	*Age <65 years* RP: 7.4% (9/122; 95% CI, 3.9 to 13.4) WW: 11.5% (15/131; 95% CI, 7.1 to 18.0) RR=0.64 (95% CI, 0.29 to 1.42) HR=0.63 (95% CI, 0.28 to 1.43)	*Low risk* RP: 4.1% (6/148; 95% CI, 1.9 to 8.6) WW: 5.4% (8/148; 95% CI, 2.8 to 10.3) RR=0.75 (95% CI, 0.27 to 2.11) HR=0.74 (95% CI, 0.26 to 2.13)	*Gleason score <7* RP: 4.7% (12/254; 95% CI, 2.7 to 8.1) WW: 7.7% (20/261; 95% CI, 5.0 to 11.5) RR=0.62 (95% CI, 0.31 to 1.23) HR=0.70 (95% CI, 0.37 to 1.32)	Race/Ethnicity *White:* RP: 7.3% (18/232; 95% CI, 4.6 to 11.4) WW: 12.7% (28/220; 95% CI, 9.0 to 17.8) RR=0.58 (95% CI, 0.32 to 1.02) HR=0.55 (95% CI, 0.30 to 1.01)

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
			Age >65 years RP: 7.4% (18/242; 95% CI, 4.8 to 11.5) WW: 11.4% (27/236; 95% CI, 8.0 to 16.1) RR=0.65 (95% CI, 0.37 to 1.15) HR=0.63 (95% CI, 0.35 to 1.15) P=0.99 for test of interaction by age	*Intermediate risk* RP: 8.5% (11/129; 95% CI, 4.8 to 14.6) WW: 15.8% (19/120; 95% CI, 10.4 to 23.4) RR=0.54 (95% CI, 0.27 to 1.08) HR=0.53 (95% CI, 0.25 to 1.11) *High risk* RP: 13.0% (10/77; 95% CI, 7.2 to 22.3) WW: 18.8% (15/80; 95% CI, 11.7 to 28.7) RR=0.69 (95% CI, 0.33 to 1.45) HR=0.64 (95% CI, 0.29 to 1.41) P=0.89 for test of interaction by tumor risk category	*Gleason score >7* RP: 15.3% (15/98; 95% CI, 9.5 to 23.7%) WW: 24.4% (21/86; 95% CI, 16.6 to 34.5) RR=0.63 (95% CI, 0.35 to 1.14) HR=0.54 (95% CI, 0.26 to 1.13) P=0.62 for test of interaction by Gleason score	*Black*: RP: 7.2% (8/111; 95% CI, 3.7 to 13.6) WW: 9.1% (11/121; 95% CI, 5.2 to 15.6) RR=0.79 (95% CI, 0.33 to 1.90) HR=0.78 (95% CI, 0.32 to 1.91) *Other:* RP: 9.5% (2/21; 95% CI, 2.7 to 28.9) WW: 11.5% (3/26; 95% CI, 4.0 to 29.0) RR=0.83 (95% CI, 0.15 to 4.49) HR= 0.82 (95% CI, 0.14 to 4.65) P=0.49 for test of interaction by race/ethnicity Comorbidities *None (Charlson score=0)* RP: 8.5% (19/206; 95% CI, 5.5 to 12.9) WW: 11.4% (25/206; 95% CI, 7.8 to 16.2) RR=0.75 (95% CI, 0.42 to 1.32) HR=0.72 (95% CI, 0.40 to 1.11) *One or more (Charlson Score>1)* RP: 5.7% (8/155; 95% CI, 2.9 to 10.9) WW: 11.6% (17/158; 95% CI, 7.4 to 17.7) RR=0.49 (95% CI, 0.22 to 1.11)

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
						HR=0.49 (95% CI, 0.21 to1.13)
						P=0.44 for test of interaction by Gleason score
						Baseline PSA _<10_ RP: 6.7% (16/238; 95% CI, 4.2 to 10.6) WW: 9.5% (23/241; 95% CI, 6.4 to 13.9) RR=0.70 (95% CI, 0.38 to 1.30) HR=0.70 (95% CI 0.37 to 1.32)
						_>10_ RP: 8.7% (11/126; 95% CI, 4.9 to 15.0) WW: 15.2% (19/125; 95% CI, 10.0 to 22.5) RR=0.57 (95% CI, 0.29 to 1.16) HR=0.54 (95% CI 0.26 to 1.13)
						P=0.62 for test of interaction by tumor risk category
		Bone metastases (at 10 y median followup)	_Age <65 years_ RP: 5.7% (7/122; 95% CI, 2.8 to 11.4) WW: 9.9% (13/131; 95% CI, 5.9 to 16.2) RR=0.58 (95% CI, 0.24 to 1.40; p=0.19) _Age >65 years_ RP: 4.1% (10/242; 95% CI, 2.3 to 7.4)	_Low risk_ RP: 4.1% (6/148; 95% CI, 1.9 to 8.6) WW: 6.7% (9/148; 95% CI 3.2 to 11.2) RR=0.67 (95% CI, 0.24 to 1.38; p=0.39) _Intermediate risk_ RP: 4.7% (6/129; 95% CI, 2.2 to 9.8)	_Gleason score <7_ RP: 3.5% (9/254; 95% CI, 1.9 to 6.6) WW: 8.1% (21/261; 95% CI, 5.3 to 12.0) RR=0.44 (95% CI, 0.21 to 0.94; p=0.02) _Gleason score >7_ RP: 7.1% (7/98; 95% CI, 3.5 to 14.0%)	Race/Ethnicity _White:_ RP: 5.2% (12/232; 95% CI 3.0 to 8.8) WW: 12.7% (28/220; 95% CI, 9.0 to 17.8) RR=0.41 (95% CI, 0.21 to 0.78; p=0.002) _Black:_

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
			WW: 11.0% (26/236; 95% CI, 7.6 to 15.7) RR=0.38 (95% CI, 0.19 to 0.76; p=0.002)	WW: 15.8% (19/120; 95% CI 10.4 to 23.4) RR=0.29 (95% CI, 0.12 to 0.71; p=0.002) *High risk* RP: 5.2% (4/77; 95% CI, 2.0 to 12.6) WW: 13.8% (11/80; 95% CI, 7.9 to 23.0) RR=0.38 (95% CI, 0.13 to 1.14; p=0.03)	WW: 20.9% (18/86; 95% CI, 13.7 to 30.7) RR=0.34 (95% CI, 0.15 to 0.78; p=0.003)	RP: 2.7% (3/111; 95% CI 0.9 to 7.7) WW: 6.6% (8/121; 95% CI, 3.4 to 12.5) RR=0.41 (95% CI, 0.11 to 1.50; p=0.15) *Other:* RP: 9.5% (2/21; 95% CI, 2.7 to 28.9) WW: 11.5% (3/26; 95% CI, 4.0 to 29.0) RR=0.83 (95% CI, 0.15 to 4.49; p=0.83) Comorbidities *None (Charlson score=0)* RP: 6.3% (14/206; 95% CI, 3.8 to 10.2) WW: 8.6% (19/206; 95% CI, 5.6 to 13.1) RR=0.51 (95% CI, 0.27 to 0.94; p=0.02) *One or more (Charlson score $\geq$1)* RP: 2.1% (3/155; 95% CI 0.7 to 6.1) WW: 8.2% (12/158; 95% CI, 4.7 to 13.7) RR=0.26 (95% CI, 0.08 to 0.91; p=0.02) Baseline PSA *$\leq$10* RP: 5.0% (12/238; 95% CI, 2.9 to 8.6%) WW: 8.7% (21/241; 95% CI, 5.8 to 13.0%) RR=0.58 (95% CI, 0.29 to 1.15; p=0.09)

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
						>10 RP: 4.0% (5/126; 95% CI, 1.7 to 9.0%) WW: 14.4% (18/125; 95% CI, 9.3 to 21.6%) RR=0.28 (95% CI, 0.11 to 0.72; p=0.001)
ProtecT Hamdy, 2016[121] Good	RCT 10.0 years (median)	Prostate cancer-specific mortality	*Age <65 years* RP: 0.5% (3/553) AS: 0.2% (1/545) *Age ≥65 years* RP: 0.4% (2/553) AS: 1.3% (7/545)	*T1c* RP: 0.5% (3/553) AS: 0.9% (5/545) *T2* RP: 0.4% (2/553) AS: 0.6% (3/545)	*Gleason score 6* RP: 0.5% (3/553) AS: 0.6% (3/545) *Gleason score ≥7* RP: 0.4% (2/553) AS: 0.9% (5/545)	NR
Bill-Axelson, 2014[117] SPCG-4 Good	RCT 13.4 years (median)	All-cause Mortality	*Age <65 years* RP: 40.0% (69/173; 95% CI, 32.7 to 49.0) WW: 65.6% (112/171; 95% CI, 58.2 to 73.9) RR=0.50 (95% CI, 0.37 to 0.68; p<0.001) *Age ≥65 years* RP: 69.8% (131/188; 95% CI, 63.1 to 77.4) WW: 71.7% (135/188; 95% CI, 64.9 to 79.3) RR=0.92 (95% CI, 0.73 to 1.18; p=0.52)	*Low risk* RP: 43.4% (51/118; 95% CI, 34.8 to 54.1) WW: 59.1% (85/144; 95% CI, 50.7 to 68.8) RR=0.57 (95% CI, 0.40 to 0.81; p=0.002) *Intermediate risk* RP: 57.1% (87/152; 95% CI, 49.0 to 66.4) WW: 72.5% (95/131; 95% CI, 64.5 to 81.6) RR=0.71 (95% CI, 0.53 to 0.95; p=0.02 *High risk* RP: 73.3% (62/85; 95% CI, 63.8 to 84.2) WW: 78.8% (67/85; 95% CI, 69.7 to 89.2) RR=0.84 (95% CI, 0.60 to 1.19; p=0.34)	NR	NR
		Prostate cancer-	*Age <65 years* RP: 18.3% (31/169; 95% CI, 13.1 to 25.7)	*Low risk* RP: 10.2% (11/108; 95% CI, 5.8 to 18.0)		

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
		specific mortality	WW: 34.1% (58/170; 95% CI, 27.3 to 42.5) RR=0.45 (95% CI, 0.29 to 0.69; p=0.002) *Age ≥65 years* RP: 17.3% (32/185; 95% CI, 12.5 to 24.0) WW: 23.9% (41/172; 95% CI, 18.2 to 31.5) RR=0.75 (95% CI, 0.47 to 1.19; p=0.19)	WW: 14.0% (20/143; 95% CI, 9.1 to 21.5) RR=0.54 (95% CI, 0.26 to 1.13; p=0.17) *Intermediate risk* RP: 15.1% (24/159; 95% CI, 10.2 to 22.2) WW: 39.3% (50/127; 95% CI, 31.3 to 49.3) RR=0.38 (95% CI, 0.23 to 0.62; p<0.001) *High risk* RP: 33.1% (28/85; 95% CI, 24.0 to 45.7) WW: 35.7%(29/81; 95% CI, 26.3 to 48.5) RR=0.87 (95% CI, 0.52 to 1.46; p=0.84)		
		Progression to metastatic disease	*Age <65 years* RP: 28.7% (45/157; 95% CI, 22.2 to 37.1) WW: 44.5% (76/171; 95% CI, 37.3 to 53.0) RR=0.49 (95% CI, 0.34 to 0.71; p<0.001) *Age ≥65 years* RP: 23.8% (44/185; 95% CI, 18.4 to 30.9) WW: 32.7% (62/190; 95% CI, 26.4 to 40.5) RR=0.68 (95% CI, 0.46 to 1.00; p=0.04)	*Low risk* RP: 13.6% (15/110; 95% CI, 8.4 to 21.9) WW: 24.2% (35/145; 95% CI, 17.8 to 33.0) RR=0.40 (95% CI, 0.21 to 0.73; p=0.006) *Intermediate risk* RP: 25.0% (37/148; 95% CI, 18.8 to 33.3) WW: 44.9% (59/131; 95% CI, 36.9 to 54.7) RR=0.49 (95% CI, 0.32 to 0.74; p<0.001) *High risk* RP: 45.9% (37/81; 95% CI, 35.8 to 58.8) WW: 50.8%(44/87; 95% CI, 40.6 to 63.5)	NR	NR

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
				RR=0.81 (95% CI, 0.52 to 1.26; p=0.39)		
Sun, 2014[131] Fair	Cohort 2-15 years (range)	All-cause Mortality	*<10 years' life expectancy* HR=0.54 (95% CI, 0.39 to 0.75) *>10 years' life expectancy* HR=0.59 (95% CI; 0.49 to 0.71)	*<10 years' life expectancy* ≤T1c: HR=0.31 (95% CI, 0.17 to 0.55) T2a/b: HR=0.60 (95% CI, 0.41 to 0.87) T2c: HR=0.35 (95% CI, 0.14 to 0.85) *>10 years' life expectancy* ≤T1c: HR=0.56 (95% CI, 0.44 to 0.71) T2a/b: HR=0.67 (95% CI, 0.50 to 0.89) T2c: HR=0.41 (95% CI, 0.21 to 0.80)	NR	NR
		Prostate cancer-specific mortality	*<10 years' life expectancy* HR=0.03 (95% CI, 0.02 to 0.42; p=0.01) *>10 years' life expectancy* HR=0.36 (95% CI, 0.19 to 0.69; p=0.002)	*<10 years' life expectancy* ≤T1c: HR=2.99 (95% CI, 0.10 to 86.80; p=0.5) T2a/b: HR=0.07 (95% CI, 0.02 to 0.83; p=0.04) T2c: NR *>10 years' life expectancy* ≤T1c: HR=0.37 (95% CI, 0.19 to 0.69; p=0.04) T2a/b: HR=0.60 (95% CI, 0.21 to 1.73; p=0.4) T2c: HR=0.03 (95% CI, 0.003 to 0.20; p<0.001)	NR	NR
Stattin, 2010[130] Fair	Cohort 8.2 years (median)	Prostate cancer-specific mortality	NR	*Low risk* RP: (0.3%) 4/3399 WW: (1.3%) 14/2021 *Intermediate risk* RP: (2.4%) 52/3399 WW: (4.7%) 442021 <u>10-year Mortality</u> *Low risk*	NR	NR

Table 15. The Effect of Radical Prostatectomy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
				RP: 0.4% (95% CI, 0.13 to 0.97%) WW: 2.4% (95% CI, 1.2 to 4.1%) RR=0.29 (95% CI, 0.09 to 0.87) *Intermediate risk* RP: 3.4% (95% CI, 2.5 to 4.7%) WW: 5.2% (95% CI, 3.7 to 6.9%) RR=0.53 (95% CI, 0.35 to 0.80)		

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: AS=active surveillance; HR=hazard ration; RP=radical prostatectomy; RR=relative risk; WW=watchful waiting

Table 16. The Effect of Radiation Therapy* Compared With Conservative Management[†] on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

Study Reference Quality Rating	Study Design Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality	Morbidity
ProtecT Hamdy, 2016[121]	RCT 10.0 years (median)	RT: 0.7% (4/545) AS: 1.5% (8/545) HR=0.51 (95% CI, 0.15 to 1.69)	RT: 10.1% (55/545) AS: 10.8% (59/545) HR=0.94 (95% CI, 0.65 to 1.36)	Progression to Metastatic Disease RT: 2.9% (16/545) AS: 6.0% (33/545)
Barocas, 2017[75] Good	Cohort 3.3 years (median)	RT: 0.3% (2/598) AS: 0% (0/429)	RT: 3.9% (21/598; 95% CI, 2.3 to 5.5%) AS: 2.9% (12/429; 95% CI, 1.3 to 4.6%)	NR
Ladjevardi, 2010[125] Fair	Cohort 4.4 years (median)	NR	HR=0.54 (95% CI, 0.49 to 0.59)	NR
Schymura, 2010[129] Fair	Cohort 5.0 years	NR	5-year survival (unadjusted) RT: 86.0% WW: 75.5% *In multivariate survival analysis with radical prostatectomy the reference category:* HR (death with RT)=1.66 (95% CI, 1.24 to 2.21) HR (death with WW)=2.30 (95% CI, 1.70 to 3.12)	NR
Stattin, 2010[130] Fair	Cohort 8.2 years (median)	RT: 2.8% (40/1429) AS: 2.9% (58/2021) 10-year cumulative mortality RT: 3.3% (95% CI, 2.5 to 5.7) AS: 3.6% (95% CI, 2.7 to 4.8) RR=0.70 (95% CI, 0.45 to 1.1)	RT: 13.7% (196/1429) AS: 20.4% (413/2021) 10-year cumulative mortality RT: 18.3% (95% CI, 15.7 to 21.3%) AS: 23.4% (95% CI, 21.3 to 25.8%) RR=0.68 (95% CI, 0.57 to 0.82)	NR
Zhuo, 2009[135] Fair	Cohort 7.0 years	EBRT: adjusted HR=0.66 (95% CI, 0.41 to 1.04); P=0.07 Brachytherapy: adjusted HR=0.45 (95% CI, 0.23 to 0.87); p=0.018	EBRT: adjusted HR=0.63 (95% CI, 0.53 to 0.75) Brachytherapy: adjusted HR=0.40 (95% CI, 0.32 to 0.52)	NR
Albertsen, 2007[115] Fair	Cohort 13.3 years (median)	RT: 18% WW: 16% RR=1.5 (95% CI, 0.9 to 2.6)	RT: 55% WW: 57% RR=1.2 (95% CI, 0.9 to 1.5)	NR
Wong, 2006[134] Good	Cohort 12.0 years	NR	Adjusted HR=0.81 (95% CI, 0.78 to 0.85)	NR

Table 16. The Effect of Radiation Therapy* Compared With Conservative Management† on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

*When studies reported outcomes for both internal (brachytherapy) and external (EBRT) radiation therapy, we abstracted data as such; however, most studies only reported radiation therapy at the aggregate level
†Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting) as well as observation or no treatment

Abbreviations: AS=active surveillance; EBRT=external beam radiation therapy; HR=hazard ration; RT=radiation therapy; RR=relative risk; WW=watchful waiting

Table 17. The Effect of Radiation Therapy* Compared With Conservative Management† on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk or Tumor Stage	Gleason Score	Other
Abdollah, 2012[114] Fair	Cohort 2-15 years (range)	Prostate cancer-specific mortality	*65-69 years* HR=0.93 (95% CI, 0.72 to 1.19; p=0.6) *70-74 years:* HR=0.84 (95% CI, 0.68 to 1.03; p=0.08) *75-80 years:* HR=0.70 (95% CI, 0.59 to 0.80; p<0.001)	*Low/intermediate risk* HR=0.91 (95% CI, 0.80 to 1.04; p=0.2) *High risk* HR=0.59 (95% CI, 0.50 to 0.68; p<.001)	NR	Comorbidity *Charlson Score=0* HR=0.81 (95% CI, 0.67 to 0.98; p=0.03) *Charlson Score=1* HR=0.87 (95% CI, 0.75 to 0.99; p=0.04) *Charlson Score≥2* HR=0.79 (95% CI, 0.65 to 0.96; p=0.01)
Stattin, 2010[130] Fair	Cohort 8.2 years (median)	Prostate cancer-specific mortality	NR	*Low risk* RT: 0.4% (5/1429) WW: 1.3% (14/2021) *Intermediate risk* RT: 2.5% (35/1429) WW: 2.2% (44/2021) <u>10-year mortality</u> *Low risk* RT: 1.8% (95% CI, 0.65 to 4.0%) WW: 2.4% (95% CI, 1.2 to 4.1) RR=0.94 (95% CI, 0.31 to 2.85) *Intermediate risk* RT: 3.8% (95% CI, 2.6 to 5.4%) WW: 5.2% (95% CI, 3.7 to 6.9) RR=0.66 (95% CI, 0.42 to 1.06)	NR	NR

*When studies reported outcomes for both internal (brachytherapy) and external (EBRT) radiation therapy, we abstracted data as such; however, most studies only reported radiation therapy at the aggregate level
†Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting) as well as observation or no treatment

Abbreviations: AS=active surveillance; EBRT=external beam radiation therapy; HR=hazard ration; RT=radiation therapy; RR=relative risk; WW=watchful waiting

Table 18. The Effect of Androgen Deprivation Therapy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality

Study Reference Quality Rating	Study Design Followup	Prostate-Cancer Specific Mortality	All-Cause Mortality	Morbidity
Lu-Yao, 2014[127] Good	Cohort 9.2 years (median)	9.2-years followup ADT: 1,890/112,769 events PY (1.7 per 100 PY) WW: 1,849/115,151 events per PY (1.6 per 100 PY) HR=1.01 (95% CI, 0.90 to 1.14)	9.2-years followup ADT: 13,633/134,658 events per PY (rate: 10.1 per 100 PY) WW: 13,314/135,202 events per PY (rate: 9.8 per 100 PY) HR=1.04 (95% CI, 0.99 to 1.09)	NR
Schymura, 2010[129] Fair	Cohort 5.0 years	NR	5-year survival[†] HT: 65.2% WW: 75.5%	NR
Zhuo, 2009[135] Fair	Cohort 7.0 years	Adjusted HR=1.32 (95% CI, 1.01 to 1.73; p=0.044)	Adjusted HR=0.89 (95% CI, 0.80 to 0.98; p=0.024)	NR

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting) as well as observation or no treatment
†This study reported adjusted hazard ratios using radical prostatectomy as the reference; this data is not presented.

Abbreviations: AS=active surveillance; ADT=androgen deprivation therapy; HR=hazard ration; PY=person years; RR=relative risk; WW=watchful waiting

Table 19. The Effect of Androgen Deprivation Therapy Compared With Conservative Management* on Prostate Cancer-Specific Morbidity and Mortality and All-Cause Mortality, by Subgroup and Risk Factor

Study Reference Quality Rating	Study Design Followup	Outcome	Age	Tumor Risk	Gleason Score	Other
Lu-Yao, 2014[127] Good	Cohort 9.2 years (median)	All-cause mortality	NR	NR	*Gleason score 5 to 7:* HR=1.03 (95% CI, 0.96 to 1.10) *Gleason score 8-10:* HR=1.03 (95% CI, 0.96 to 1.10)	NR
		Prostate cancer-specific mortality	NR	NR	*Gleason score 5 to 7:* HR=1.00 (95% CI, 0.85 to 1.18) *Gleason score 8-10:* HR=0.99 (95% CI, 0.84 to 1.17)	NR

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting) as well as observation or no treatment

Abbreviations: AS=active surveillance; ADT=androgen deprivation therapy; HR=hazard ration; PY=person years; RR=relative risk; WW=watchful waiting

Table 20. The Effect of Radical Prostatectomy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
ProtecT Donovan, 2016[144] Good	RCT 6.0 years	*Use of one or more pads per day in the past 4 weeks* RP: 17.4% (79/455) AS: 8.4% (38/453)	*Erectile dysfunction characterized by patients as a "moderate or big problem"* RP: 49.7% (227/457) AS: 39.8% (147/437) *Erections not firm enough for intercourse* RP: 83.5% (385/461) AS: 70.3 % (318/452)	*Fecal incontinence more than once per week:* RP: 1.9% (9/468) AS: 2.6% (12/462) *Loose stools about half the time or more frequently:* RP: 12.2% (57/468) AS: 13.1% (61/466) *Bloody stools about half the time or more frequently* RP: 1.1% (5/470) AS: 1.3% (6/465)
PIVOT Wilt, 2012[133] Good	RCT 2.0 years	*Urinary incontinence characterized by patients as "have lots of problems with urinary dribbling," "lose larger amounts of urine than dribbling but not all day," "have no control over urine," or "have an indwelling catheter"* RP: 17.1% (49/287) WW: 6.3% (18/284) p<0.001	*Inability to have an erection or an erection sufficient for vaginal penetration* RP: 81.1% (231/285) WW: 44.1% (124/281) p<0.001)	*Bowel dysfunction characterized by patients as a "moderate" or "big" problem* RP: 12.2% (35/286) WW: 11.3% (32/281) p=0.74
SPCG-4 Johansson, 2009[147] Good	RCT 4.1 years (mean) 2 to 8 years (range)	*Urinary incontinence* 2 to 3 years RP: 42.3% (22/52) WW: 11.3% (6/53) RR=3.7 (95% C, 1.6 to 8.5) 4 to 5 years RP: 47% (26/55) WW: 28% (15/54) RR=1.7 (95% CI, 1.0 to 2.8) 6 to 8 years RP: 56% (31/55) WW: 25% (12/48) RR=2.3 (95% CI, 1.3 to 3.9) Overall	*Erectile dysfunction* 2 to 3 years RP: 80.4% (41/51) WW: 37.3% (19/51) RR=2.2 (95% CI, 1.5 to 3.2) 4 to 5 years RP: 77.8% (42/54) WW: 42.6% (23/54) RR=1.8 (95% CI, 1.3 to 2.6) 6 to 8 years RP: 83.3% (45/54) WW: 54.7% (29/53) RR=1.5 (95% CI, 1.2 to 2.0) Overall	*Fecal leakage* 2 to 3 years RP: 1.9% (1/52) WW: 5.7% (3/53) RR=0.3 (95% CI, 0.04 to 3.2) 4 to 5 years RP: 0% (0/53) WW: 7.5% (4/53) 6 to 8 years RP: 0% (0/57) WW: 3.9% (2/51) Overall RP: 0.6% (1/162) WW: 5.7% (9/157)

Table 20. The Effect of Radical Prostatectomy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		RP: 48.8% (79/162) WW: 21.3% (33/155) RR=2.3 (95% CI, 1.6 to 3.2)	RP: 80.5% (128/159) WW: 44.9% (71/158) RR=1.8 (95% CI, 1.5 to 2.2)	
Barocas, 2017[75] Good	Cohort 3.3 years	*Urinary leakage characterized by patients as a "moderate or big problem"* Baseline RP: 7% (110/1523) AS: 5% (20/429) 6 months RP: 19% (268/1448) AS: 3% (13/411) OR=10.3 (95% CI, 5.8-18.1) 1 year RP: 15% (211/1425) AS: 4% (16/387) OR=6.0 (95% CI, 3.6-9.9) 3 years RP: 14% (175/1307) AS: 6% (20/349) OR=2.9 (95% CI, 1.8-4.7)	*Erection insufficient for penetration* Baseline RP: 39% (573/1523) AS: 41% (166/429) 6 months RP: 80% (1128/1448) AS: 43% (169/411) OR=12.6 (95% CI, 9.4-16.9) 1 year RP: 74% (1027/1425) AS: 41% (152/387) OR=7.6 (95% CI, 5.8-10.1) 3 years RP: 70% (893/1307) AS: 51% (168/349) OR=3.4 (95% CI, 2.5-4.6)	*Bowel urgency characterized by patients as a moderate or big problem* Baseline RP: 5% (72/1523) AS: 4% (16/429) 6 months RP: 3% (47/1448) AS: 4% (17/411) OR=1.1 (95% CI, 0.6-2.1) 1 year RP: 4% (50/1425) AS: 3% (13/387) OR=0.9 (95% CI, 0.5-1.6) 3 years RP: 3% (34/1307) AS: 5% (18/349) OR=0.5 (95% CI, 0.3-0.9)
Chen, 2017[76] Good	Cohort 2.0 years	*Urinary obstruction and irritation characterized by patients as having at least 1 very distressful symptom* RP: 17% (62/374) AS: 39% (86/222) *Urinary incontinence characterized by patients as having at least 1 very distressful symptom* RP: 16% (58/360) AS: 10% (21/206)	*Poor sexual function characterized by patients as having at least 1 very distressful symptom* RP: 76% (285/373) AS: 57% (130/227)	*Poor bowel function characterized by patients as having at least 1 very distressful symptom* RP: 10% (33/333) AS: 13% (26/198)
Smith, 2009[159] Fair	Cohort 3.8 years	*Urinary leakage that required one or more pads per day to control* Baseline RP: 1.1% (11/981) AS: 6.0% (12/200)	*Being unable to obtain an erection sufficient for sexual intercourse* Baseline RP: 21.0% (206/981) AS: 26.5% (53/200)	*Bowel dysfunction characterized by patients as a "moderate" or "big" problem* Baseline RP: 4.4% (43/981) AS: 13.5% (27/200)

Table 20. The Effect of Radical Prostatectomy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		3 years RP: 12.3% (111/981) AS: 3.4% (6/200) RR=3.7 (95% CI, 2.4 to 5.7)	3 years RP: 70.8% (695/981) AS: 47.0% (94/200) RR=1.5 (95% CI, 1.3 to 1.8)	3 years RP: 3.3% (32/981) AS: 5.5% (11/200)
Hoffman, 2003[145] Fair	Cohort 2.0 years	*Urinary leakage once per week or less:* RP: 27.2% (367/1373) WW: 14.9% (40/230) *Urinary leakage daily or more often* RP: 35.3% (484/1373) WW: 8.3% (19/230) RR=4.3 (95% CI, 2.8 to 6.6)	*Some or a lot of erectile dysfunction* RP: 25.7% (351/1373) WW: 34.2% (75/230) *No erections at all* RP: 58.4% (757/1373) WW: 32.5% (60/230); RR=2.1 (95% CI, 1.7 to 2.6)	*Bowel urgency some days* RP: 14.1% (201/1373) WW: 15.9% (38/230) *Bowel urgency almost every day* RP: 0.9%(11/1373) WW: 0.2% (1/230)
Schapira, 2001[156] Fair	Cohort 1.0 years	*Use of ≥1 pad per day for control of urine* Baseline RP: 2.4% (1/42) AS: 0% (0/25) 3 Months RP: 73.8% (31/42) AS: 0% (0/27) 12 months RP: 43.2% (16/37) AS: 4.0% (1/25) RR=11.0 (95% CI, 1.6 to 7.8)	*Not having an erection firm enough for sexual intercourse* Baseline RP: 33.3% (14/42) AS: 64.0% (16/25) 3 Months RP: 100.0% (42/42) AS: 63.0% (17/27) 12 months RP: 89.2% (33/37) AS:68.0% (17/25)) RR=1.3 (CI, 0.98 to 1.8)	NR
Siegal, 2001[158] Fair	Cohort 4.3 years	NR	*Erection insufficient for intercourse* Pretreatment RP: 22.7% (89/392) WW: 45.3% (29/64) Posttreatment RP: 90.1% (53/392) WW: 62.5% (40/64) RR=1.4 (CI, 1.2 to 1.8)	NR

Table 20. The Effect of Radical Prostatectomy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

| Smith, 2000[160]

Fair | Cohort

3.8 years | *Frequent dribbling*
Aged <70 years
Pretreatment
RP:3%
WW: 5%

12 months
RP:6%
WW: 6%

18 months
RP: 7%
WW: 5%

Aged ≥70 years
Pretreatment
RP: 4%
WW: 6%

12 months
RP: 11%
WW: 6%

18 months
RP: 7%
WW: 4%

No urinary control
Aged <70 years
Pretreatment
RP: 0%
WW: 0%

12 months
RP: 1%
WW: 0%

18 months
RP: 1%
WW: 0%

Aged ≥70 years
Pretreatment
RP: 1% | *Not firm enough for sexual activity*
Aged <70 years
Pretreatment
RP: 9%
WW: 0

12 months
RP: 18%
WW: 13%

18 months
RP: 17%
WW: 27%

Aged ≥70 years
Pretreatment
RP: 23%
WW: 17%

12 months
RP: 26%
WW: 4%

18 months
RP: 25%
WW: 32%

No erections at all
Aged <70 years
Pretreatment
RP: 3%
WW: 0%

12 months
RP:33%
WW: 0%

18 months
RP: 32%
WW: 0%

Aged ≥70 years
Pretreatment
RP: 11% | NR |

Table 20. The Effect of Radical Prostatectomy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		WW: 0%	WW: 7%	
		12 months RP:1% WW: 0%	12 months RP: 57% WW: 8%	
		18 months RP: 1% WW: 0%	18 months RP: 57% WW: 11%	
Litwin, 1995[149] Fair	Cohort 6.0 years	*Occasional dribbling* RP: 45% (42/94) WW: 29%(18/63) *Frequent dribbling* RP: 11% (10/94) WW: 6% (4/63) *No urinary control* RP: 10% (9/94) WW: 3% (2/63)	*Poor ability to function sexually during the last 4 weeks:* RP: 12.5% (12/96) WW: 11.1% (7/63) *Very poor ability to function sexually during the last 4 weeks:* RP: 66.7% (64/96) WW: 38.1% (24/63)	*Rectal urgency about once a week* RP: 15.5% (15/97) WW: 9.5% (6/63) *Rectal urgency more than once a week* RP: 7.2% (7/97) WW: 4.8% (3/63) *Rectal urgency about once a day* RP: 9.3% (9/97) WW: 12.7% (8/63) *Rectal urgency more than once a day* RP: 4.1% (4/97) WW: 4.8% (3/63

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: AS=active surveillance; HR=hazard ration; RP=radical prostatectomy; RR=relative risk; WW=watchful waiting

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
ProtecT Donovan, 2016[144] Good	RCT 6.0 years	*Use of one or more pads per day in the past 4 weeks* RT: 3.5% (16/452) AS: 8.4% (38/453)	*Erectile dysfunction characterized by patients as a "moderate or big problem"* RT: 36.2% (162/447) AS: 39.8% (147/437)	*Fecal incontinence more than once per week:* RT: 4.1% (19/465) AS: 2.6% (12/462) *Loose stools about half the time or more frequently:* RT: 15.5% (72/466) AS: 13.1% (61/466) *Bloody stools about half the time or more frequently* RT: 5.6% (26/466) AS: 1.3% (6/465)
Fransson, 2001[70] Fair	RCT 2.5 years (median)	*Regular use of pads for urinary incontinence* RT: 17.5% (10/59) WW: 2.0% (1/49) RR=8.3 (95% CI, 1.1 to 6.3)	NR	Use of sanitary shields for stool leakage RT: 8.6% (5/59) WW: 2.1% (1/49) P=0.346
Barocas, 2017[75] Good	Cohort 3.3 years	*Urinary leakage characterized by patients as a "moderate or big problem"* Baseline RT: 4% (24/598) AS: 5% (20/429) 6 months RT: 5% (31/580 AS: 3% (13/411) OR=1.5 (95% CI, 0.8-3.0) 1 year RT: 6% (32/560) AS: 4% (16/387) OR=1.2 (95% CI, 0.6-2.3) 3 years RT: 5% 24/482) AS: 6% (20/349) OR=0.7 (95% CI, 0.4-1.2)	*Erection insufficient for penetration* Baseline RT: 56% (319/598) AS: 41% (166/429) 6 months RT: 71% (371/580) AS: 43% (169/411) OR=2.6 (95% CI, 1.9-3.5) 1 year RT: 72% (387/560) AS: 41% (152/387) OR=2.3 (95% CI, 1.7-3.2) 3 years RT: 71% (326/482) AS: 51% (168/349) OR=1.6 (95% CI, 1.1-2.3)	*Bowel urgency characterized by patients as a moderate or big problem* Baseline RT: 4% (21/598) AS: 4% (16/429) 6 months RT: 7% 43/580) AS: 4% (17/411) OR=2.5 (95% CI, 1.4-4.6) 1 year RT: 7% (40/560) AS: 3% (13/387) OR= 1.5 (95% CI, 0.8-2.8) 3 years RT: 7% (34/482) AS: 5% (18/349) OR=1.5 (95% CI, 0.8-2.9)

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Chen, 2017[76] Good	Cohort 2.0 years	*Urinary obstruction and irritation characterized by patients as having at least 1 very distressful symptom* BT: 37% (29/80) EBRT: 35% (65/187) AS: 39% (86/222) *Urinary incontinence characterized by patients as having at least 1 very distressful symptom* BT: 13% (10/77) EBRT: 9% (15/168) AS: 10% (21/206)	*Poor sexual function characterized by patients as having at least 1 very distressful symptom* BT: 62% (48/77) EBRT: 63% (120/189) AS: 57% (130/227)	*Poor bowel function characterized by patients as having at least 1 very distressful symptom* BT: 12% (9/72) EBRT: 19% (29/156) AS: 13% (26/198)
Shah, 2012[157] Fair	Uncontrolled Observational 6.6 years (median)	*Dysuria* EBRT African American: NR White: NR Brachytherapy: African American: 34.4% White: 22.9% p=0.31 *Urinary retention* EBRT African American: 3.4% White: 10.4% p=0.60 Brachytherapy: African American: 19.2% White: 25.7% p=0.59 *Urinary frequency/urgency* EBRT African American: 24.1% White: 30.7% p=0.83 Brachytherapy: African American: 53.8%	NR	*Diarrhea* EBRT African American: 0% White: 5.9% p=0.61 Brachytherapy African American: 3.7% White: 7.5% p=0.89 *Rectal pain/tenesmus* EBRT African American: 3.4% White: 8.0% p=0.64 Brachytherapy African American: NR White: NR *Rectal bleeding* EBRT African American: 10.3% White: 17.8% p=0.74 Brachytherapy African American: NR

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		White: 54.8% p=0.80 *Urinary incontinence* EBRT African American: 6.7% White: 8.9% p<0.001 Brachytherapy: African American: 3.8% White: 8.7% p=0.82 *Urinary stricture* EBRT African American: 0% White: 2.6% p=0.68 Brachytherapy: African American: 0% White: 3.9% p=0.79		White: NR
Thong, 2010[161] Fair	Cohort 5 to 10 years	NR	*Problem maintaining an erection occasionally* RT: 6.7% (4/60) AS: 5.0% (3/60) Nearly Always RT: 71.6% (43/60) AS: 48.3% (29/60) *Problem getting an erection* Occasionally RT: 15.9% (10/63) AS: 8.3% (5/60) Nearly Always RT: 68.3% (43/63) AS: 46.7% (28/60) RR=1.5 (95% CI, 1.1 to 2.0)	NR

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Smith, 2009[159] Fair	Cohort 3.8 years (mean)	*Urinary leakage that required one or more pads per day to control* Baseline EBRT: 0% AS: 6.0% (12/200) 3 years EBRT: 2.4% (3/123) AS: 3.4% (6/200) RR=0.81 (95% CI, 0.21 to 3.2)	*Being unable to obtain an erection sufficient for sexual intercourse* Baseline EBRT: 28.4% (35/123) AS: 26.5% (53/200) 3 years EBRT: 58.5% (72/123) AS: 47.0% (94/200) RR=1.2 (95% CI, 1.0 to 1.5)	*Bowel dysfunction characterized by patients as a "moderate" or "big" problem* Baseline EBRT: 10.6% (13/123) AS: 13.5% (27/200) 3 years EBRT: 13.0% (16/123) AS: 5.5% (11/200)
Hoffman, 2003[145] Fair	Cohort 2.0 years	*Urinary leakage once per week or less* RT: 22.2% (133/583) WW: 14.9% (40/230) *Urinary leakage daily or more often* RT: 12.2% (71/583) WW: 8.3% (19/230) RR=1.5 (95% CI, 0.91 to 2.39)	*Some or a lot of erectile dysfunction* RT: 34.3% (186/583) WW: 34.2% (75/230) *No erections at all* RT: 39.1% (228/583) WW: 26.1% (60/230) RR=1.5 (95% CI, 1.2 to 1.9)	*Bowel urgency some days* RT: 28.6% (168/583) WW: 15.9% (38/230) *Bowel urgency almost every day* RT: 3.2% (19/583) WW: 0.2% (1/230)
Schapira, 2001[156] Fair	Cohort 1.0 years	*Use of >1 pad per day for control of urine* Baseline RT: 4.5% (2/44) AS: 0% 3 Months RT: 9.3% (4/43) AS: 0% 12 months RT: 7.9% (3/38) AS: 4.0% (1/25) RR=2.0 (95% CI, 0.22 to 18.0)	*Not having an erection firm enough for sexual intercourse* Baseline RT: 68.2% (30/44) AS: 0% 3 Months RT: 76.7% (33/43) AS: 0% 12 months RT: 75.0% (30/40) AS: 68.0% (17/25) RR=1.1 (95% CI, 0.80 to 1.5)	NR
Siegel, 2001[158] Fair	Cohort 4.3 years (median)	NR	*Erection insufficient for intercourse* Pretreatment RT: 38.9% (123/315) WW: 45.3% (29/64) Posttreatment (4.3 years) RT: 85.4% (269/315) WW: 62.5% (40/64)	NR

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
			RR=1.4 (95% CI, 1.1 to 1.7)	
Smith, 2000[160] Fair	Cohort 3.8 years	*Frequent dribbling* Aged <70 years Pretreatment RT: 4% WW: 5% 12 months RT: 2% WW: 6% 18 months RT: 2% WW: 5% Aged ≥70 years Pretreatment RT: 1% WW: 6% 12 months RT: 7% WW: 6% 18 months RT: 7% WW: 4% *No Control* Aged <70 years Pretreatment RT: 0% WW: 0% 12 months RT: 0% WW: 0% 18 months RT: 0% WW: 0%	*Not firm enough for sexual activity* Aged <70 years Pretreatment RT: 24% WW: 0 12 months *<70 years* RT: 25% WW: 13% 18 months RT: 26% WW: 14% Aged ≥70 years Pretreatment RT: 24% WW: 17% 12 months RT: 35% WW: 27% 18 months RT: 36% WW: 32% *No Erections at All* Aged <70 years Pretreatment RT: 2% WW: 0% 12 months RT:21% WW: 0% 18 months RT: 21% WW: 0%	NR

Table 21. The Effect of Radiation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function and Other Physical Harms

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		Aged ≥70 years Pretreatment RT: 0% WW: 0% 12 months RT: 0% WW: 0% 18 months RT: 0% WW: 0%	Aged ≥70 years Pretreatment RT: 18% WW: 7% 12 months RT: 36% WW: 8% 18 months RT: 40% WW: 11%	
Litwin, 1995b[149] Fair	Cohort 6.0 years	*Occasional urinary dribbling* RT: 40.7% (22/54) WW: 28.6% (18/63) *Frequent urinary dribbling* RT: 5.6% (3/54) WW: 6.3% (4/63) *No urinary control* RT: 1.8% (1/54) WW: 3.2% (2/63)	*Poor ability to function sexually during the last 4 weeks* RT: 9.1% (5/55) WW: 11.1% (7/63) *Very poor ability to function sexually during the last 4 weeks* RT: 61.8% (34/55) WW: 38.1% (24/63)	*Rectal urgency about once a week* RT: 3.7% (2/54) WW: 9.5% (6/63) *Rectal urgency more than once a week* RT: 7.4% (4/54) WW: 4.8% (3/63) *Rectal urgency about one a day* RT: 5.6% (3/54) WW: 12.7% (8/63) *Rectal urgency more than once a day* RT: 16.7% (9/54) WW: 4.8% (3/63)

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: AS=active surveillance; BT=brachytherapy; EBRT=external beam radiation therapy; HR=hazard ratio; RT=radiation therapy; RR=relative risk; WW=watchful waiting

Table 22. The Effect of Androgen Deprivation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Smith, 2009[159] Fair	Cohort 3.8 years (mean)	*Urinary leakage that required one or more pads per day to control* Baseline ADT: 6.6% (4/61) AS: 6.0% (12/200) 3 years ADT: 3.3% (2/61) AS: 3.4% (6/200) RR=1.1 (95% CI, 0.23 to 5.3)	*Being unable to obtain an erection sufficient for sexual intercourse* Baseline ADT: 39.3% (24/61) AS: 26.5% (53/200) 3 years ADT: 73.8% (45/61) AS: 47.0% (94/200) RR=1.6 (95% CI, 1.3 to 1.9)	*Bowel dysfunction characterized by patients as a "moderate" or "big" problem* Baseline ADT: 9.8% (6/61) AS: 13.5% (27/200) 3 years ADT: 6.4% (3/61) AS: 5.5% (11/200)
Hoffman, 2003[145] Fair	Cohort 2.0 years	Urinary leakage once per week or less ADT: 29.2% (50/179) WW: 14.9% (40/230) Urinary leakage daily or more often ADT: 11.2% (20/179) WW: 8.3% (19/230) RR=1.4 (95% CI, 0.74 to 2.5)	Some or a lot of erectile dysfunction ADT: 8.1% (17/179) WW: 34.2% (75/230) No erections at all ADT: 85.8% (135/179) WW: 26.1% (60/230) RR=2.9 (95% CI, 2.3 to 3.6)	Bowel urgency some days ADT: 15.8% (30/179) WW: 15.9% (38/230) Bowel urgency almost every day ADT: 3.3% (7/179) WW: 0.2% (1/230)
Potosky, 2002[154] Fair	Cohort 1.0 years	NR	*Impotence* ADT: 77.3% (68/88) WW: 26.9% (60/223) RR=2.9 (95% CI, 2.2 to 3.7)	NR
Smith, 2000[160] Fair	Cohort 3.8 years	*Frequent dribbling* *Aged <70 years* Pretreatment ADT: 0% WW: 5% 12 months ADT: 0% WW: 6% 18 months ADT: 0% WW: 5% *Aged ≥70 years* Pretreatment ADT: 8% WW: 6%	*Not firm enough for sexual activity* *Aged <70 years* Pretreatment ADT: 14% WW: 0% 12 months ADT: 43% WW: 13% 18 months ADT: 40% WW: 14% *Aged ≥70 years* Pretreatment ADT: 30% WW: 17%	NR

Table 22. The Effect of Androgen Deprivation Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		12 months ADT:13% WW: 6% 18 months ADT: 13% WW: 4% *No control* *Aged <70 years* Pretreatment ADT: 0% WW: 0% 12 months ADT: 14% WW: 0% 18 months ADT: 17% WW: 0% *Aged ≥70 years* Pretreatment ADT: 0% WW: 0% 12 months ADT: 0% WW: 0% 18 months ADT: 0% WW: 0%	12 months ADT: 18% WW: 4% 18 months ADT: 18% WW: 32% *No erections at all* Aged <70 years Pretreatment ADT:14% WW: 0% 12 months ADT:43% WW: 0% 18 months ADT: 40% WW: 0% *Aged ≥70 years* Pretreatment ADT: 18% WW: 7% 12 months ADT: 73% WW: 8% 18 months ADT: 71% WW: 11%	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: ADT=androgen deprivation therapy; AS=active surveillance; HR=hazard ration; RR=relative risk; WW=watchful waiting

Table 23. The Effect of Cryotherapy Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Smith, 2000[160] Fair	Cohort 3.8 years	*Frequent dribbling* *Aged <70 years* Pretreatment Cryotherapy: 0% WW: 6% 12 months Cryotherapy: 0% WW: 0% 18 months Cryotherapy: 0% WW: 5% *Aged ≥70 years* Pretreatment Cryotherapy: 0% WW: 2% 12 months Cryotherapy: 0% WW: 0% 18 months Cryotherapy: 0% WW: 4% *No Control* *Aged <70 years* Pretreatment Cryotherapy: 0% WW: 0% 12 months Cryotherapy: 0% WW: 0% 18 months Cryotherapy: 0% WW: 0%	*Not firm enough for sexual activity* *Aged <70 years* Pretreatment Cryotherapy: 20% WW: 0% 12 months Cryotherapy: 13% WW: 13% 18 months Cryotherapy: 0% WW: 14% *Aged ≥70 years* Pretreatment Cryotherapy: 25% WW: 18% 12 months Cryotherapy: 50% WW: 27% 18 months Cryotherapy: 0% WW: 32% *No Erections at All* Aged <70 years Pretreatment Cryotherapy: 0% WW: 0% 12 months Cryotherapy: 40% WW: 0% 18 months Cryotherapy: 33% WW: 0%	NR

Table 23. The Effect of Cryotherapy Therapy Compared With Conservative Management* on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
		Aged ≥70 years Pretreatment Cryotherapy: 0% WW: 0% 12 months Cryotherapy: 0% WW: 0% 18 months Cryotherapy: 0% WW: 0%	*Aged ≥70 years* Pretreatment Cryotherapy: 25% WW: 7% 12 months Cryotherapy: 50% WW: 8% 18 months Cryotherapy: 100% WW: 11%	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: AS=active surveillance; HR=hazard ration; RR=relative risk; WW=watchful waiting

Table 24. The Effect of High-Intensity Focused Ultrasound on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Uchida, 2015[163] Fair	Uncontrolled observational study 47 to 108 months	*Urinary incontinence* 2.3% (21/918) *Urethral stricture* (19.7%) 181/981 *Epididymitis* (6.2%) 57/918 *Rectourethral fistula* (0.1%) 1/981 *Bladder neck contracture* (0.8%) 7/918 *Acute pyelonephritis* (0.3%) 3/918	*Erectile dysfunction* 6-months: 57.5% (77/134) 1-year: 50.8% (65/128) 2-years: 34.9% (37/106)	NR
Crouzet, 2014[143] Fair	Uncontrolled observational study 6.4 years (median)	*Urinary incontinence (grade 1)* 18.7% (187/1002) *Urinary incontinence (grade 2 or 3)* 5.0% (50/1002) *Urinary tract infection* 3.9% (39/1002) *Acute urinary retention* 7.6% (76/1002) *Bladder outlet obstruction* 16.6% (166/1002) *Hematuria* 5.5% (55/1002) *Stenosis* 9.0% (90/1002) *Fistula* 0.4% (4/1002)	NR	NR

Table 24. The Effect of High-Intensity Focused Ultrasound on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Pfeiffer, 2012[153] Fair	Uncontrolled observational study 5.8 years (median)	*Urinary incontinence (grade 1)* 26.5% (51/191) *Urinary incontinence (grade 2 or 3)* 7.3% (14/191) *Recurrent urinary tract infection* 26.5% (51/191) *Rectourethral fistulas* 1.6% (3/191)	NR	NR
Inoeu, 2011[146] Fair	Uncontrolled observational study 6 to 24 months	*Urinary incontinence (grade 1)* 3 months: 10.8% (16/137) 6 months: 0.7% (1/137) *Urethral stricture* 6.8% (10/137) *Urinary tract infection* 4.1% (6/137) *Acute epididymitis* 2.7% (4/137)	*Erectile dysfunction* Post-treatment (among potent men pre-treatment): 37.3% (22/59)	NR
Blana, 2008[141] Fair	Uncontrolled observational study 4.8 years (mean)	*Urinary incontinence (grade 1)* 6.1% (10/163) *Urinary incontinence (grade 2 or 3)* 1.8% (3/163) *Bladder outlet obstruction* 24.5% (40/163) *Urinary tract infection* 6.7% (11/163)	*Erectile dysfunction* Post-treatment (among potent men pre-treatment): 44.7% (34/76)	NR

Table 24. The Effect of High-Intensity Focused Ultrasound on Urinary, Sexual, and Bowel Function

Study Reference Quality Rating	Study Design Followup	Urinary Function	Sexual Function	Bowel Function
Blana, 2004[142] Fair	Uncontrolled observational study 23 months (mean)	*Urinary incontinence (grade 1)* 5.8% (8/137) *Urinary incontinence (grade 2-3)* 0% *Urinary tract infection* 4.4% (6/137) *Rectourethral fistula* 0.7% (1/137) *Urethral obstruction* 11.7% (16/137)	*Erectile dysfunction* Post-treatment (among potent men pre-treatment): 52.7%	NR
Thuroff, 2003[162] Fair	Uncontrolled observational study 407 days (mean)	*Urinary incontinence (grade 1)* 10.9% (44/402) *Urinary incontinence (grade 2 or 3)* 4.5% (18/402) *Urinary tract infection* 14.0% (56/402) *Urethrorectal fistula* 1.2% (5/402)	*Erectile dysfunction* 8.7% (35/402)	NR

Table 25. Surgical Complications and Mortality Associated With Radical Prostatectomy

Study Reference Quality Rating	Study Design Followup	Surgical Complications	Surgical Mortality
ProtecT Hamdy, 2016[121] Good	RCT 90-days	Blood transfusion: 2.5% (14/553) Thromboembolic or cardiovascular events: 1.6% (9/553) Requiring intervention for anastomotic problems: 1.6% (9/553) Rectal injury: 0.18% (1/553)	0% (0/5553)
PIVOT Wilt, 2012[133] Good	RCT 30-days	Any complication: 21.4% (60/280) Wound infection: 4.3% (12/280) Urinary tract infection: 2.5% (7/280) Additional surgical repair: 2.5% (7/280) Bleeding requiring transfusion: 2.1% (6/280) Urinary catheter present > 30 days after surgery: 2.1% (6/280) Sepsis: 1.1% (3/280) Bowel injury requiring surgical repair: 1.1% (3/280) Myocardial infarction: 1.1% (3/280) Deep vein thrombosis: 0.7% (2/280) Pneumonia: 0.7% (2/280) Stroke: 0.4% (1/280) Pulmonary embolism: 0.7% (2/280) Renal failure or dialysis: 0.4% (1/280) Other event: 10.0% (28/280)	0.4% (1/280)
Bjorklund, 2016[140] Fair	Uncontrolled observational study 90-days	NR	0.17% (39/22344) *Age at surgery (per 1-year increase):* OR=1.07 (95% CI, 1.00 to 1.13) *Comorbidity:* 0=reference 1: OR=1.02 (95% CI, 0.31 to 3.36) ≥2: OR=2.23 (95% CI, 0.77 to 6.40) *Tumor risk:* Low risk=reference Intermediate risk: OR=1.23 (95% CI, 0.55 to 2.74) High risk: OR=2.89 (1.18 to 7.06)

Table 25. Surgical Complications and Mortality Associated With Radical Prostatectomy

| Rabbani, 2010[155]

Fair | Uncontrolled observational study

37 months | Open retropubic radical prostatectomy
Any complication: 27.5% (950/3458)

Early complications (<30 days)
Hypotension: 0.4% (14/3458)
Respiratory distress: 0.2% (7/3458)
Acute renal insufficiency: 0.2% (7/3458)
Lymphocele: 0.8% (28/3458)
Rectal or bowel injury: 0.7% (24/3458)
Hematoma: 0.5% (17/3458)

Intermediate complications (31-90 days)
Sepsis: 0.03% (1/3458)
Bladder neck contracture: 2.3% (80/3458)
Urethral stricture: 0.6% (21/3458)
Urinary retention: 0.4% (14/3458)

Late complications (>90 days)
Cerebrovascular accident or transient ischemic attack: 0.09% (3/3458)
Acute renal insufficiency: 0.03% (1/3458)
Bladder neck contracture: 2.8% (97/3458)
Inguinal hernia: 1.2% (41/3458)
Urethral stricture: 0.4% (14/3458)

Laparoscopic radical prostatectomy
Any complication 39.0% (442/1134)

Early complications (<30 days)
Hypotension: 0.5% (6/1134)
PE: 0.4% (5/1134)
MI/ischemia: 0.3% (3/1134)
Urinoma/urine leak: 1.3%(15/1134)
Lymphocele: 1.1% (12/1134)
Abscess: 1.1% (12/1134)

Intermediate complications (31-90 days)
Lymphocele: 1.1% (5/1134)
Incisional hernia: 0.2% (2/1134)
Urethral stricture: 0.2% (2/1134)

Late complications (>90 days)
Incisional hernia: 1.1%(12/1134)
Bladder neck contracture:0.7% (8/1134)
Inguinal hernia: 0.5%(6/1134) | 0.13% (6/4592) |

Table 25. Surgical Complications and Mortality Associated With Radical Prostatectomy

Study Reference Quality Rating	Study Design Followup	Surgical Complications	Surgical Mortality
		Hazard ratios *Risk of any medical complication, RP vs. LP:* HR=1.9 (95% CI, 1.5 to 2.4; p<0.001) *Risk of any surgical complication, RP vs. LP:* HR=1.6 (95% CI, 1.3 to 1.9; p<0.001) *Risk of complication according to race, black vs. white*: HR=1.4 (95% CI, 1.0 to 2.0; p=0.027)	
Walz, 2008[164] Fair	Uncontrolled observational study 30-days	NR	0.52% (48/9208) *Age* ≥69 years: 0.33% <69 years: 1.19% OR=3.1 (p<0.001) *Comorbidity* None: 0.23% One: 0.80% OR=3.0 (p=0.002)
Alibhai, 2005[137] Fair	Uncontrolled observational study 30-days	Genitourinary: 7.53% (829/11010) Wound: 5.04% (555/11010) Misc. Surgical: 5.23% (576/11010) Misc. Medical: 3.88% (427/11010) Cardiac: 2.81% (309/11010) Respiratory: 2.66% (293/11010) Vascular: 1.95% (215/11010)	0.48% (53/11,010) *Age*: <60 years: 0.19% (6/3199) 60 to 69 years: 0.58% (38/6587) 70 to 79 years: 0.66% (8/1217)
Augustin, 2003[138] Fair	Uncontrolled observational study 30-days	Any adverse event: 19.9% (247/1243) Major complication: 4.0% (50/1243) Readmission due to major complication: 0.6% (8/1243) Minor complications: 15.8% (197/1243) Any intraoperative AE: 0.7% (9/1243) • AV blockage: 0.1% (1/1243) • Orturator nerve injury: 0.1% (1/1243) • Rectal injury: 0.2% (3/1243) • Ureteral injury: 0.1% (4/1243) Any postoperative AE: 4% (51/1243) • Arrhythmia: 0.2% (2/1243) • CHF: 0.2% (3/1243) • MI: 0.1% (1/1243)	0% (0/1243)

Table 25. Surgical Complications and Mortality Associated With Radical Prostatectomy

Study Reference Quality Rating	Study Design Followup	Surgical Complications	Surgical Mortality
		• Myocardial ischemia: 0.1% (1/1243) • Severe hypotension: 0.1% (1/1243) • Deep vein thrombosis: 1.0% (12/1243) • Pulmonary embolism: 0.2% (2/1243) • Acute renal insufficiency: 0.2% (2/1243) • Sepsis: 0.2% (3/1243) • Wound infection: 0.1% (1/1243) • Postoperative bleeding: 0.2% (3/1243)	
Yao, 1999[165] Fair	Uncontrolled observational study 30-days	Serious cardiac event: 3% Serious pulmonary event: 6% • Pulmonary embolism: 0.4% • Deep vein thrombosis: 0.05% Serious wound: 0.7% Serious surgical complication: 0.8%	0.5%

Abbreviations: AE=adverse event; AV=atrioventricular; CHF=congestive heart failure; HR=hazard ratio; MI=myocardial infarction; OR=odds ratio; PE=pulmonary embolism

Table 26. Summary of Cohort Study-Based UCLA-PCI and SF-36 Scores for Radical Prostatectomy, Radiation Therapy, and Androgen Deprivation Therapy Compared With Conservative Management*

Scale	Measure	Radical Prostatectomy		Radiation Therapy		Androgen Deprivation Therapy	
		Number of Studies (References)	Median Difference in Mean Scores (Range)[†]	Number of Studies (References)	Median Difference in Mean Scores (Range)[†]	Number of Studies (References)	Median Difference in Mean Scores (Range)[†]
UCLA-PCI	Urinary function	6 ([139, 150, 152, 156, 159, 160])	-17.0 (-30.0 to -6.0)	7 ([139, 150, 152, 156, 159-161])	-3.3 (-6.0 to7.2)	3 ([138, 159, 160])	-4.0 (-9.0 to 1.2)
	Urinary bother	6 ([139, 150, 152, 156, 159, 160])	-7.0 (-17.0 to 0.7)	7 ([139, 150, 152, 156, 159-161])	-4.5 (-18.5 to 0.3)	3 ([138, 159, 160])	-10.7 (-17.0 to -5.0)
	Sexual function	6 ([139, 150, 152, 156, 159, 160])	-22.0 (-35.0 to -2.0)	6 ([139, 150, 152, 156, 159, 160])	-12.1 (-20.0 to 9.9)	3 ([138, 159, 160])	-31.0 (-35.8 to -29.0)
	Sexual bother	6 ([139, 150, 152, 156, 159, 160])	-24.0 (-35.0 to 21.8)	6 ([139, 150, 152, 156, 159, 160])	-8.0 (-23.0 to 7.5)	3 ([138, 159, 160])	-15.0 (-20.0 to 0.6)
	Bowel function	5 ([139, 150, 152, 156, 159])	0.2 (0.5 to 2.0)	6 ([139, 150, 152, 156, 159, 161])	-6.0 (-11.0 to 2.1)	2 ([139, 159])	NA (-10.0 to -4.6)
	Bowel bother	5 ([139, 150, 152, 156, 159])	1.1 (-5.0 to 5.0)	6 ([139, 150, 152, 156, 159, 161])	-8.3 (-17.0 to 3.0)	2 ([139, 159])	NA (-6.0 to -0.9)
SF-36	Physical component summary score	2 ([139, 159])	NA (1.8 to 3.2)	3 ([139, 159, 161])	0.8 (-3.0 to 2.1)	2 ([139, 159])	NA (-8.1 to -3.0)
	Mental component summary score	2 ([139, 159])	NA (0.0 to 0.6)	3 ([139, 159, 161])	-0.6 (-1.6 to 0.9)	2 ([139, 159])	NA (-3.0 to 0.1)
	Physical function	6 ([75, 139, 150, 152, 156, 160])	8.6 (2.0 to 16.8)	7 ([75, 139, 150, 152, 156, 160, 161])	-7.4 (-18.0 to 11.0)	2 ([139, 159])	NA (-13.0 to -3.0)
	Physical role function	5 ([139, 150, 152, 156, 160])	5.3 (-2.0 to 9.5)	6 ([139, 150, 152, 156, 160, 161])	-7.4 (-22.0 to 0.4)	3 ([139, 154, 160])	-11.0 (-23.0 to -11.0)
	Bodily pain	5 ([139, 150, 152, 156, 160])	4.0 (-5.0 to 10.0)	6 ([139, 150, 152, 156, 160, 161])	-2.0 (-7.0 to 0.5)	3 ([139, 154, 160])	-6.0 (-8.0 to -1.0)
	General health	5 ([139, 150, 152, 156, 160])	5.0 (2.2 to 20.8)	6 ([139, 150, 152, 156, 160, 161])	1.0 (-9.2 to 7.0)	2 ([139, 159])	NA (-5.0 to -2.0)
	Vitality	7 ([75, 139, 150-152, 156, 160])	4.5 (-2.0 to 13.8)	7 ([75, 139, 150-152, 156, 160, 161])	-3.0 (-5.0 to 7.0)	3 ([139, 154, 160])	-7.0 (-7.0 to -7.0)
	Social function	6 ([139, 150-152, 156, 160])	2.0 (-2.0 to 11.0)	6 ([139, 150-152, 156, 160, 161])	-0.5 (-27.1 to 5.0)	2 ([139, 159])	NA (-10.0 to -4.0)
	Emotional role function	7 ([75, 139, 150-152, 156, 160])	4.7 (-5.0 to 12.8)	7 ([75, 139, 150-152, 156, 160, 161])	-0.4 (-8.0 to 18.2)	3 ([139, 154, 160])	-15.0 (-16.0 to -3.0)
	Mental health	6 ([139, 150-152, 156, 160])	0.0 (-4.0 to 10.1)	6 ([139, 150-152, 156, 160, 161])	0.5 (-6.0 to 1.7)	3 ([139, 154, 160])	-4.0 (-6.0 to 0.0)

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

[†]Differences of 5 to 10 points are generally thought to indicate clinically meaningful changes (Litwin et al, 1998).

Table 27. Study Characteristics, Discrimination, and Calibration of Externally Validated Prostate Cancer Risk Calculators for Significant Prostate Cancer*

Reference	Risk Calculator	Setting and Sample	Discrimination		Calibration	Comments
			AUC With PSA Alone	AUC With Risk Calculator		
Maruf, 2017[78]	PCPT (v2.0)	595 men with no prior prostate cancer diagnosis undergoing fusion-guided and standard biopsy at a single U.S. center; 139 men (23.4%) with significant prostate cancer on standard biopsy	NR	0.71 (predicting significant cancer on standard biopsy)	Underestimated actual risk of significant cancer when estimated risks were 18% to 50%.	High-risk referral cohort with family history of prostate cancer in 29% and prior biopsy in 70%.
Park, 2017[79]	PCPT (v2.0)	2,313 Asian men undergoing biopsy at an academic medical center in South Korea; 614 (26.5%) with significant prostate cancer	NR	0.79 (95% CI, 0.77 to 0.81)	Overestimated actual risk of significant cancer across except when predicted risk was <10%	At a threshold probability of significant cancer for biopsy of 7%, calculator use would avert 19.5% of biopsies but result in missed diagnosis of 6.4% of significant cancers.
Foley, 2016[167]	PCPT (v2.0)	2,001 men undergoing biopsy at 6 Irish tertiary referral centers; 699 men (35%) with significant cancer	NR	0.69 (95% CI, 0.67 to 0.72)	Underestimated actual risk across range of predicted risks	Decision curve analyses suggest that harms of false-positives would outweigh potential benefits in this high-risk referral population.
Poyet, 2016[168]	PCPT (v2.0)	1,996 men undergoing core biopsy in Switzerland academic center; 226 men (11%) with significant prostate cancer	0.65[†]	0.70	Good calibration below 20% pre-biopsy risk; slightly overestimated risk from 20% to 40% risk	Decision curve analysis suggests true-positives would outweigh false-positives in men with a 8% to 40% pre-biopsy risk of significant cancer.
Lundon, 2015[169]	PCPT (v1.0)	556 men undergoing biopsy at single Irish referral centers, 190 (34%) with significant prostate cancer	NR.	0.79	Good calibration for Gleason ≥7 cancers	Decision curve analyses suggest benefits of true-positives would slightly outweigh harms of false-positives for men with intermediate pre-biopsy risk. High prevalence of cancer in this referral population.
Ankerst, 2014[170] Ankerst, 2014[171]	PCPT (v2.0)	Development of PTPC 2.0 (n=6664 biopsies in 5,826 men) 10 external biopsy cohorts from Europe and U.S. (n=25,449 biopsies for AUC; n=25,512 biopsies for calibration)	NR	0.75 (median across 11 cohorts) Range: 0.62-0.88	Calibration mixed (poor in some cohorts, adequate in others)	Mixed results in decision curve analyses. Due to sample sizes, number of cohorts, and cohort diversity, provides broad perspective on calculator performance.

Table 27. Study Characteristics, Discrimination, and Calibration of Externally Validated Prostate Cancer Risk Calculators for Significant Prostate Cancer*

Reference	Risk Calculator	Setting and Sample	Discrimination		Calibration	Comments
			AUC With PSA Alone	AUC With Risk Calculator		
Roobol, 2012[172]	PCPT (v1.0)	ERSPC Rotterdam (n=322 men referred for biopsy during later screening rounds)	0.68 (95% CI: 0.57-0.78)	0.72 (95% CI, 0.61-0.82)	NR	Small sample size. Larger ERSPC biopsy cohorts included in Ankerst, 2014.
Nam, 2011[173]	PCPT (v1.0)	2130 men undergoing biopsy at 5 Canadian centers; 18.9% diagnosed with significant cancer	NR	0.67 (95% CI, 0.64 to 0.70)	Fair-to-good calibration in men with pre-biopsy predicted risk from 5% to 40%	Decision curve analyses suggest benefits of true-positives would outweigh harms of false-positives among men with 15-50% threshold probabilities.
Ngo, 2011[174]	PCPT (v1.0)	636 men undergoing biopsy at single U.S. academic center; 34.9% with significant cancer	NR	0.51	NR	High-risk referral population.
Trottier, 2011[175]	PCPT (v1.0)	982 men undergoing biopsy at single Canadian center; 225 (22.9%) with high-grade disease (defined as Gleason score ≥4)	0.61** (95% CI, 0.47 to 0.76)	0.68**(95% CI, 0.65 to 0.72)	Good calibration across the range of predicted risks.	Definition of high-grade included lower-grade cancers than other studies.
Nguyen, 2010[176]	PCPT (v1.0)	3,482 men undergoing 4,515 biopsies at U.S. academic center; 23.3% with significant cancer	0.56	0.60 (95% CI, 0.58 to 0.62)	Overestimated risk at low predicted risk; underestimated risk at high predicted risk	
Hernandez, 2009[177]	PCPT (v1.0)	1,108 men enrolled in a multicenter trial undergoing biopsy; 14% with significant cancer	0.71	0.74	NR	
Foley, 2016[167]	ERSPC	2,001 Irish men undergoing biopsy at 6 tertiary referral centers; 699 (35%) with significant cancer	NR	0.74† (95% CI, 0.72 to 0.76)	Underestimated actual risk across broad range of pre-test risks	In decision curve analyses, harms of false-positives would outweigh benefits of true-positives in this sample. Used TRUS volume estimates. High-risk referral population.
Gomez-Gomez, 2016[77]	ERSPC	749 men undergoing biopsy at a single Spanish center; 133 (17.8%) with significant cancer	NR	0.74 (95% CI, 0.70 to 0.79)	Acceptable calibration below 25% predicted risk of high-grade cancer	Decision curve analyses suggest benefit of true-positives would outweigh harms of false-positives above a threshold probability of 9% for biopsy.

Table 27. Study Characteristics, Discrimination, and Calibration of Externally Validated Prostate Cancer Risk Calculators for Significant Prostate Cancer*

Reference	Risk Calculator	Setting and Sample	Discrimination AUC With PSA Alone	Discrimination AUC With Risk Calculator	Calibration	Comments
Park, 2017[79]	ERSPC	2,313 Asian men undergoing biopsy at an academic medical center in South Korea; 614 (26.5%) with significant prostate cancer	NR	0.83 (95% CI, 0.81 to 0.85)	Good calibration across range of predicted risks	At a threshold probability of significant cancer for biopsy of 7%, use of the ERSPC calculator would avert 37% of biopsies but result in missed diagnosis of 10.3% of significant cancers.
Poyet, 2016[168]	ERSPC	1,996 men undergoing core biopsy in Switzerland academic center; 226 (11%) with significant prostate cancer	0.65†	0.73†	Underestimated at low calculated risk and over estimated at high calculated risk for Gleason ≥7 cancers	Used TRUS estimated volume rather than DRE. Decision curve analysis suggests benefits of true-positives would outweigh harms of false-positives in men with a 8% to 40% pre-biopsy risk of significant cancer.
Lundon, 2015[169]	ERSPC RC3	556 Irish men undergoing biopsy at single referral center; 190 (34%) with significant prostate cancer	NR	0.69*	Good calibration across entire risk range	Used TRUS estimated prostate volume, rather than DRE. Decision curve analyses suggest benefits of true-positives and harms of false-positives closely balanced. High cancer prevalence in this referral population
Roobol, 2012[172]	ERSPC	ERSPC Rotterdam (n=3,624 for development sample; n=322 for validation sample in later screening rounds)	0.68† (95% CI, 0.57 to 0.78)	0.78† (95% CI, 0.69 to 0.87)	NR	Development and validation samples from same clinical trial population. TRUS volume estimates used in development (rather than DRE).
Trottier, 2011[175]	ERSPC	982 men undergoing biopsy at single Canadian center; 225 (22.9%) with high-grade disease (defined as Gleason ≥4)	0.61 (95% CI, 0.47 to 0.76)	0.78 (95% CI, 0.74 to 0.81)	NR	Definition of high-grade included lower-grade cancers than other studies.

*Significant prostate cancer is defined as Gleason score >7 or stage T2b or higher
†Results given for validation sample

Table 27. Study Characteristics, Discrimination, and Calibration of Externally Validated Prostate Cancer Risk Calculators for Significant Prostate Cancer*

Abbreviations: AUC=area under the curve; ERSPC=European Randomized Study of Screening for Prostate Cancer; NR=not reported; PCPT=Prostate Cancer Prevention Trial; TRUS=transrectal ultrasound

Table 28. Estimates of Benefits and Harms of PSA Screening per 1,000 Men Invited to Screening

Trial	PLCO	ERSPC (Core-Age Group)	Gotebörg, Sweden	Notes
Screening population and strategy	Men aged 55-74 y; screened annually for 6 years; PSA threshold for biopsy recommendation 4.0 ng/mL	Men aged 55-69 y; screened every 4 years (biennially in Sweden); PSA threshold for biopsy referral most commonly 3.0 ng/mL	Men aged 50-64 y; invited biennially up to age 70 y; PSA threshold for biopsy referral 3.0-3.5 ng/mL before 2005 and 2.5 ng/mL from 2005-2008	Data for PLCO and Goteborg derived from reports with 13.0[80] and 14.0[85] y of median followup as more recent reports (with 14.8[90] and 18.0[81] y of median followup, respectively) lack some required data.
Median followup, y	13.0	13.0	14.0	
Outcome	**Number of Men Affected**			**Source/Assumption**
Men invited to screening	1,000	1,000	1,000	
≥1 positive screens	282	243	248	PLCO,[80] ERSPC,[96] and Goteborg[85] trial reports; ERSPC study investigators (personal communication)
≥1 biopsy	130	220	231	
Additional men hospitalized for biopsy complications	1.7	2.9	3.0	ProbE cohort study (1.3% hospitalized due to biopsy complications)[102]
Additional prostate cancers diagnosed due to screening*	11.3	34.8	42.0	Absolute cumulative incidence differences and numbers needed to invite in trial reports
Additional men with erectile dysfunction due to treatment	1.8	6.9	8.3	Men with cancer allocated to primary treatments as in trial screening arms.
Additional men with urinary incontinence after prostatectomy	0.6	1.8	2.5	For treatment harms, number needed to harm from pooled meta-analyses (KQ4)
Men treated with prostatectomy or radiation without benefits during followup period	NC	23.9	25.8	Number computed by subtracting number of men with prostate cancer death or metastasis averted from number of men actively treated
Metastatic cases averted	NR	2.9	3.5	ERSPC core-age group absolute risk reduction in metastatic disease cumulative incidence (and number needed to diagnose)
Prostate cancer deaths averted	0	1.3	3.4	Absolute risk reduction in prostate cancer deaths (and numbers needed to diagnose)

*Based on trial data, 99.5, 68.3, and 72.1 would be diagnosed with prostate cancer among 1,000 men not invited to screening in the PLCO, ERSPC (core-age group), and Goteborg, Sweden settings, respectively.

Abbreviations: PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ERSPC=European Randomized Study of Screening for Prostate Cancer; NR=Not reported; NC=Not calculable; ProbE=Prostate Biopsy Effect cohort study; EPC=Evidence-based Practice Center; KQ4=Key Question 4

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ1									
PSA-based screening vs. no screening among asymptomatic men	Prostate cancer mortality	k=2 RCTs (PLCO and ERSPC) n=239,081 (ages 55 to 74 years in PLCO, ages 55 to 69 in ERSPC core age group)	PLCO RR=1.04 (95% CI, 0.87 to 1.24) at median 14.8 years followup ERSPC RR=0.79 (95% CI, 0.69 to 0.91) at median 13 years followup (core age group) RR=0.83 (95% CI, 0.73 to 0.94) (ages 50 to 74 years) NNI to prevent 1 prostate cancer death=781 (95% CI, 490 to 1929) NND=27 (95% CI, 17 to 66)	Inconsistent; Reasonably precise	Undetected	Fair	PLCO trial limited by contamination in control group. ERSPC PSA thresholds for biopsy were generally lower than in U.S. Among ERSPC enrollees diagnosed with prostate cancer, men randomized to screening were more likely to be treated with RP compared to controls.	Moderate	Applicability of ERSPC results to U.S. practice is uncertain because of the lower thresholds for biopsy and high rate of biopsy after positive screens at the 2 ERSPC sites demonstrating prostate cancer specific-mortality or all-cause mortality reduction.
	All-cause mortality	k=2 RCTs (PLCO and ERSPC) n=239,081 (ages 55 to 74 years in PLCO, ages 55 to 69 in ERSPC core age group)	PLCO RR=0.98 (95% CI, 0.95 to 1.00; p=0.11) at median 14.8 years followup ERSPC RR=1.00 (95% CI, 0.98 to 1.02; p=0.82) (core age group) at median 13 years followup	Reasonably consistent; Imprecise	Undetected	Fair	Trials were underpowered to detect the small differences in all-cause mortality that might be expected with prostate cancer screening.	Low-to-moderate	
	Cumulative incidence of metastatic prostate cancer	k=1 RCT (ERSPC, 4 sites) n=76,813 men ages 55 to 69 years	RR of metastatic cancer in screening arm vs. control= 0.70 (95% CI, 0.60 to 0.82) ARR=3.1 cases of metastatic cancer per 1,000 men randomized	Reasonably precise	Undetected	Fair	Data derived from only 4 of 7 ERSPC trial sites, including the only 2 sites that demonstrated prostate cancer mortality reductions.	Low-to-moderate	PSA thresholds for biopsy were lower (2.5 to 3.0 ng/mL) than in U.S. practice; uncertain whether similar reductions in metastatic disease incidence would be achieved with a

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
									higher PSA threshold for biopsy.
KQ2									
PSA-based screening among asymptomatic men	False-positive PSA tests *(positive PSA test but no cancer diagnosis within 1 year of screening)*	k=2 RCT (PLCO, ERSPC, 5 sites; PLCO) n=130,040 men	PLCO: 10.4% of men with ≥1 PSA screen had ≥1 false-positive screens. The cumulative risk of receiving ≥1 false positives was 5.4% with 1 screening test, 7.9% with 2, 10.4% with 3, and 12.9% with 4 tests. ERSPC 17.8% of screened men had ≥1 false-positive screening tests. 44.9% of screened men in Sweden had ≥1 false-positive screens (biennial screening with 2.5 ng/mL positive threshold)	Reasonably precise	Undetected	Fair	ERSPC sites had variable screening intervals, thresholds for positive tests	Moderate	PLCO results should be generalizable to U.S. practice.
	Biopsy post-positive PSA test	K=3 (2 RCTs, 1 cohort); n=133,969	PLCO 12.6% of men randomized to screening had a prostate biopsy (67.7% were negative for cancer) 4.6% men screened had a moderately-invasive procedure (mostly biopsies) as a result of a false-positive The cumulative risk of receiving ≥1 moderately-invasive procedures as a result of a false-positive	Inconsistent; Reasonably precise	Undetected	Fair	PLCO diagnostic followup was coordinated by community physicians, so biopsy rate after positive screening was lower in PLCO than in ERSPC (44.8% vs. 85.6%).	Moderate	Rate of biopsy after positive PSA in U.S. may be lower than both the PLCO and ERSPC, as many men may undergo monitoring (e.g., repeat PSA measurement) instead of biopsy for initial PSA elevation on screening.

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			increased with each PSA test to 5.5% of screened men with 4 tests. ERSPC 27.7 biopsies per 100 men randomized to screening (75.8% were negative for cancer) VA cohort 2.8% of screened men underwent biopsy due to positive screens. 51.2% had repeat PSA rather than biopsy.						
	Overdiagnosis of screen-detected prostate cancer	k=2 RCTs (PLCO and ERSPC) n=239,081 (ages 55 to 74 years in PLCO, ages 55 to 69 in ERSPC core age group)	PLCO 20.7% of screen-detected cancer overdiagnosed ERSPC 50.4% of screen-detected cancer overdiagnosed	Inconsistent; Reasonably precise	Undetected	Fair	13 year median followup may be too short to observe full catch-up incidence in control arms. Use of PSA screening in control arms would bias estimates toward null.	Low	ERSPC screening protocols used a lower PSA cutoff for biopsy referral than is typical in U.S. practice, which may have increased overdiagnosis.
Men receiving prostate biopsy after a positive PSA test	Biopsy-related symptoms	k=2 (1 RCT, ERSPC, and 1 cohort, U.K. cohort) n=6,823	ERSPC Hematuria 3 days: 22.6% Hematospermia: 50.4% Rectal bleeding: 1.3% Pain after biopsy: 7.5% Fever: 3.5% Nausea/sickness: 0.3% UK Cohort *Symptoms rated as "major/ moderate" within 35 days of biopsy:*	Reasonably precise	Undetected	Good	Men ages 50-69 years and participating in the U.K. ProtecT trial screening phase (ProBE cohort).	Moderate	Likely to be generalizable to asymptomatic men receiving biopsy in the U.S. for abnormal PSA screening.

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			Pain: 7.3% (95% CI, 5.7 to 9.1%) Fever: 5.5% (95% CI, 4.2 to 7.1%) Hematuria: 6.2% (95% CI: 4.7 to 7.9%) Hemejaculate: 26.6% (23.3 to 30.2%)						
	Biopsy-related medical complications	k=2 (1 RCT, 1 cohort) n=13,149	PLCO 20.2 complications per 1000 biopsies (7.8 infectious vs. 13.0 non-infectious) VA cohort 5.6% with infectious or urinary complications within 7 days	Reasonably consistent; reasonably precise	Undetected	Fair	Minor complications not requiring medical may not have been ascertained in either study	Moderate	Likely to be generalizable to U.S. practice
	Biopsy-related health care utilization	k=2 (2 cohorts) n=9,460	U.K. cohort study: 1.3% hospitalized within 35 days (95% CI, 0.8 to 2.1%), 0.6% for sepsis 10.4% sought outpatient care for biopsy-related symptoms (95% CI, 8.7 to 12.3%) VA cohort: 1.6% hospitalized	Reasonably consistent; reasonably precise	Undetected	1 good, 1 fair	Small number of studies based in either U.K. or U.S. VA settings	Moderate	Study samples generally similar to men undergoing biopsy after screening in U.S.
	Biopsy-related mortality	k=2 (1 RCT, 1 cohort) n=5,943	PLCO Mortality vs. men with negative screens (120 days post-biopsy): RR=0.49 (95% CI, 0.2 to 1.1). U.K. cohort: 0% died (95% CI, 0.0% to 0.4%)	Reasonably consistent; imprecise	Undetected	Fair	Sample sizes do not allow adequate power to detect meaningful increase in mortality after biopsy	Low	Study samples generally similar to men undergoing biopsy after screening in U.S.

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
PSA-based screening among asymptomatic men and men receiving a prostate biopsy after a positive PSA test	Psychological harms of PSA screening	k=3 cohorts (U.S., U.K.); n=1,179	Men with abnormal PSA screens have increased prostate-cancer specific worry up to 1 years after screening but no increase in state-anxiety or depression	Consistent, somewhat imprecise	Undetected	Fair	Small study samples	Moderate	Results should apply to U.S. practice
	Adverse effects of screening on health-related quality of life	k=1 RCT (Finnish ERSPC; men randomized to screening [n, range: 215-386 for each screening event]); 1 U.S. cohort (n=210)	Compared to measures invitation to participate in RCT, median scores were similar after later screening events for all domains of the SF-36. No evidence of adverse impact of abnormal screening on mental or physical health status in U.S. cohort.	Imprecise, consistent	Undetected	Fair	Small sample sizes limited power.	Moderate	Finnish RCT population may not generalize to U.S. practice
KQ3									
RP vs. CM among men with early-stage or screen-detected cancer	Prostate cancer mortality	k=7 (3 RCTs, 4 cohorts); n=17,375	ProtecT HR=0.63 (95% CI, 0.21 to 1.93) at 10 years median followup PIVOT HR=0.63 (95% CI, 0.39 to1.02; p=0.06) at 12.7 years median followup SPCG-4 RR=0.56 (95% CI, 0.41 to 0.77; p=0.001) at 13.4 years median followup Cohorts RP was associated with statistically significantly reduced prostate cancer mortality (median HR, 0.36	Reasonably consistent, imprecise	Undetected	Fair	Only the ProtecT trial randomized exclusively men with screen-detected prostate cancer. Low event rate in this trial led to imprecise estimates with regard to prostate cancer mortality. Active surveillance protocol consisted chiefly of PSA monitoring.	Low	Active surveillance protocols in many U.S. settings include routine rebiopsy, physical exam, and selected use of imaging. ProtecT results may not generalize to U.S. practice or to men with low-risk cancers who are managed with surveillance.

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			[range, 0.25 to 0.59]) compared to CM						
	All-cause mortality	k=11 (3 RCTs, 8 cohorts); n=103,516	ProtecT HR=0.93 (95% CI, 0.65 to 1.35) at 10 years median followup PIVOT HR=0.84 (95% CI, 0.70 to 1.01; p=0.06) at 12.7 years median followup SPCG-4 RR=0.71 (95% CI, 0.59 to 0.86; p<0.001) at 13.4 years median followup Cohorts RP was associated with statistically significantly decreased risk for all-cause mortality in 5 of 7 studies (median adjusted HR, 0.44 [range, 0.32 to 0.50]) and no significant difference in all-cause mortality in 2 cohort studies.	Reasonably consistent, imprecise	Undetected	Fair	ProtecT not adequately powered to detect differences in all-cause mortality	Low	
	Progression to metastatic disease	k=3 (3 RCTs, 0 cohorts); n=3,069	ProtecT Absolute incidence with RP 2.4 (95% CI, 1.4 to 4.2) per 1,000 person-years vs. 6.3 (95% CI, 4.5 to 8.8) with CM at 10 years median followup PIVOT HR=0.64 (95% CI, 0.42 to 0.97) at 12.7 years median followup SPCG-4	Reasonably consistent, Reasonably precise	Undetected	Good	See above regarding active surveillance protocol in ProtecT trial. PIVOT and SPCG-4 included men with clinically detected rather than screen-detected prostate cancer.	Moderate	

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			RR=0.57 (95% CI, 0.44 to 0.75; p<0.001) at 13.4 years median followup						
RT vs. CM among men with early-stage or screen-detected cancer	Prostate cancer mortality	k=5 (1 RCT, 4 cohorts); n=15,024	ProtecT HR=0.51 (95% CI, 0.15 to 1.69) at 10 years median followup Cohorts RT was not associated with a statistically significant reduction in 2 studies, while brachytherapy was associated with statistically significantly reduced prostate cancer-specific mortality in the third (HR, 0.45 [95% CI, 0.23 to 0.87]).	Inconsistent, imprecise	Undetected	Fair	Single trial with limited power and few cohort studies assessing this outcome	Low	
	All-cause mortality	k=8 (1 RCT, 7 cohorts); n=101,165	ProtecT HR=0.94 (95% CI, 0.65 to 1.36) Cohorts RT was associated with a statistically significant reduction in all-cause mortality in 4 studies (median HR, 0.62 [range, 0.40 to 0.81]), but no statistically significant difference in 3.	Inconsistent, imprecise	Undetected	Fair	ProtecT was not adequately powered to detect meaningful differences in all-cause mortality	Low	
	Progression to metastatic disease	k=1 (1 RCT) n=1,643	ProtecT Absolute incidence with RT 3.0 (95% CI, 1.9 to 4.9) per 1000 py vs. 6.3 (95% CI, 4.5 to 8.8) with CM at 10 years median followup	Consistency NA reasonably precise	Undetected	Fair	Only 1 study assessed morbidity, therefore the results may not be generalizable	Low-to-moderate	

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
ADT vs. CM among men with early-stage or screen-detected cancer	Prostate cancer mortality	k=2 (2 cohorts); n=70,033	In an instrumental variable analysis, ADT was not associated with any difference in prostate cancer-specific mortality (adjusted HR, 1.01 [95% CI, 0.90 to 1.14]). Results from other cohorts mixed.	Inconsistent, imprecise	Undetected	Fair	Few studies, all with cohort design. Potential confounding by indication in cohort studies of treatment efficacy.	Low	Potential bias in study estimates may limit applicability to U.S. clinical populations.
	All-cause mortality	k=3 (3 cohorts); n=74,333	In an instrumental variable analysis, ADT was not associated with any difference in all-cause mortality (adjusted HR, 1.04 [95% CI, 0.99 to 1.09]). Results from other cohorts were mixed.	Inconsistent, imprecise	Undetected	Fair	As above	Low	
	Morbidity	k=0	NA	NA	NA	NA	Lack of evidence	Insufficient	Unknown
Cryotherapy vs. CM among men with early-stage or screen-detected cancer	Prostate cancer mortality, all-cause mortality, or morbidity	k=0	NA	NA	NA	NA	Lack of evidence	Insufficient	Unknown
HIFU vs. CM among men with early-stage or screen-detected cancer	Prostate cancer mortality, all-cause mortality, or morbidity	k=0	NA	NA	NA	NA	Lack of evidence	Insufficient	Unknown

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ4									
RP vs. CM among men with early-stage or screen-detected cancer	Urinary incontinence	k=9 (3 RCTs, 6 cohorts) n=7,529	Pooled RR in the RCTs=2.3 (95% CI, 1.8 to 2.8; I^2=0.0%) Pooled RR in the cohorts= 2.8 (95% CI, 1.8 to 4.2; I^2=63.0%)	Reasonably consistent; Reasonably precise	Undetected	5 good; 4 fair	Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection. Approximately half of men in ProtecT who were randomized to CM received RP by the end of the trial.	Moderate	Likely to be generalizable to U.S. practice
	Erectile dysfunction	k=10 (3 RCTs, 7 cohorts) n=8,012	Pooled RR in 2 of the RCTs=1.8 (95% CI, 1.6 to 2.0; I^2=0.0%) Pooled RR in the cohorts= 1.5 (95% CI, 1.3 to 1.9; I^2=59.2%)	Reasonably consistent; Reasonably precise	Undetected	5 good; 5 fair	Excluded ProtecT trial from meta-analysis because it introduced large heterogeneity (I^2=97.4%). Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection.	Moderate	
	Bowel function	k=8 (3 RCTs, 5 cohorts) n=7,458	RCTs found high fecal incontinence in men undergoing CM (2.6% to 5.7%) vs. RP (0.6% to 1.9%); results from cohort studies were inconsistent	Inconsistent; Imprecise	Undetected	5 good; 3 fair	Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection. Approximately half of men in ProtecT who were randomized to CM received RP	Low	

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
							by the end of the trial.		
	Surgical complications	k=8 (2 RCTs, 6 uncontrolled observational); n=150,001	30-day perioperative mortality ranged from 0.0% to 0.52% (4 studies). Common complications included thromboembolic/ cardiovascular events (0.4% to 9.0%) and reintervention (1.7% to 5.3%)	*Perioperative mortality:* reasonably consistent; Reasonably precise *Complications* Reasonably consistent; Imprecise	Undetected	2 good; 6 fair	Trials did not present data on mortality or complications among men randomized to CM; uncontrolled observational studies included large sample sizes of men receiving RP but no comparison group	Moderate	
RT vs. CM among men with early-stage or screen-detected cancer	Urinary incontinence	k=8 (2 RCTs, 6 cohorts) n=3,748	RR (range): 0.4 to 8.31. Estimates not pooled due to high variability in outcome across studies	Inconsistent; Imprecise	Undetected	3 good; 5 fair	Wide variation in risk of urinary incontinence; larger RCT favored RT and smaller RCT favored CM, while cohorts showed no significant differences. Approximately half of men in ProtecT who were randomized to CM received RT by the end of the trial. Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection.	Low	Likely to be generalizable to U.S. practice

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
	Erectile dysfunction	k=9 (1 RCT, 8 cohorts) n=4,165	Only one RCT (RR=0.9 [95% CI, 0.8 to 1.1]). Pooled RR in the cohorts= 1.3 (95% CI, 1.2 to 1.4; I^2=0.0%)	Reasonably consistent (cohorts); Relatively precise	Undetected	3 good; 6 fair	Approximately half of men in ProtecT who were randomized to CM received RT by the end of the trial. Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection.	Moderate	
	Bowel function	k=7(2 RCTs, 5 cohorts); n=3,677	Trials and cohorts found that fecal incontinence or rectal urgency was more common among men receiving RT (3.2% to 16.7%) than CM (0.2% to 4.8%)	Relatively consistent; Relatively precise	Undetected	3 good; 4 fair	Approximately half of men in ProtecT who were randomized to CM received RT by the end of the trial. Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection.	Moderate	
ADT vs. CM among men with early-stage or screen-detected cancer	Urinary incontinence	k=2 (2 cohorts); n=670	Studies found no significant difference in men receiving ADT vs. CM	Relatively consistent; Imprecise	Undetected	Fair	Small number of studies with small sample size. Studies used varying outcome definitions and inconsistent timing or cross-sectional data collection.	Low	Likely to be generalizable to U.S. practice
	Erectile dysfunction	k=3 (3 cohorts); n=1,331	RR (range): 1.6 to 2.9	Relatively consistent; Relatively precise	Undetected	Fair		Moderate	
	Bowel function	k=2 (2 cohorts); n=670	More men receiving ADT reported bowel problems, but no assessment of statistical significance	Relatively consistent; Imprecise	Undetected	Fair		Low	

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
Cryotherapy vs. CM among men with early-stage or screen-detected cancer	Urinary incontinence, erectile dysfunction, bowel function	k=0	No studies reported this outcomes	NA	NA	NA	Lack of evidence	Insufficient	Unknown
HIFU vs. CM among men with early-stage or screen-detected cancer	Urinary incontinence	k=7 (7 uncontrolled observational) n=2,239	Range of grade 2 urinary incontinence (leaking with mild activity, such as walking or standing up) or worse: 0.0% to 7.3% after 23 months to 6.4 years post-treatment	Relatively consistent; imprecise	Undetected	Fair	No studies comparing HIFU with CM; only 1 study had a sample size exceeding 1,000 men	Low	Likely to be generalizable to U.S. practice
	Erectile dysfunction	k=5 (5 uncontrolled observational) n=1,046	Among potent men pre-treatment (k=3), 37.3% to 52.7% had erectile dysfunction after 6 months to 4.8 years post-treatment	Relatively consistent; imprecise	Undetected	Fair	Not all studies reported pre-treatment potency so unable to ascertain impact of ADT treatment	Low	
	Bowel function	k=0	No studies reported this outcomes	NA	NA	NA	Lack of evidence	Insufficient	Unknown
KQ5									
Use of pre-biopsy risk calculator in combination with PSA vs. PSA alone to predict high-grade prostate cancer (i.e., Gleason ≥7 and/or stage T2b)	Discrimination	k=14 (evaluating calculators in 21 total cohorts) n=48,234 biopsies in North America, Europe, or South Korea All articles evaluated either the	Median AUC with PCPT calculator=0.72 (range, 0.51 to 0.88 across 21 cohorts) Median AUC with ERSPC calculator=0.74 (range, 0.69 to 0.78 across 7 cohorts) Median AUC with PSA alone=0.68 (range, 0.59 to 0.82 across 16 cohorts)	Inconsistent; reasonably precise	Undetected	Fair	Many biopsy cohorts consisted largely of symptomatic men rather than men undergoing biopsy after abnormal screening PSA. ERSPC calculator derived with ultrasound-derived prostate volume measure.	Low	Since most biopsy cohorts included many symptomatic men, results may not generalize to men referred for biopsy after abnormal PSA screening. It is unclear whether risk information from calculators can be accurately communicated to patients in actual
	Calibration		Mixed for each calculator with acceptable calibration in some cohorts but under- or overestimation in others						

Table 29. Summary of Evidence: Main Findings

Intervention or Population	Outcome	No. of Studies (k), No. of Observations (n)	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
	Clinical utility	PCPT calculator (k=14) or the ERSPC calculator (k=7)	Decision curve analyses (k=14 for PCPT, k=4 for ERSPC) were mixed with net clinical harm found with calculator use in 2 cohorts for PCPT and 1 cohort for ERSPC calculator						practice and whether such information would modify decisions or long-term outcomes.

*Results for subgroups are not included, as there was limited data available across all KQs. For information about screening and treatment impacts on subgroups, please refer to the Results section of the report or Tables 7, 8, 16, 18 and 20.

Abbreviations: ADT=androgen deprivation therapy; ARR=absolute risk reduction; CM=conservative management; ERSPC=European Randomized Study of Screening for Prostate Cancer; HIFU=high-intensity focused ultrasound; HR=hazard ratio; NND=number needed to diagnose; NNI=number needed to invite; PLCO=Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ProBE=Prostate Biopsy Effects study; RP=radical prostatectomy; RR=relative risk; RT=radiation therapy

Appendix A. Detailed Methods

Literature Search Strategy

Cochrane

#1   MeSH descriptor: [Mass Screening] explode all trees
#2   screening
#3   MeSH descriptor: [Prostatic Neoplasms] explode all trees
#4   prostate
#5   (#1 or #2) and #4
#6   MeSH descriptor: [Early Detection of Cancer] explode all trees
#7   MeSH descriptor: [Early Diagnosis] explode all trees
#8   early stage
#9   #6 or #7 or #8
#10   #5 and #9
#11   MeSH descriptor: [Prostate-Specific Antigen] explode all trees
#12   #10 and #11 Publication Year from 2011 to 2016

Ovid MEDLINE

1   exp "Prostatic Neoplasms"/ or prostate cancer.ti. or prostatic neoplasm*.ti. (115794)
2   "Risk Assessment"/ (209015)
3   "Survival Analysis"/ (113137)
4   "Treatment Outcome"/ (764101)
5   screening.mp. or Mass Screening/ (467821)
6   "Prostate-Specific Antigen"/ or PSA.mp. or prostate specific antigen.mp. (41541)
7   early diagnosis/ or early stage.mp. (89074)
8   "Watchful Waiting"/ or watchful waiting.ti,ab. (3945)
9   2 or 3 or 4 or 8 (1002677)
10   6 or 7 (129868)
11   1 and 9 and 10 (5667)
12   limit 11 to (yr="2007 -Current" and english) (3355)
13   exp "sensitivity and specificity"/ (489386)
14   (sensitivity or specificity).tw. (851972)
15   ((pre-test or pretest) adj probability).tw. (1699)
16   ((post-test or post test) adj probability).tw. (450)
17   likelihood ratio*.tw. (11693)
18   test performance.mp. (6762)
19   "predictive value of tests"/ or negative predictive value.mp. or positive predictive value.mp. (193939)
20   diagnostic accuracy.mp. (31481)
21   pca 3.mp. (86)
22   dd3.mp. (99)
23   4k score.mp. (1)
24   prostate health index.mp. (133)
25   four-kallikrein panel.mp. (9)
26   kallikreins/ (8482)

27   "early detection of cancer".mp. or "Early Detection of Cancer"/ (15663)
28   "Kallikreins"/ and ("Prostate-Specific Antigen"/ or ("Tumor Markers, Biological"/ and prostat*.mp.)) [mp=title,
abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary
concept word, rare disease supplementary concept word, unique identifier] (873)
29   or/13-20,27 (1227873)
30   prostate cancer gene 3.mp. (76)
31   or/21-26,28,30 (8848)
32   29 and 31 (902)
33   limit 32 to (yr="2007 -Current" and english) (468)
34   12 or 33 (3753)
35   Minority Groups/ (11981)
36   ethnology.fs. (141458)
37   exp Continental Population Groups/ (188428)
38   35 or 36 or 37 (279407)
39   risk.mp. or exp Risk/ (2010071)
40   1 and 38 and 39 (1447)
41   limit 40 to (english language and yr="2007 -Current") (888)
42   34 or 41 (4570)
43   treatment outcome.mp. or exp Treatment Outcome/ (801440)
44   prognosis/ or disease-free survival/ or prognos*.ti. or disease free.tw. (503696)
45   43 or 44 (1232919)
46   1 and 7 and 45 (351)
47   limit 46 to (english language and yr="2007 -Current") (156)
48   42 or 47 (4630)
49   (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (319580)
50   side effect$.ti,ab. (204402)
51   (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (1111)
52   (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (175)
53   (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (4963)
54   (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (5142)
55   (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (6613)
56   Harm Reduction/ (2016)
57   (ae or co).fs. (3083573)
58   or/48-57 (3392846)
59   1 and (5 or 6) and 58 (7541)
60   27 and 59 (411)
61   limit 60 to (english language and yr="2007 -Current") (397)
62   48 or 61 (4710)

63   remove duplicates from 62 (4459)
64   limit 63 to (english language and yr="2011 -Current") (2859)
65   from 64 keep 1-2492 (2492)
66   quality of life.mp. or "Quality of Life"/ (252030)
67   6 and 7 and 66 (60)
68   limit 67 to (english language and yr="2011 -Current") (22)
69   1 and 68 (15)
70   69 not 65 (9)
71   "Patient Acceptance of Health Care"/ (36136)
72   exp Attitude to Health/ (343442)
73   1 and (5 or 6) and (71 or 72) (996)
74   (7 or 27) and 73 (244)
75   limit 74 to (english language and yr="2011 -Current") (173)
76   75 not 65 (117)
77   remove duplicates from 76 (108)
78   limit 77 to (english language and yr="2011 -Current") (108)
79   70 or 78 (116)
80   remove duplicates from 79 (116)
81   limit 80 to ed=20160201-20161005 (22)

Embase

#16 OR #19
#19
'prostate'/exp OR prostate AND ('cancer'/exp OR cancer) AND ('screening'/exp OR screening) AND ('prostate specific antigen'/exp/dd_ct AND [humans]/lim OR (prostate AND specific AND antigen:ti) OR psa:ti) AND ('risk benefit analysis'/exp OR 'risk' OR 'risk reduction'/exp OR 'attributable risk'/exp OR 'low risk patient'/exp OR 'risk management'/exp OR 'genetic risk'/exp) AND [english]/lim AND [1-2-2016]/sd
#16
'prostate specific antigen'/exp/dd_ct AND [humans]/lim OR (prostate AND specific AND antigen:ti) OR psa:ti AND ('sensitivity and specificity'/exp OR 'sensitivity and specificity') AND ('health care quality'/exp OR 'health care quality') NOT ('psoriatic arthritis'/exp OR 'psoriatic arthritis') OR ('prostate'/exp OR prostate AND ('cancer'/exp OR cancer) AND ('screening'/exp OR screening) AND ('sensitivity and specificity'/exp OR 'sensitivity and specificity')) AND [english]/lim AND ('early diagnosis'/exp OR 'cancer classification'/exp) AND [1-2-2016]/sd

Web of Science

14
469
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011) AND DOCUMENT TYPES: (ARTICLE OR REVIEW) AND LANGUAGES: (ENGLISH)

Appendix A. Detailed Methods

Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years

13

483

For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial

Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011) AND DOCUMENT TYPES: (ARTICLE OR REVIEW)

Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years

12

580

For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial

Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011)

Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years

11

715

For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial

Refined by: TOPIC: (prostate)

Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years

10

7,537

For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial

9

424

#8 AND #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

8

591,381

TOPIC: (effectiveness)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

7

22

#6 AND #5

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

6

1,033

Appendix A. Detailed Methods

TOPIC: (risk) AND TOPIC: (calculator*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 5
1,384
#4 AND #3
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 4
368,489
TOPIC: (early stage) OR TOPIC: (screen detected)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 3
4,282
#2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 2
27,989
TOPIC: (prostate cancer antigen)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 1
11,025
TOPIC: (prostate cancer) AND TOPIC: (screening)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Appendix A Figure 1. Literature Flow Diagram

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Population	**KQs 1, 2, 5:** Asymptomatic men* **KQs 3, 4:** Men with screen-detected or early-stage prostate cancer (defined as stage I or II)	**KQs 1, 2, 5:** Symptomatic men **KQs 3, 4:** Men with later-stage prostate cancer†; men with refractory, hormone refractory, or recurrent prostate cancer
Setting	Primary care or specialty care settings in countries categorized as "Very High" on the Human Development Index (as defined by the United Nations Development Programme)	Countries not categorized as "Very High" on the Human Development Index
Interventions	**KQs 1, 2:** PSA-based screening (single-threshold PSA test, age-specific thresholds, velocity, doubling time, variable screening intervals) **KQs 3, 4:** • Surgery (radical prostatectomy, including different surgical techniques, such as nerve sparing, robotics) • Cryosurgery • Hormone therapy (androgen deprivation therapy via luteinizing hormone-releasing hormone agonists, antiandrogen therapy, and/or orchiectomy) • Ultrasonography (high-intensity focused ultrasonography) • Radiation therapy (external-beam radiation therapy, proton beam therapy, brachytherapy) • Ablative therapy • Watchful waiting • Active surveillance **KQ 5:** Risk prediction models to predict clinically important prostate cancer	**KQs 1, 2:** Non–PSA-based methods of screening for prostate cancer, performed alone (e.g., digital rectal examination) **KQs 3, 4:** Chemotherapy (typically used for the treatment of later-stage cancer) **KQ 5:** Risk prediction models for any prostate cancer
Comparisons	**KQs 1, 2:** Usual care; no screening **KQs 3, 4:** No treatment **KQ 5:** PSA-based screening only, usual care	
Outcomes	**KQ 1:** Prostate cancer mortality; all-cause mortality; prostate cancer–specific morbidity (i.e., bone pain from metastases, urinary obstruction); incidence of advanced-stage cancer **KQ 2:** False positives; physical harms of screening or biopsy; psychological harms; overdiagnosis **KQs 3, 4:** Mortality (overall and disease-specific); quality of life (overall and disease-specific); functioning (overall and disease-specific); bowel, urinary, and sexual dysfunction; psychological effects (e.g., mental status, depression, cognitive dysfunction); endocrinological effects (e.g., bone health, hot flashes, gynecomastia); surgical complications **KQ 5:** Test performance (area under the curve, sensitivity, specificity); detection of clinically significant or high-grade prostate cancer; positive predictive value of biopsy	
Duration	**KQ 1:** Long-term prostate cancer mortality, long-term all-cause mortality **KQs 3, 4:** 30 days for perioperative complications; >12 months for other harms	

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Study designs	**KQ 1:** Randomized, controlled trials; systematic reviews (of included study designs); meta-analyses **KQs 2–5:** Randomized, controlled trials; cohort studies; uncontrolled observational studies of harms‡	Other study designs
Study quality	Good- and fair-quality studies	Poor-quality studies
Language	English	Non-English
Timeframe	**KQs 1–4:** January 1, 2011 to present§ **KQ 5:** January 2006 to present	**KQs 1–4:** Published before January 1, 2011 **KQ 5:** Published before January 2006

*We will consider asymptomatic men as those without symptoms that are highly suspicious for prostate cancer. Many older men have chronic, stable lower urinary tract symptoms (e.g., due to benign prostate hyperplasia) that are not generally associated with an increased risk for prostate cancer (1).

†Treatments for men with later-stage prostate cancer (stages III or IV) differ from those for men with early-stage prostate cancer (stages I or II); large, population-based PSA-based screening studies have primarily detected early-stage cancer (90% to 96% of cancers detected) (2, 3).

‡Sample size of at least 1,000; smaller samples sizes are to be included only if randomized, controlled trials, cohort studies, and larger uncontrolled studies are not available.

§Although the review's search dates for trials of prostate cancer screening effectiveness will cover 2011 through the present, the USPSTF will consider evidence from older trials included in prior systematic reviews. That is, the evidence review will primarily search for new studies or updates of previous trials but the USPSTF, in making its recommendation, will consider the totality of evidence available, not just studies published since 2011.

Appendix A Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[48]	Was there valid random assignment? Was allocation concealed? Was eligibility criteria specified? Were groups similar at baseline? Was a difference in attrition between the groups after randomization not present? Were outcome assessors blinded? Were measurements equal, valid and reliable? Was the risk of contamination very low or not present? Was there adequate adherence to the intervention? Were statistical methods acceptable? Was the handling of missing data appropriate?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottowa Scale and the NICE methodology checklists [61, 62]	Was there representativeness of the exposed cohort? Was the non-exposed cohort systematically selected? Was the ascertainment of exposure reported? Was eligibility criteria specified? Were groups similar at baseline? Was the outcome of interest not present at baseline? Were measurements equal, valid, and reliable? Were outcome assessors blinded? Was followup long enough for the outcome to occur? Was there acceptable followup? Was there adjustment for confounders?
Assessment of Multiple Systematic Reviews (AMSTAR)[219]	Was an 'a priori' design provided? Was there dual study selection? Was there dual data extraction? Was a comprehensive literature search performed? Was a list of studies included provided? Was a list of studies excluded provided? Were the characteristics of the included studies provided? Was the scientific quality of the included studies assessed and documented? Was the scientific quality of the included studies used appropriately in formulating conclusions? Were the methods used to combine the findings of the studies (i.e., pooled results) appropriate? Was the likelihood of publication bias assessed? Were potential conflicts of interest/source(s) of support of the systematic review stated? Were potential conflicts of interest/source(s) of support of the included studies stated?

Appendix B. Excluded Studies

Reason for Exclusion
E1. Study relevance
E2. Setting   a. Non-HDI country

E3. Intervention
    a. Screening study of DRE alone
    b. Treatment study of chemotherapy

E4. Comparator

E5. Population
    a. Screening studies in men with elevated PSA or who have undergone prostate biopsy, or other high risk
       screening populations
    b. Treatment studies with more than 10% of men having later-stage (stage III-IV) prostate cancer

E6. Outcomes   a. No additional relevant data (primary article is included) or duplicate data

E7. Study design
    a. Uncontrolled observational study of radical prostatectomy, radiation therapy, or androgen deprivation therapy
       with sample size of 1,000 men or less
    b. Uncontrolled observational study of high-intensity focused ultrasound with sample size of 100 men or less

E8. Non-English
E9. Poor quality
E10. Unable to locate article

1. PSA-based screening for prostate cancer. Too many adverse effects. Prescrire Int. 2012;21(130):215-7. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**

2. Ahmad S, O'Kelly F, Manecksha RP, et al. Survival after incidental prostate cancer diagnosis at transurethral resection of prostate: 10-year outcomes. Irish Journal of Medical Science. 2012;181(1):27-31. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

3. Aizer AA, Chen MH, Hattangadi J, D'Amico AV. Initial management of prostate-specific antigen-detected, low-risk prostate cancer and the risk of death from prostate cancer. BJU International. 2014;113(1):43-50. **KQ1E1, KQ2E1, KQ3E9, KQ4E6, KQ5E1**

4. Alicikus ZA, Yamada Y, Zhang Z, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer. 2011;117(7):1429-37. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

5. Ankerst DP, Boeck A, Freedland SJ, et al. Evaluating the PCPT risk calculator in ten international biopsy cohorts: Results from the Prostate Biopsy Collaborative Group. World Journal of Urology. 2012;30(2):181-7. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6a**

6. Ankerst DP, Boeck A, Thompson IM, et al. Internationalmulti-validation of the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC): Results from the Prostate Biopsy Collaborative Group (PBCG). Tumor Biology. 2011;32:S42. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

7. Ankerst DP, Till C, Boeck A, et al. The impact of prostate volume, number of biopsy cores and American Urological Association symptom score on the sensitivity of cancer detection using the Prostate Cancer Prevention Trial risk calculator. Journal of Urology. 2013;190(1):70-6. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

8. Auprich M, Augustin H, Budaus L, et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. BJU International. 2012;109(11):1627-35. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

9. Auprich M, Bjartell A, Chun FK, et al. Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. European Urology. 2011;60(5):1045-54. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E7, X9**

10. Auvinen A, Moss S, Tammela TL, et al. Absolute Effect of Prostate Cancer Screening: Balance of benefits and harms by center within the European Randomized Study of Prostate Cancer Screening. Clin Cancer Res. 2015. **KQ1E6a, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

11. Axén E, Hugosson J, Khatami A, Lodding P, Stranne J. PSA doubling time predicts outcome after active surveillance in screening detected prostate cancer. European Urology, Supplements. 2011;10(2):236. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

12. Azevedo N, Roobol MJ. The Rotterdam prostate cancer risk calculator: improved prediction with more relevant pre-biopsy information, now in the palm of your hand. European Urology, Supplements. 2014;13(5):110-1. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

13. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study.[Erratum appears in Eur Urol. 2015 Jun;67(6):e126; PMID: 25944041]. European Urology. 2014;66(3):489-99. **KQ1E7, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

Appendix B. Excluded Studies

14. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. European Urology. 2013;63(4):618-22. **KQ1E1, KQ2E1, KQ3E5, KQ4E6, KQ5E1**

15. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med. 2002;346(15):1138-44. **KQ1E1, KQ2E1, KQ3E7, KQ4E5b, KQ5E1**

16. Birkhahn M, Penson DF, Cai J, et al. Long-term outcome in patients with a Gleason score <6 prostate cancer treated by radical prostatectomy. BJU International. 2011;108(5):660-4. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**

17. Blanker MH, Noordzij MA. [Prostate cancer screening benefit very low, even after 13 years]. Ned Tijdschr Geneeskd. 2014;158:A8349. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8, X10**

18. Bokhorst LP, Kranse R, Venderbos LD, et al. Differences in treatment and outcome after treatment with curative intent in the screening and control arms of the ERSPC Rotterdam. Eur Urol. 2015;68(2):179-82. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

19. Bokhorst LP, Zappa M, Carlsson SV, et al. Correlation between stage shift and differences in mortality in the European Randomised study of Screening for Prostate Cancer (ERSPC). BJU Int. 2016;118(5):677-80. **KQ1E5, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

20. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. 2005;366(9485):572-8. **KQ1E1, KQ2E1, KQ3E5b, KQ4E5b, KQ5E1**

21. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012;380(9858):2018-27. **KQ1E1, KQ2E1, KQ3E5b, KQ4E5b, KQ5E1**

22. Bollito E, De Luca S, Cicilano M, et al. Prostate cancer gene 3 urine assay cutoff in diagnosis of prostate cancer: a validation study on an Italian patient population undergoing first and repeat biopsy. Analytical & Quantitative Cytology & Histology. 2012;34(2):96-104. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

23. Bul M, van den Bergh RC, Zhu X, et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. BJU International. 2012;110(11):1672-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**

24. Bul M, Van Leeuwen PJ, Zhu X, Schröder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival of men with initial prostate-specific antigen less than 3.0 ng/ml who are participating in ERSPC Rotterdam. European Urology. 2011;59(4):498-505. **KQ1E5, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

25. Bul M, Van Leeuwen PJ, Zhu X, Schröder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival in men participating in the ERSPC with an initial PSA less than 3.0 ng/mL. Journal of Clinical Oncology. 2011;29(7). **KQ1E5, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

26. Bul M, Zhu X, Rannikko A, et al. Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. European Urology. 2012;62(2):195-200. **KQ1E1, KQ2E1, KQ3E6, KQ4E7, KQ5E1**

27. Busch J, Magheli A, Leva N, et al. Higher rates of upgrading and upstaging in older patients undergoing radical prostatectomy and qualifying for active surveillance. BJU International. 2014;114(4):517-21. **KQ1E1, KQ2E1, KQ3E5, KQ4E6, KQ5E1, X8**

28. Byar DP, Corle DK. VACURG randomised trial of radical prostatectomy for stages I and II prostatic cancer. Veterans Administration Cooperative Urological Research Group. Urology. 1981;17(4 Suppl):7-11. **KQ1E10, KQ2E10, KQ3E10, KQ4E10, KQ5E10**

29. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ. 2014;348:g2296. **KQ1E7, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X15**

30. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood levels of prostate-specific antigen at age 60 on the benefits and harms of prostate cancer screening. Journal of Urology. 2014;191(4):e818. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

31. Carlsson S, Aus G, Bergdahl S, et al. The excess burden of side-effects from treatment in men allocated to screening for prostate cancer. The Goteborg randomised population-based prostate cancer screening trial. European Journal of Cancer. 2011;47(4):545-53. **KQ1E1, KQ2E1, KQ3E6, KQ4E7, KQ5E1**

32. Carlsson S, Maschino A, Schroder F, et al. Predictive value of four kallikrein markers for pathologically insignificant compared with aggressive prostate cancer in radical prostatectomy specimens: results from the European Randomized Study of Screening for Prostate Cancer section Rotterdam. European Urology. 2013;64(5):693-9. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E5, X10**

33. Chamie K, Williams SB, Hershman DL, Wright JD, Nguyen PL, Hu JC. Population-based assessment of determining predictors for quality of prostate cancer surveillance. Cancer. 2015;121(23):4150-7. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1, X3**

34. Chang P, Regan MM, Ferrer M, et al. Relief of urinary symptom burden after primary prostate cancer treatment. J Urol. 2017;197(2):376-84. **KQ1E1, KQ2E1, KQ3E6, KQ4E4, KQ5E1**

35. Chen H, Sun J, Ankerst D, et al. Added value of genetic risk score to the prostate cancer prevention trial (PCPT) risk calculator: findings from the PCPT study. Journal of Urology. 2014;191(4):e818-e9. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7, X9**

Appendix B. Excluded Studies

36. Chen WC, Tokita KM, Ravera J, et al. Four-year outcomes of hypofractionated high-dose-rate prostate brachytherapy and external beam radiotherapy. Brachytherapy. 2013;12(5):422-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

37. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol. 2002;167(4):1664-9. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**

38. Choo R, Long J, Gray R, Morton G, Gardner S, Danjoux C. Prospective survey of sexual function among patients with clinically localized prostate cancer referred for definitive radiotherapy and the impact of radiotherapy on sexual function. Support Care Cancer. 2010;18(6):715-22. **KQ1E1, KQ2E1, KQ3E6, KQ4E5, KQ5E1**

39. Chua M, Tanseco P, Mendoza J, Castillo J, Morales Jr M, Luna Jr S. Configuration and validation of a novel prostate disease nomogram predicting prostate biopsy outcome: a prospective study correlating clinical indicators among filipino adult males with elevated psa level. Journal of Urology. 2015;193(4):e740. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

40. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. Med Care. 2001;39(10):1118-30. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

41. Cordeiro ER, Cathelineau X, Thuroff S, Marberger M, Crouzet S, de la Rosette JJ. High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer. BJU Int. 2012;110(9):1228-42. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

42. Crawford ED, Grubb R 3rd, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. Journal of Clinical Oncology. 2011;29(4):355-61. **KQ1E6a, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X3**

43. Crawford ED, Rove KO, Trabulsi EJ, et al. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases. Journal of Urology. 2012;188(5):1726-31. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

44. Dahabreh IJ, Chung M, Balk EM, et al. Active surveillance in men with localized prostate cancer: a systematic review. Annals of Internal Medicine. 2012;156(8):582-90. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

45. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. European Urology. 2012;62(6):976-83. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

46. Daskivich TJ, Lai J, Dick AW, et al. Comparative effectiveness of aggressive versus nonaggressive treatment among men with early-stage prostate cancer and differing comorbid disease burdens at diagnosis. Cancer. 2014;120(16):2432-9. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

47. Dell'Oglio P, Stabile A, Gandaglia G, et al. Inclusion of mpMRI into the european randomized study of screening for prostate cancer (ERSPC) risk calculator: a new proposal to improve the accuracy of prostate cancer detection. Journal of Urology. 2017;197(4):e1027. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**

48. Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ. 2010;341:c4543. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

49. El Fegoun AB, Barret E, Prapotnich D, et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. International Braz J Urol. 2011;37(2):213-9; discussion 20-2. **KQ1E1, KQ2E1, KQ3E6, KQ4E7, KQ5E1**

50. Elterman DS, Barkin J, Radomski SB, et al. Results of high intensity focused ultrasound treatment of prostate cancer: early Canadian experience at a single center. Canadian Journal of Urology. 2011;18(6):6037-42. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

51. Franlund M, Carlsson S, Lilja H, Hugosson J. Men with total PSA levels between 1-2.99 ng/mL at initial screening have an elevated risk of future prostate cancer diagnosis: results from the Gothenburg randomized screening trial. European Urology, Supplements. 2013;12(1):e4. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

52. Gadia R, Leite ET, Gabrielli FG, et al. Outcomes of high-dose intensity-modulated radiotherapy alone with 1 cm planning target volume posterior margin for localized prostate cancer. Radiation Oncology. 2013;8:285. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

53. Galbraith ME, Ramirez JM, Pedro LW. Quality of life, health outcomes, and identity for patients with prostate cancer in five different treatment groups. Oncol Nurs Forum. 2001;28(3):551-60. **KQ1E1, KQ2E1, KQ3E6, KQ4E9, KQ5E1**

54. Gayet M, Mannaerts CK, Nieboer D, et al. Prediction of prostate cancer: external validation of the ERSPC risk calculator in a contemporary Dutch clinical cohort. European Urology Focus. 2016. **KQ1E10, KQ2E10, KQ3E10, KQ4E10, KQ5E10**

55. Gershman B, Van Houten HK, Herrin J, et al. Impact of prostate-specific antigen (PSA) screening trials and revised PSA screening guidelines on rates of prostate biopsy and postbiopsy complications. European Urology. 2017;71(1):55-65. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

56. Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised population-based prostate cancer screening trial. European Urology. 2013;63(1):101-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1, X3**

Appendix B. Excluded Studies

57. Graefen M, Schlomm T, Steuber T, Sauter G. Current results on PSA-based prostate cancer detection. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 2014;57(3):312-7. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8, X10**
58. Graversen PH, Nielsen KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. Urology. 1990;36(6):493-8. **KQ1E10, KQ2E10, KQ3E10, KQ4E10, KQ5E10**
59. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. European Urology. 2013;64(5):703-9. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
60. Grill S, Fallah M, Leach RJ, et al. Incorporation of detailed family history from the Swedish family cancer database into the PCPT risk calculator. Journal of Urology. 2015;193(2):460-5. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
61. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen--based prostate cancer screening strategies: model estimates of potential benefits and harms. Ann Intern Med. 2013;158(3):145-53. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7, X1, X6**
62. Haines IE, Gabor Miklos GL. Prostate-specific antigen screening trials and prostate cancer deaths: the androgen deprivation connection. Journal of the National Cancer Institute. 2013;105(20):1534-9. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1, X19**
63. Hakimi AA, Agalliu I, Ho GY, et al. Detection of prostate cancer in an ethnically diverse, disadvantaged population with multiple prostate specific antigen measurements before biopsy. Journal of Urology. 2012;187(4):1234-40. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X8, X15**
64. Haythorn MR, Ablin RJ. Prostate-specific antigen testing across the spectrum of prostate cancer. Biomarkers in Medicine. 2011;5(4):515-26. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**
65. Hilton JF, Blaschko SD, Whitson JM, Cowan JE, Carroll PR. The impact of serial prostate biopsies on sexual function in men on active surveillance for prostate cancer. Journal of Urology. 2012;188(4):1252-8. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**
66. Hoffman RM. Periodic PSA-based screening in men 55 to 69 years of age reduced prostate cancer mortality. Annals of Internal Medicine. 2012;157(2):JC2-4. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
67. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database of Systematic Reviews. 2013(1):78. **KQ1E6, KQ2E6A, KQ3E1, KQ4E1, KQ5E1**
68. Ilic D, O'Connor D, Green S, Wilt TJ. Screening for prostate cancer: an updated Cochrane systematic review. BJU Int. 2011;107(6):882-91. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**
69. Ip S, Dahabreh IJ, Chung M, et al. An evidence review of active surveillance in men with localized prostate cancer. Evidence Report/Technology Assessment. 2011(204):1-341. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**
70. Iremashvili V, Manoharan M, Lokeshwar SD, Rosenberg DL, Pan D, Soloway MS. Comprehensive analysis of post-diagnostic prostate-specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. BJU International. 2013;111(3):396-403. **KQ1E1, KQ2E1, KQ3E5, KQ4E5, KQ5E1**
71. Iremashvili V, Pelaez L, Manoharan M, Jorda M, Rosenberg DL, Soloway MS. Pathologic prostate cancer characteristics in patients eligible for active surveillance: a head-to-head comparison of contemporary protocols. European Urology. 2012;62(3):462-8. **KQ1E1, KQ2E1, KQ3E5, KQ4E5, KQ5E1**
72. Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. Journal of Urology. 2012;187(5):1594-9. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**
73. Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. Scand J Urol Nephrol Suppl. 1995;172:65-72. **KQ1E10, KQ2E10, KQ3E10, KQ4E10, KQ5E10**
74. Izard MA, Morris LM, Wan WY, Martin J. Long-term outcome for prostate cancer using pseudo pulse-dosed rate brachytherapy, external beam radiotherapy, and hormones. Brachytherapy. 2013;12(6):608-14. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**
75. Jacobs BL, Zhang Y, Schroeck FR, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. JAMA. 2013;309(24):2587-95. **KQ1E1, KQ2E1, KQ3E5b, KQ4E5b, KQ5E1, X3**
76. Janu J, Lakomy T, Tuma J. Age specific PSA and PSA velocity-comparison on the basis of prostate biopsies. European Urology, Supplements. 2013;12(4):e1196. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
77. Jeong CW, Lee S, Jung JW, et al. Mobile application-based Seoul National University prostate cancer risk calculator: Development, validation, and comparative analysis with two western risk calculators in Korean men. PLoS ONE. 2014;9(4). **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
78. Kasperzyk JL, Shappley WV 3rd, Kenfield SA, et al. Watchful waiting and quality of life among prostate cancer survivors in the Physicians' Health Study. Journal of Urology. 2011;186(5):1862-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

Appendix B. Excluded Studies

79. Keto CJ, Aronson WJ, Terris MK, et al. Detectable prostate-specific antigen Nadir during androgen-deprivation therapy predicts adverse prostate cancer-specific outcomes: results from the SEARCH database. European Urology. 2014;65(3):620-7. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6**

80. Kilpelainen TP, Tammela TL, Malila N, et al. The Finnish prostate cancer screening trial: analyses on the screening failures. International Journal of Cancer. 2015;136(10):2437-43. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

81. Kim J, Ebertowski J, Janiga M, et al. Many young men with prostate-specific antigen (PSA) screen-detected prostate cancers may be candidates for active surveillance. BJU Int. 2013;111(6):934-40. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

82. Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol. 2009;181(4):1615-21; discussion 21. **KQ1E9, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

83. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33(3):272-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

84. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010;28(1):126-31. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

85. Komura K, Inamoto T, Masuda H, Watsuji T, Azuma H. Experience with high-intensity focused ultrasound therapy for management of organ-confined prostate cancer: critical evaluation of oncologic outcomes. Acta Bio-Medica de l Ateneo Parmense. 2012;83(3):189-96. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**

86. Komura K, Inamoto T, Takai T, et al. Single session of high-intensity focused ultrasound for localized prostate cancer: treatment outcomes and potential effect as a primary therapy. World Journal of Urology. 2014;32(5):1339-45. **KQ1E1, KQ2E1, KQ3E7, KQ4E1, KQ5E1**

87. Kotecha R, Yamada Y, Pei X, et al. Clinical outcomes of high-dose-rate brachytherapy and external beam radiotherapy in the management of clinically localized prostate cancer. Brachytherapy. 2013;12(1):44-9. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

88. Koukourakis MI, Kyrgias G, Papadopoulou A, et al. Treatment of low-risk prostate cancer with radical hypofractionated accelerated radiotherapy with cytoprotection (HypoARC): an interim analysis of toxicity and efficacy. Anticancer Research. 2011;31(5):1745-51. **KQ1E1, KQ2E1, KQ3E6, KQ4E5, KQ5E1**

89. Kukielka AM, Dabrowski T, Walasek T, Olchawa A, Kudzia R, Dybek D. High-dose-rate brachytherapy as a monotherapy for prostate cancer--Single-institution results of the extreme fractionation regimen. Brachytherapy. 2015;14(3):359-65. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

90. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate. 2004;59(3):311-8. **KQ1E9, KQ2E9, KQ3E1, KQ4E1, KQ5E1**

91. Lavallée LT, Binette A, Witiuk K, et al. Reducing the harm of prostate cancer screening: repeated prostate-specific antigen testing. Mayo Clinic Proceedings. 2016;91(1):17-22. **KQ1E1, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

92. Lazzeri M, Haese A, Abrate A, et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU International. 2013;112(3):313-21. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

93. Lee DH, Jung HB, Park JW, et al. Can Western based online prostate cancer risk calculators be used to predict prostate cancer after prostate biopsy for the Korean population? Yonsei Medical Journal. 2013;54(3):665-71. **KQ1E1, KQ2E2, KQ3E1, KQ4E1, KQ5E5**

94. Lee YJ, Park JE, Jeon BR, Lee SM, Kim SY, Lee YK. Is prostate-specific antigen effective for population screening of prostate cancer? A systematic review. Annals of Laboratory Medicine. 2013;33(4):233-41. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

95. Leidinger P, Keller A, Milchram L, et al. Combination of autoantibody signature with PSA level enables a highly accurate blood-based differentiation of prostate cancer patients from patients with benign prostatic hyperplasia. PLoS ONE. 2015;10(6). **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

96. Liang Y, Ankerst DP, Feng Z, Fu R, Stanford JL, Thompson IM. The risk of biopsy-detectable prostate cancer using the prostate cancer prevention trial risk calculator in a community setting. Urologic Oncology. 2013;31(8):1464-9. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**

97. Lilleby W, Tafjord G, Raabe NK. Implementation of high-dose-rate brachytherapy and androgen deprivation in patients with prostate cancer. International Journal of Radiation Oncology, Biology, Physics. 2012;83(3):933-9. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

98. Lippi G, Aloe R, Mattiuzzi C. Prostate-specific antigen (PSA) isoform p2PSA in prostate cancer screening: systematic review of current evidence and further perspectives. Rivista Italiana della Medicina di Laboratorio. 2012;8(4):231-8. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9, X10**

99. Liss M, Xu J, Chen H, Kader AK. The prostate genetic score (PGS) stratifies baseline risk of prostate cancer and improves PSA performance in the PLCO trial. Journal of Urology. 2015;193(4):e896-e7. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

Appendix B. Excluded Studies

100. Loeb S, Berglund A, Stattin P. Population based study of use and determinants of active surveillance and watchful waiting for low and intermediate risk prostate cancer. Journal of Urology. 2013;190(5):1742-9. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1, X3**

101. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. J Urol. 2011;186(5):1830-4. **KQ1E6, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

102. Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of Oncology. 2015;26(5):848-64. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E7, X10**

103. Lujan M, Paez A, Berenguer A, Rodriguez JA. [Mortality due to prostate cancer in the Spanish arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Results after a 15-year follow-up]. Actas Urol Esp. 2012;36(7):403-9. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**

104. Lukka H, Waldron T, Chin J, et al. High-intensity focused ultrasound for prostate cancer: a systematic review. Clinical Oncology (Royal College of Radiologists). 2011;23(2):117-27. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

105. Lumen N, Fonteyne V, de Meerleert G, et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. International Journal of Urology. 2012;19(2):100-8. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X10, X11**

106. Luo Y, Gou X, Huang P, Mou C. Prostate cancer antigen 3 test for prostate biopsy decision: a systematic review and meta analysis. Chinese Medical Journal. 2014;127(9):1768-74. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9, X10**

107. Mearini L, Ferri C, Lazzeri M, et al. Evaluation of prostate-specific antigen isoform p2PSA and its derivates, %p2PSA, prostate health index and prostate dimension-adjusted related index in the detection of prostate cancer at first biopsy: an exploratory, prospective study. Urologia Internationalis. 2014;93(2):135-45. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

108. Mendhiratta N, Lee T, Prabhu V, Llukani E, Lepor H. 10-Year mortality after radical prostatectomy for localized prostate cancer in the prostate-specific antigen screening era. Urology. 2015;86(4):783-8. **KQ1E1, KQ2E1, KQ3E5b, KQ4E6, KQ5E1**

109. Merglen A, Schmidlin F, Fioretta G, et al. Short- and long-term mortality with localized prostate cancer. Arch Intern Med. 2007;167(18):1944-50. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

110. Mitra AV, Bancroft EK, Barbachano Y, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU International. 2011;107(1):28-39. **KQ1E7, KQ2E5, KQ3E1, KQ4E1, KQ5E1**

111. Murray NP, Reyes E, Tapia P, et al. A performance analysis of the presence of malignant circulating prostate cells as a predictive factor for the detection of prostate cancer in the first, second and third prostate biopsy. Arch Esp Urol. 2013;66(4):335-41. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**

112. Murray NP, Reyes E, Tapia P, et al. Diagnostic performance of malignant prostatic cells detection in blood for early detection of prostate cancer: comparison to prostatic biopsy. Arch Esp Urol. 2011;64(10):961-71. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**

113. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. 2008;38(3):192-9. **KQ1E1, KQ2E1, KQ3E7, KQ4E7a, KQ5E1**

114. Myers MA, Hagan MP, Todor D, et al. Phase I/II trial of single-fraction high-dose-rate brachytherapy-boosted hypofractionated intensity-modulated radiation therapy for localized adenocarcinoma of the prostate. Brachytherapy. 2012;11(4):292-8. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

115. Na R, Zhang N, Wu Y, et al. The evaluation of prostate cancer prevention trial (PCPT) risk calculator and logistic regression based models for predicting prostate cancer in Chinese population. Urology. 2014;84(4):S306. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

116. Newcomb LF, Thompson IM, Boyer HD, et al. Outcomes of active surveillance for clinically localized prostate cancer in the prospective, multi-institutional Canary PASS Cohort. Journal of Urology. 2016;195(2):313-20. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E7**

117. Ochiai A, Okihara K, Kamoi K, et al. Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. BJU International. 2013;111(6):928-33. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

118. Odom BD, Mir MC, Hughes S, et al. Active surveillance for low-risk prostate cancer in African American men: a multi-institutional experience. Urology. 2014;83(2):364-8. **KQ1E1, KQ2E1, KQ3E7, KQ4E6, KQ5E1**

119. Parekh DJ, Ankerst DP, Higgins BA, et al. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. Urology. 2006;68(6):1152-5. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**

120. Park JJ, Chen MH, Loffredo M, D'Amico AV. Prostate-specific antigen velocity before and after elimination of factors that can confound the prostate-specific antigen level. Int J Radiat Oncol Biol Phys. 2012;82(3):1217-21. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

121. Park JY, Yoon S, Park MS, et al. Initial biopsy outcome prediction in Korean patients-comparison of a novel web-based Korean prostate cancer risk calculator versus prostate-specific antigen testing. Journal of Korean Medical Science. 2011;26(1):85-91. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E5**

Appendix B. Excluded Studies

122. Park JY, Yoon S, Park MS, et al. Can the Prostate Risk Calculator based on Western population be applied to Asian population? European Urology, Supplements. 2012;11(1):e147. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

123. Perdona S, Cavadas V, Di Lorenzo G, et al. Prostate cancer detection in the "grey area" of prostate-specific antigen below 10 ng/ml: head-to-head comparison of the updated PCPT calculator and Chun's nomogram, two risk estimators incorporating prostate cancer antigen 3. European Urology. 2011;59(1):81-7. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

124. Pinsky PF, Black A, Parnes HL, et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiology. 2012;36(6):e401-6. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X1**

125. Pohle M, Magheli A, Fischer T, et al. The effect of evolving strategies in the surgical management of organ-confined prostate cancer: comparison of data from 2005 to 2014 in a multicenter setting. Advances in Therapy. 2017;34(2):576-85. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E2**

126. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. Journal of Clinical Oncology. 2013;31(31):3860-8. **KQ1E1, KQ2E1, KQ3E4, KQ4E4, KQ5E1**

127. Poyet C, Nieboer D, Wiederkehr C, Sulser T, Hermanns T. The ERSPC risk calculator outperforms the PCPC-2.0 risk calculator in prostate cancer risk prediction in a contemporary tertiary center in Europe. European Urology, Supplements. 2015;14(2):e22. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

128. Poyet C, Umbehr M, Wiederkehr C, Largo R, Sulser T, Hermanns T. Comparison of three different risk calculator to predict prostate cancer before biopsy - Results from a retrospective study in Zürich. Journal of Urology. 2014;191(4):e712. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

129. Poyet C, Wettstein MS, Lundon DJ, et al. External evaluation of a novel prostate cancer risk calculator (ProstateCheck) based on data from the Swiss arm of the ERSPC. Journal of Urology. 2016;196(5):1402-7. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E7**

130. Prada PJ, Gonzalez H, Fernandez J, Jimenez I, Iglesias A, Romo I. Biochemical outcome after high-dose-rate intensity modulated brachytherapy with external beam radiotherapy: 12 years of experience. BJU International. 2012;109(12):1787-93. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

131. Pron G. Prostate-specific antigen (PSA)–based population screening for prostate cancer: an evidence-based analysis. Ontario Health Technology Assessment Series. 2015;15(10). **KQ1E6. KQ2E6. KQ3E6, KQ4E6, KQ5E1, X1, X3, X11, X17**

132. Rahal AK, Badgett RG, Hoffman RM. Screening coverage needed to reduce mortality from prostate cancer: a living systematic review. PLoS One. 2016;11(4):11. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**

133. Randazzo M, Beatrice J, Huber A, et al. Future risk for intermediate or high risk prostate cancer in men with baseline PSA of 1-3 ng/ml and low free-to-total PSA-ratio in a prospective population-based screening trial (ERSPC AARAU). Journal of Urology. 2014;191(4):e815. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

134. Randazzo M, Müller A, Carlsson S, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU International. 2016;117(4):576-83. **KQ1E7, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

135. Randazzo M, Seiler D, Beatrice J, et al. Prostate specific antigen (PSA)-pyramid in men with low range PSA: prostate cancer incidence and mortality-a plea for risk-based prostate cancer screening strategy in the European randomized study of screening for prostate cancer (ERSPC), AARAU. Journal of Urology. 2013;189(4):e793. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

136. Recker F, Randazzo M, Wyler SF, et al. Risk-adapted PSA screening-a way to reduce the harms of prostate cancer screening. Oncology Research and Treatment. 2015;38:109-10. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

137. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. New England Journal of Medicine. 2013;368(5):436-45. **KQ1E1, KQ2E1, KQ3E6, KQ4E4, KQ5E1**

138. Rider JR, Sandin F, Andren O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. European Urology. 2013;63(1):88-96. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

139. Roobol M, Verbeek J, Kweldam C, Van Leenders A. Updating of the ERSPC Rotterdam Prostate Cancer Risk Calculator for initial prostate biopsy to contemporary practice including the 2014 ISUP Gleason grading and cribriform growth patterns. European Urology, Supplements. 2016;15(13):e1622-e4. **KQ1E1, KQ2E1KQ3E1, KQ4E1, KQ5E6**

140. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). BJU Int. 2003;92 Suppl 2:48-54. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

141. Roobol MJ, Nieboer D, Houlgatte A, et al. Reducing unnecessary biopsies for suspicion of prostate cancer: Extension and validation of an ERSPC based risk calculator with phi and comparison with the PCPT risk calculator including %free and -2propsa. Journal of Urology. 2013;189(4):e843. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

Appendix B. Excluded Studies

142. Roobol MJ, Nieboer D, Houlgatte A, et al. Reducing unnecessary biopsies for suspicion of prostate cancer: extension and validation of an ERSPC based risk calculator with Phi. European Urology, Supplements. 2013;12(1):e139-e40. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
143. Roobol MJ, Nieboer D, Semnojow A, et al. The DRE based ERSPC prostate cancer risk calculator and the additional value of Phi. Tumor Biology. 2012;33:S48-S9. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
144. Roobol MJ, Schroder FH, Hugosson J, et al. Importance of prostate volume in the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators: results from the prostate biopsy collaborative group. World Journal of Urology. 2012;30(2):149-55. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
145. Roobol MJ, Schröder FH, Trottier G, Fernandes KA, Kranse R, Fleshner NE. Development of the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator for high grade PCa and assessing and comparing its performance with the PCPT risk calculator in a Canadian cohort. European Urology, Supplements. 2011;10(2):33. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
146. Roobol MJ, Schröder H, Bangma H, Steyerberg W. A risk calculator for prostate cancer risk 4 years after negative screening findings: ERSPC Rotterdam. European Urology, Supplements. 2012;11(1):e145-ea. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**
147. Roobol MJ, Semjonow A, Bangma CH. Performance of the european randomized study of screening for prostate cancer (ERSPC) risk calculator for high grade PC in a clinical setting and the additional value of the prostate health index (PHI). Clinical Chemistry and Laboratory Medicine. 2011;49:S268. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
148. Roobol MJ, Van Vugt HA, Loeb S, et al. The development and validation of a prostate cancer risk calculator including information on prostate volume from digital rectal examination: ERSPC Rotterdam. Tumor Biology. 2011;32:S42. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
149. Roobol MJ, Verbeek JFM, van der Kwast T, Kümmerlin IP, Kweldam CF, van Leenders GJ. Improving the Rotterdam European randomized study of screening for prostate cancer risk calculator for initial prostate biopsy by incorporating the 2014 International Society of Urological Pathology Gleason grading and cribriform growth. European Urology. 2017;72(1):45-51. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**
150. Roobol MJ, Zhu X, Schroder FH, et al. A Calculator for prostate cancer risk 4 years after an initially negative screen: findings from ERSPC Rotterdam. European Urology. 2013;63(4):627-33. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E5**
151. Rubio-Briones J, Casanova J, Dumont R, et al. Prospective randomized controlled study of the role of PSA and PCA3 testing in a sequential manner in an opportunistic screening program for early diagnosis of prostate cancer. European Urology, Supplements. 2015;14(2):e315. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
152. Salami S, Fakhoury M, Ryniker L, et al. Comparison of the prostate cancer prevention trial (PCPT) risk calculator and magnetic resonance imaging in selecting men for prostate biopsies. Journal of Urology. 2014;191(4):e549. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
153. Salami SS, Schmidt F, Laxman B, et al. Combining urinary detection of TMPRSS2:ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. Urologic Oncology. 2013;31(5):566-71. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**
154. Salami SS, Vira MA, Turkbey B, et al. Multiparametric magnetic resonance imaging outperforms the Prostate Cancer Prevention Trial risk calculator in predicting clinically significant prostate cancer. Cancer. 2014;120(18):2876-82. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**
155. Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ. 2011;342:d1539. **KQ1E9, KQ2E6, KQ3E1, KQ4E1, KQ5E1**
156. Sasaki M, Ishidoya S, Ito A, et al. Low percentage of free prostate-specific antigen is a strong predictor of later detection of prostate cancer among men with serum levels of total PSA 4.0 ng/ml or under. Urology. 2013;82(3):S69-S70. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
157. Sasaki M, Ishidoya S, Ito A, et al. Low percentage of free prostate-specific antigen (PSA) is a strong predictor of later detection of prostate cancer among Japanese men with serum levels of total PSA of 4.0 ng/mL or less. Urology. 2014;84(5):1163-7. **KQ1E1, KQ2E1, KQ3E5, KQ4E5, KQ5E1**
158. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol. 2015;67(4):627-36. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**
159. Seiler D, Randazzo M, Switzerland A, et al. Long-term risk assessment of prostate cancer diagnosis in men with initial psa-values <1.0 ng/ml; results from the swiss arm of the european randomized study of screening for prostate cancer (ERSPC). Journal of Urology. 2012;187(4):e402. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
160. Shoag J, Mittal S, Halpern JA, Scherr D, Hu JC, Barbieri CE. Lethal prostate cancer in the PLCO Cancer Screening Trial. European Urology. 2016;70(1):2-5. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E6**
161. Spratt DE, Zumsteg ZS, Ghadjar P, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU International. 2014;114(3):360-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

Appendix B. Excluded Studies

162. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med. 2002;347(11):790-6. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

163. Stephan C, Jung K, Semjonow A, et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clinical Chemistry. 2013;59(1):280-8. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

164. Stone NN, Stone MM, Rosenstein BS, Unger P, Stock RG. Influence of pretreatment and treatment factors on intermediate to long-term outcome after prostate brachytherapy. Journal of Urology. 2011;185(2):495-500. **KQ1E1, KQ2E1, KQ3E7, KQ4E6 KQ5E1**

165. Stovsky M, Ponsky L, Vourganti S, et al. Prostate-specific antigen/solvent interaction analysis: a preliminary evaluation of a new assay concept for detecting prostate cancer using urinary samples. Urology. 2011;78(3):601-5. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

166. Strobl AN, Thompson IM, Vickers AJ, Ankerst DP. The next generation of clinical decision making tools: development of a real-time prediction tool for outcome of prostate biopsy in response to a continuously evolving prostate cancer landscape. Journal of Urology. 2015;194(1):58-64. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E6a**

167. Taira AV, Merrick GS, Butler WM, et al. Long-term outcome for clinically localized prostate cancer treated with permanent interstitial brachytherapy. International Journal of Radiation Oncology, Biology, Physics. 2011;79(5):1336-42. **KQ1E1, KQ2E1, KQ3E7, KQ4E6 KQ5E1**

168. Takeda K, Takai Y, Narazaki K, et al. Treatment outcome of high-dose image-guided intensity-modulated radiotherapy using intra-prostate fiducial markers for localized prostate cancer at a single institute in Japan. Radiation Oncology. 2012;7:105. **KQ1E1, KQ2E1, KQ3E5b, KQ4E5b, KQ5E1**

169. Talcott JA, Manola J, Clark JA, et al. Time course and predictors of symptoms after primary prostate cancer therapy. J Clin Oncol. 2003;21(21):3979-86. **KQ1E1, KQ2E1, KQ3E6, KQ4E5, KQ5E1**

170. Taylor KL, Luta G, Miller AB, et al. Long-term disease-specific functioning among prostate cancer survivors and noncancer controls in the prostate, lung, colorectal, and ovarian cancer screening trial. Journal of Clinical Oncology. 2012;30(22):2768-75. **KQ1E1, KQ2E1, KQ3E6, KQ4E7, KQ5E1, X3**

171. Tewari A, Divine G, Chang P, et al. Long-term survival in men with high grade prostate cancer: a comparison between conservative treatment, radiation therapy and radical prostatectomy--a propensity scoring approach. J Urol. 2007;177(3):911-5. **KQ1E1, KQ2E1, KQ3E5b, KQ4E6, KQ5E1**

172. Tyson MD 2nd, Castle EP. Racial disparities in survival for patients with clinically localized prostate cancer adjusted for treatment effects. Mayo Clinic Proceedings. 2014;89(3):300-7. **KQ1E1, KQ2E1, KQ3E9, KQ4E6, KQ5E1, X8**

173. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int. 2006;97(1):56-61. **KQ1E1, KQ2E1, KQ3E7, KQ4E6a, KQ5E1**

174. van den Bergh RC, de Blok W, van Muilekom E, Tillier C, Venderbos LD, van der Poel HG. Impact on quality of life of radical prostatectomy after initial active surveillance: more to lose? Scandinavian Journal of Urology. 2014;48(4):367-73. **KQ1E1, KQ2E1, KQ3E6, KQ4E7, KQ5E1**

175. Van Den Ende A, Rietbergen JB, Wildhagen MF, Bangma CH. Use of a risk calculator in a prostate unit to reduce overdiagnosis of prostate cancer. European Journal of Cancer. 2013;49:S709-S10. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

176. van Leeuwen PJ, van den Bergh RC, Wolters T, et al. Critical assessment of prebiopsy parameters for predicting prostate cancer metastasis and mortality. Canadian Journal of Urology. 2011;18(6):6018-24. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E3, X4, X8, X10**

177. Van Vugt H, Kranse R, Van Leeuwen P, Bangma C, Roobol M. Validation of the prostate cancer risk calculator in a clinical setting. Journal of Urology. 2011;185(4):e768-e9. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

178. van Vugt HA, Kranse R, Steyerberg EW, et al. Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort. European Journal of Cancer. 2012;48(12):1809-15. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

179. Van Vugt HA, Kranse R, Van Leeuwen PJ, Bangma CH, Roobol MJ. Validation of the ERSPC risk calculator in a clinical setting. European Urology, Supplements. 2011;10(2):34. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

180. van Vugt HA, Roobol MJ, Kranse R, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. European Journal of Cancer. 2011;47(6):903-9. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

181. Van Vugt HA, Roobol MJ, Van Leeuwen PJ, Steyerberg EW, Korfage I. Compliance with biopsy recommendations by a prostate cancer risk calculator. European Urology, Supplements. 2011;10(2):35. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

182. Vickers AJ, Sjoberg D, Ankerst DP, Tangen CM, Goodman PJ, Thompson IM. The prostate cancer prevention trial (PCPT) risk calculator and the relationship between PSA and biopsy outcome. Journal of Urology. 2012;187(4):e492-e3. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1**

Appendix B. Excluded Studies

183. Vora SA, Wong WW, Schild SE, et al. Outcome and toxicity for patients treated with intensity modulated radiation therapy for localized prostate cancer. Journal of Urology. 2013;190(2):521-6. **KQ1E1, KQ2E1, KQ3E7, KQ4E5, KQ5E1**

184. Wallner LP, Jacobsen SJ. Prostate-specific antigen and prostate cancer mortality: a systematic review. Am J Prev Med. 2013;45(3):318-26. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X10, X11**

185. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? Journal of Clinical Oncology. 2014;32(36):4066-72. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9**

186. Weißbach L. "PSA screening - pros and cons". Onkologie. 2012;35:1-2. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**

187. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. Journal of Urology. 2015;193(3):807-11. **KQ1E1, KQ2E1, KQ3E7a, KQ4E6, KQ5E1**

188. Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. International Journal of Radiation Oncology, Biology, Physics. 2015;91(2):288-94. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

189. Wilt TJ. Management of low risk and low PSA prostate cancer: long term results from the prostate cancer intervention versus observation trial. Minneapolis VA Center for Chronic Diseases Outcomes Research, Minneapolis MN. 2014;202:149-69. **KQ1E1, KQ2E1, KQ3E6a, KQ4E6a, KQ5E1**

190. Womble PR, Montie JE, Ye Z, Linsell SM, Lane BR, Miller DC. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. Eur Urol. 2015;67(1):44-50. **KQ1E1, KQ2E1, KQ3E6, KQ4E5, KQ5E1**

191. Xia J, Gulati R, Au M, Gore JL, Lin DW, Etzioni R. Effects of screening on radical prostatectomy efficacy: the prostate cancer intervention versus observation trial. Journal of the National Cancer Institute. 2013;105(8):546-50. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1, X3, X6**

192. Xue WJ, Ying XL, Jiang JH, Xu YH. Prostate cancer antigen 3 as a biomarker in the urine for prostate cancer diagnosis: a meta-analysis. Journal of Cancer Research and Therapeutics. 2014;10:C218-C21. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1, X9, X10**

193. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388(10049):1057-66. **KQ1E1, KQ2E1, KQ3E6, KQ4E6, KQ5E1**

194. Yorozu A, Kuroiwa N, Takahashi A, et al. Permanent prostate brachytherapy with or without supplemental external beam radiotherapy as practiced in Japan: outcomes of 1300 patients. Brachytherapy. 2015;14(2):111-7. **KQ1E1, KQ2E1, KQ3E7, KQ4E7, KQ5E1**

195. Zavaski ME, Meyer CP, Sammon JD, et al. Differences in prostate-specific antigen testing among urologists and primary care physicians following the 2012 USPSTF recommendations. JAMA Intern Med. 2016;176(4):546-7. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1, X3, X17**

196. Zhu X, van Leeuwen PJ, Bul M, et al. Disease-specific survival of men with prostate cancer detected during the screening interval: results of the European randomized study of screening for prostate cancer-Rotterdam after 11 years of follow-up. European Urology. 2011;60(2):330-6. **KQ1E6, KQ2E6, KQ3E1, KQ4E1, KQ5E1**

197. Zhu Y, Wang JY, Shen YJ, et al. External validation of the Prostate Cancer Prevention Trial and the European Randomized Study of Screening for Prostate Cancer risk calculators in a Chinese cohort. Asian Journal of Andrology. 2012;14(5):738-44. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E2a**

Appendix C. Ongoing Studies

Study	Aim	Population Country	Intervention	Comparator	Relevant Outcomes	Status
KQ1 & KQ2 (PSA screening effectiveness and harms)						
No ongoing trials of PSA screening versus no PSA screening were identified. No trials or cohort studies of harms related to PSA screening and diagnostic testing were identified						
KQs 3& 4 (prostate cancer treatment effectiveness and harms)						
SPCG17: Prostate Cancer Active Surveillance Trigger Trial (PCASTT) NCT02914873	Determine whether an active surveillance protocol with specified triggers for repeat biopsies and initiation of subsequent treatment can reduce overtreatment and subsequent side effects, without increasing risk of disease progression or death	Males with diagnosed with early-stage prostate cancer Sweden	Active surveillance w/ trigger protocol	Active surveillance w/ standard protocol	Disease progression; quality of life	Recruiting Estimated completion date: December 2030
Active Surveillance of Two Groups of Patients with Localized Prostate Cancer NCT01795365	Validate the treatment option active surveillance in men with localized, well differentiated prostate cancer, in order to limit the amount of overtreatment	Males ages 18 to 75 years with localized prostate cancer (Gleason score of 3+3 or 3+4) Switzerland	Active surveillance	NA	Time on AS before active treatment; mortality rates; time to metastatic disease; quality of life	Ongoing but not recruiting Estimated completion date: October 2017
Focal Therapy Using High Intensity Focused Ultrasound for Localized Prostate Cancer NCT02016040	Evaluate the impact of HIFU treatment on continence, sexuality and quality of life at one year	Males $\geq$50 years diagnosed with stage T1c prostate cancer Canada	HIFU	NA	Incidence of harms (erectile and sexual function, quality of life)	Ongoing but not recruiting Estimated completion date: November 2017
Intervention Trial Evaluating Focal Therapy Using High Intensity Focused Ultrasound for the Treatment of Prostate Cancer NCT02265159	Evaluate cancer control, genitourinary, rectal and overall health-related quality of life outcomes for localized prostate cancer using HIFU	Men with stage T1-T2c prostate cancer Switzerland	HIFU	NA	Incidence of harms (erectile, sexual and bowel function, quality of life)	Ongoing but not recruiting Estimated completion date: May 2020
Initial Experience in Brazilian Single Center With High Intensity Focalized Ultrasound (HIFU) Prostate Cancer Therapy: Morbidity, Oncological and Functional Outcomes NCT03255135	Evaluate prospectively the initial experience with 50 patients submitted to HIFU therapy for low risk prostate cancer in Brazilian single center	Men with low or intermediate prostate cancer staging Brazil	HIFU	NA	Patient-reported quality of life using IEFF-5, EPIC, IPSS, and SF-36	Not yet open for recruitment Estimated completion date: December 2017

Appendix C. Ongoing Studies

Study	Aim	Population Country	Intervention	Comparator	Relevant Outcomes	Status
Effectiveness of Three Primary Treatments for Localized Prostate Cancer: Radical Prostatectomy, External-beam Radiotherapy, and Prostate Brachytherapy NCT01492751	Assess the quality of life impacts of treatments' side effects on patients with localized prostate cancer at short, mid, and long-range followup	Males with stage T1 or T2 prostate cancer Spain	Radical prostatectomy; external-beam radiation therapy; brachytherapy	NA	Quality of life; harms (urinary, sexual function); survival	Ongoing but not recruiting Estimated completion date: December 2017
Active Surveillance for Cancer of the Prostate (ASCaP) NCT00949819	Establish a structured program of non-interventional follow-up for localized prostate cancer	Males ages 30 to 85 years with stage T1 or T2 (NX, N0, MX or M0) prostate cancer United States	Active surveillance	NA	Clinical parameters to predict aggressive disease; clinical predictors of disease progression	Recruiting Estimated completion date: December 2019
Active Surveillance in Prostate Cancer: A Prospective Cohort Study NCT00490763	Determine whether men classified as having "low risk" prostate cancer can safely not be treated for the disease	Males with low-risk prostate cancer who choose active surveillance United States	Active surveillance	NA	Time to disease progression; quality of life	Ongoing but not recruiting Estimated completion date: February 2020

Appendix D. Poor-Quality Studies Excluded From Previous USPSTF Evidence Syntheses

Quebec Trial

This trial randomized 46,486 men to PSA-based screening versus usual care and showed no statistically significant difference in prostate cancer mortality between screening-invited and control groups when data were analyzed via intention-to-treat (relative risk [RR], 1.09 [95% CI, 0.82 – 1.43]).[220] The trial was rated as poor-quality due to low adherence to the intervention in the screening arm (23.6%), uncertain levels of contamination due to out-of-trial screening, uncertainty about potential treatment differences across study arms, and outcome assessments that may not have been blinded to study arm allocation.

Norrkoping Trial

This study selected a cohort of men aged 50 to 69 years living in Norrkoping, Sweden from the National Population Register. Every sixth man (n=1,494) was invited to participate in a multiyear screening program; the remaining men who were not contacted served as controls (n=7,532). The first two rounds of screening (in 1987 and 1990) consisted only of DRE; the screening protocol changed during the third and fourth rounds (1993 and 1996) to include DRE plus PSA testing. The study used a PSA cut-off point of >4.0 ng/mL; a positive screening result led to a biopsy and confirmed prostate cancer was treated according to a standardized management program common to that region of Sweden. After 20 years of followup, the authors found no statistically significant difference in prostate cancer mortality between the screened and control groups (RR, 1.16 [95% CI, 0.78 to 1.73]).[178] This study was rated as poor quality for several reasons, including non-ideal method of randomization, lack of information on the baseline comparability of the two groups, uncertain levels of contamination in the control group, and insufficient information regarding the method of outcome assessment. Finally, the sample size was originally calculated to assess the acceptance and feasibility of a prostate cancer screening program, rather than mortality outcomes.

Stockholm Trial

This study selected a cohort of men aged 55 to 70 years living in Stockholm, Sweden (n=2,400) from census records and invited them to a single prostate cancer screening (which included a PSA test, DRE, and TRUS) in 1988; the remaining 27,804 men in the source population served as the control group. Of the men invited, 75 percent attended the screening. A PSA exceeding 10.0 ng/mL led to a prostate biopsy and a lower PSA of 7.0 to 10.0 ng/mL led to a repeat TRUS. The cohort was followed for 15 years. Neither the relative risk of prostate cancer-specific mortality (RR, 1.10 [95% CI, 0.83 to 1.46]) or all-cause mortality (RR, 0.98 [95% CI, 0.92 to 1.05]) was statistically significantly different in the screening group compared with the controls. Only three of the 65 cases of prostate cancer (4.6%) found during screening were detected by an elevated PSA alone.[179] This study was rated as poor quality because of there was no reporting of baseline differences between the screening and comparison groups, and it was unclear whether the review committee was blinded to group allocation, potentially leading to attribution bias in outcomes assessment. The trial also has internal discrepancies about the total number of participants because the file containing the registration numbers of the original cohort could not be retrieved. In addition to the study's risk of bias, the study's findings are not generalizable to the United States due to the high PSA cut-off points.

Appendix E Table 1. Use of PSA by Study Arm During the Screening Phase of the PLCO Trial

Time period of latest test	Study Arm		
	Control*		Screening†
	Routine Screening PSA, %	PSA for Any Purpose, %	Routine Screening, %
<1 year	46	52	78
1-2 years	14	16	8
2-3 years	5	6	3
>3 years	4	4	2
Never tested for any reason	21		9

Note: table adapted from Pinsky et al (2010)

*Based on annual surveys of control arm subjects during years 0 to 5 of the trial (N=2225; range per study year 181-435)

†Based on adherence to trial screening protocol

Appendix E Table 2. Initial Non-Metastatic Prostate Cancer Treatment by Study Arm and Clinical Risk Group at Diagnosis Among ERSPC Participants

	Risk Group*						Overall (n=8,010)	
	Low Risk		Intermediate Risk		High Risk			
Initial Treatment	Screening, % (n=2,766)	Control, % (n=873)	Screening, % (n=1,319)	Control, % (n=976)	Screening, % (n=1,027)	Control, % (n=1,049)	Screening, % (n=5,112)	Control, % (n=2,898)
Radical prostatectomy	39.7	39.2	50.3	41.3	34.2	19.6	41.3	32.8
Radiation therapy	25.1	28.2	31.8	37.4	47.0	45.9	31.1	37.7
Hormonal therapy	2.0	3.9	6.4	8.0	14.7	29.5	5.7	14.5
Conservative management†	33.1	28.8	11.6	13.3	4.1	5.1	21.7	15.0

Note: Table adapted from Wolters et al (2010). Differences in treatment distribution were statistically significant in all risk group ($p<0.05$)

*Low risk prostate cancers were defined as stage<=T2a, PSA<10 ng/mL, and Gleason<7. High-risk cancers were stage>=T2c, PSA>20 ng/mL, or Gleason>=8. All other cancers were intermediate risk (i.e., stage T2b, PSA 10-20 ng/mL, Gleason=7).

†Conservative management includes active surveillance, watchful waiting, or no treatment.

Appendix E Table 3. Definitions of Clinical Risk in Prostate Cancer Screening Trials

Trial Name	Location	Low Risk	Intermediate Risk	High Risk	Advanced/Metastatic
PLCO	United States	NA	NA	NA	NA
ERSPC	Europe (Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, France, Portugal)	Clinical stage T1-2 and Gleason score <6	Clinical stage T1-2 and Gleason score 7 OR clinical stage T3 and Gleason score ≤7	Clinical stage T1-3 and Gleason score 8-10 OR clinical stage T4 and any Gleason score	M1 or PSA>100 ng/mL
	Goteborg (Sweden)	T1, not N1 or M1, Gleason score ≤6, and PSA <10 ng/mL	T1-2, not N1 or M1, and Gleason score ≤7 and/or PSA <20 ng/mL	T1-4, not N1 or M1, and Gleason score ≥8 and/or PSA <100 ng/mL	N1 and/or M1 and/or PSA ≥100 ng/mL
	Madrid (Spain)	NA	NA	NA	NA
	Rotterdam (Netherlands)	Clinical stage T1 or T2 with Gleason score ≤6	Clinical stage T1 or T2 with Gleason score 7, or T3 with Gleason score ≥7	Clinical stage T1, T2 or T3 with Gleason score 8-10 or clinical stage T4 with any Gleason score	Any clinical stage or Gleason score with M1 found at imaging and/or PSA >100
	Finland	T1 to T2 and Gleason score ≤6	T1 to T2 and Gleason score 7 or T3 with a Gleason score ≤7	T1 to T3 and Gleason score 8-10 or T4 or M1 or N1 (with any Gleason score)	T3 to T4, M1 or N1

Appendix E Table 4. Positive Predictive Value of Biopsy Based on Prostate Cancer Screening Trials

	ERSPC	PLCO
Randomized to screening	72,891 men	35,870
Positive PSA test	23,574 men	10,798
Underwent biopsy	20,188 men	4,836
Prostate cancer detected	4,883 men	1,562
Positive predictive value (PPV)	24.2%	32.3%

Appendix E Table 5. Prostate Cancer Mortality by ERSPC Site

Site/Group	Median Followup (years)	Prostate Cancer Mortality RR (95% CI)
Sweden, ERSPC core-age group (n=11,852, ages 55 to 69 years)	13.0	0.62 (0.41 to 0.92)
Netherlands	13.0	0.67 (0.51 to 0.88)
Finland	13.0	0.91 (0.75 to 1.10)
Spain	13.0	0.54 (0.10 to 2.94)
Belgium	13.0	0.77 (0.41 to 1.42)
Italy	13.0	0.81 (0.48 to 1.35)
Switerland	13.0	1.14 (0.56 to 2.33)
All sites, core age group (ages 55 to 69 years)	13.0	0.79 (0.69 to 0.91)

* p=0.43 for test of heterogeneity across all sites (core age group, 13 year followup for all sites)

Appendix E Table 6. Raw SF-36 Scores for Radical Prostatectomy Compared With Conservative Management*

		Donovan, 2016[144] RCT (6.0 years)	Barocas, 2017 Cohort (3.0 years)[75]	Smith, 2009[159] Cohort (3.8 years) Nerve Sparing	Smith, 2009[159] Cohort (3.8 years) Non-nerve Sparing	Bacon, 2001[139] Cohort (5.0 years)	Schapira, 2001[156] Cohort (1.0 years)	Litwin, 2002[151] Cohort (2.0 years)	Smith, 2000[160] Cohort (3.8 years)	Lubeck, 1999[152] Cohort (2.0 years)	Litwin, 1995[150] Cohort (6.0 years)	Median Diff. (range)
Physical Component Summary Score	RP	48.8	NR	50.1	48.7	NR	52.0	NR	NR	NR	NR	2.5 (1.8 to 3.2)
	CM	46.9	NR	46.9	46.9	NR	49.0	NR	NR	NR	NR	
	Diff	1.9	NR	3.2	1.8	NR	3.0	NR	NR	NR	NR	
Mental Component Summary Score	RP	53.5	NR	53.3	53.7	NR	55.0	NR	NR	NR	NR	0.3 (0.0 to 0.6)
	CM	53.0	NR	53.1	53.1	NR	55.0	NR	NR	NR	NR	
	Diff	0.5	NR	0.2	0.6	NR	0.0	NR	NR	NR	NR	
Physical Function	RP	NR	86.7	NR	NR	NR	90.0	87.0	84.4	85.8	74.9	8.6 (2.0 to 16.8)
	CM	NR	84.0	NR	NR	NR	79.0	85.0	67.6	70.8	70.8	
	Diff	NR	2.7	NR	NR	NR	11.0	2.0	16.8	15.0	4.1	
Physical Role Function	RP	NR	NR	NR	NR	NR	86.0	78.0	72.2	72.3	60.5	5.3 (-2.0 to 9.5)
	CM	NR	NR	NR	NR	NR	85.0	80.0	64.0	62.8	55.2	
	Diff	NR	NR	NR	NR	NR	1.0	-2.0	8.2	9.5	5.3	
Bodily Pain	RP	NR	NR	NR	NR	NR	85.0	82.0	78.3	84.4	77.0	4.0 (-5.0 to 10.2)
	CM	NR	NR	NR	NR	NR	81.0	87.0	68.1	76.1	73.5	
	Diff	NR	NR	NR	NR	NR	4.0	-5.0	10.2	8.3	3.5	
General Health	RP	NR	NR	NR	NR	NR	80.0	76.0	70.9	74.6	65.2	5.0 (2.2 to 20.8)
	CM	NR	NR	NR	NR	NR	71.0	71.0	68.4	53.8	63.0	
	Diff	NR	NR	NR	NR	NR	9.0	5.0	2.5	20.8	2.2	
Vitality	RP	NR	70.9	NR	NR	73.0	71.0	67.0	68.7	70.9	60.0	4.5 (-2.0 to 13.8)
	CM	NR	70.2	NR	NR	66.0	68.0	69.0	59.6	57.1	60.0	
	Diff	NR	0.7	NR	NR	7.0	3.0	-2.0	9.1	13.8	0.0	
Social Function	RP	NR	NR	NR	NR	100.0	92.0	90.0	88.0	88.8	80.3	2.0 (-2.0 to 11.0)
	CM	NR	NR	NR	NR	89.0	87.0	92.0	86.0	77.9	80.1	
	Diff	NR	NR	NR	NR	11.0	5.0	-2.0	2.0	10.9	0.2	
Emotional Role Function	RP	NR	81.7	NR	NR	94.0	90.0	86.0	82.7	84.4	70.2	4.7 (-5.0 to 12.8)
	CM	NR	82.1	NR	NR	86.0	90.0	91.0	77.3	72.5	57.4	
	Diff	NR	-0.4	NR	NR	8.0	0.0	-5.0	5.4	11.9	12.8	
Mental Health	RP	NR	NR	NR	NR	85.0	84.0	81.0	77.1	86.0	75.7	0.0 (-4.0 to 10.1)
	CM	NR	NR	NR	NR	83.0	81.0	81.0	82.0	75.9	77.2	
	Diff	NR	NR	NR	NR	1.0	-4.0	4.0	-1.0	10.1	-1.5	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: CM=conservative management; Diff=difference; RP=radical prostatectomy; NR=not reported

Appendix E Table 7. Raw PCI Scores for Radical Prostatectomy Compared With Conservative Management*

		Smith, 2009[159] (nerve sparing) Cohort (3.8 years)	Smith, 2009[159] (non-nerve sparing) Cohort (3.8 years)	Bacon, 2001[139] Cohort (5.0 years)	Schapira, 2001[156] Cohort (1.0 years)	Smith, 2000[160] Cohort (3.8 years)	Lubeck, 1999[152] Cohort (2.0 years)	Litwin, 1995[150] Cohort (6.0 years)	Median Difference (range)
Urinary Function	RP	85.5	83.3	76.0	62.0	75.0	70.7	65.0	-17.0 (-30 to -6.0)
	CM	91.6	91.6	93.0	92.0	94.0	87.4	86.0	
	Diff	-6.1	-8.3	-17.0	-30.0	-19.0	-16.7	-21.0	
Urinary Bother	RP	84.8	83.1	82.0	67.0	78.0	80.7	68.0	-7.0 (-17.0 to 0.7)
	CM	84.1	84.1	89.0	84.0	88.0	83.6	80.0	
	Diff	0.7	-1.0	-7.0	-17.0	-10.0	-2.9	-12.0	
Sexual Function	RP	34.7	22.0	26.0	20.0	26.0	26.8	19.0	-22.0 (-34.0 to -2.0)
	CM	44.1	44.1	54.0	36.0	60.0	29.1	41.0	
	Diff	-9.4	-22.1	-28.0	-16.0	-34.0	-2.3	-22.0	
Sexual Bother	RP	52.2	53.6	43.0	29.0	34.0	46.7	13.0	-24.0 (-35.0 to 21.8)
	CM	65.9	65.9	74.0	62.0	69.0	24.9	37.0	
	Diff	-13.7	-12.3	-31.0	-33.0	-35.0	21.8	-24.0	
Bowel Function	RP	88.1	88.5	86.0	88.0	NR	88.1	82.0	0.2 (0.5 to 2.0)
	CM	86.7	86.7	91.0	86.0	NR	89.1	84.0	
	Diff	1.4	1.8	-5.0	2.0	NR	-1.0	-2.0	
Bowel Bother	RP	90.0	90.5	86.0	86.0	NR	90.2	80.0	1.1 (-5.0 to 5.0)
	CM	88.1	88.1	89.0	81.0	NR	90.0	85.0	
	Diff	1.9	2.4	-3.0	5.0	NR	0.2	-5.0	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: CM=conservative management; Diff=difference; RP=radical prostatectomy; NR=not reported

Appendix E Table 8. Raw SF-36 Scores for Radiation Therapy Compared With Conservative Management*

		Barocas, 2017 Cohort (3.0 years)[75]	Donovan, 2016[144] RCT (6.0 years)	Thong, 2010[161] Cohort (5-10 years)	Smith, 2009[159] (EBRT) Cohort (3.8 years)	Smith, 2009[159] (LD brachy) Cohort (3.8 years)	Smith, 2009[159] (HD brachy) Cohort (3.8 years)	Litwin, 2002[151] Cohort (2.0 years)	Bacon, 2001[139] (EBRT) Cohort (5.0 years)	Bacon, 2001[139] (brachy) Cohort (5.0 years)	Schapira, 2001[156] Cohort (1.0 years)	Smith, 2000[160] Cohort (3.8 years)	Lubeck, 1999[152] Cohort (2.0 years)	Litwin, 1995[150] Cohort (6.0 years)	Median Diff (range)
Physical Component Summary Score	RP	NR	48.4	42.0	46.5	49.0	48.5	NR	49.0	51.0	NR	NR	NR	NR	1.5 (-3.0 to 2.1)
	CM	NR	46.9	45.0	46.9	46.9	46.9	NR	49.0	49.0	NR	NR	NR	NR	
	Diff	NR	1.5	-3.0	-0.4	2.1	1.6	NR	0.0	2.0	NR	NR	NR	NR	
Mental Component Summary Score	RP	NR	53.8	50.0	52.9	54.0	51.5	NR	53.0	54.0	NR	NR	NR	NR	-0.2 (-1.6 to 0.9)
	CM	NR	53.0	47.9	53.1	53.1	53.1	NR	55.0	55.0	NR	NR	NR	NR	
	Diff	NR	0.8	2.1	-0.2	0.9	-1.6	NR	-2.0	-1.0	NR	NR	NR	NR	
Physical Function	RP	74.5	NR	62.0	NR	NR	NR	NR	83.0	90.0	57.6	80.0	65.1	74.0	-3.7 (-18.0 to 11.0)
	CM	84.0	NR	80.0	NR	NR	NR	NR	79.0	79.0	67.6	85.0	70.8	70.8	
	Diff	-9.5	NR	-18.0	NR	NR	NR	NR	4.0	11.0	-10.0	-5.0	-5.7	3.2	
Physical Role Function	RP	NR	NR	56.0	NR	NR	NR	NR	72.0	79.0	42.0	71.0	55.4	55.6	-7.4 (-22.0 to 0.4)
	CM	NR	NR	57.0	NR	NR	NR	NR	85.0	85.0	64.0	80.0	62.8	55.2	
	Diff	NR	NR	-1.0	NR	NR	NR	NR	-13.0	-6.0	-22.0	-9.0	-7.4	0.4	
Bodily Pain	RP	NR	NR	70.0	NR	NR	NR	NR	79.0	81.0	61.2	82.0	73.8	74.0	-2.3 (-7.0 to 0.5)
	CM	NR	NR	77.0	NR	NR	NR	NR	81.0	81.0	68.1	87.0	76.1	73.5	
	Diff	NR	NR	-7.0	NR	NR	NR	NR	-2.0	0.0	-6.9	-5.0	-2.3	0.5	
General Health	RP	NR	NR	60.0	NR	NR	NR	NR	74.0	78.0	59.2	70.0	53.9	66.5	1.0 (-9.2 to 7.0)
	CM	NR	NR	59.0	NR	NR	NR	NR	71.0	71.0	68.4	71.0	53.8	63.0	
	Diff	NR	NR	1.0	NR	NR	NR	NR	3.0	7.0	-9.2	-1.0	0.1	3.5	
Vitality	RP	65.2	NR	62.0	NR	NR	NR	73.0	64.0	66.0	54.6	65.0	54.1	61.4	-2.0 (-5.0 to 7.0)
	CM	70.2	NR	65.0	NR	NR	NR	66.0	68.0	68.0	59.6	69.0	57.1	60.0	
	Diff	-5.0	NR	-3.0	NR	NR	NR	7.0	-4.0	-2.0	-5.0	-4.0	-3.0	1.4	
Social Function	RP	NR	NR	81.0	NR	NR	NR	86.0	87.0	92.0	58.9	88.0	76.9	81.3	-0.5 (-27.1 to 5.0)
	CM	NR	NR	79.0	NR	NR	NR	89.0	87.0	87.0	86.0	92.0	77.9	80.1	
	Diff	NR	NR	2.0	NR	NR	NR	-3.0	0.0	5.0	-27.1	-4.0	-1.0	1.2	
Emotional Role Function	RP	80.3	NR	78.0	NR	NR	NR	81.0	82.0	86.0	70.2	85.0	75.8	75.6	-0.4 (-8.0 to 18.2)
	CM	82.1	NR	71.0	NR	NR	NR	86.0	90.0	90.0	77.3	91.0	72.5	57.4	
	Diff	-1.8	NR	7.0	NR	NR	NR	-5.0	-8.0	-4.0	-7.1	-6.0	3.3	18.2	
Mental Health	RP	NR	NR	73.0	NR	NR	NR	75.0	81.0	84.0	76.4	82.0	77.6	78.7	0.5 (-6.0 to 1.7)
	CM	NR	NR	77.0	NR	NR	NR	81.0	83.0	83.0	81.3	82.0	75.9	77.2	
	Diff	NR	NR	-4.0	NR	NR	NR	-6.0	-2.0	1.0	-4.9	0.0	1.7	1.5	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: Brachy=brachytherapy; CM=conservative management; Diff=difference; EBRT=external beam radiation therapy; HD=high dose; LD=low dose; RT=radiation therapy; NR=not reported

Appendix E Table 9. Raw PCI Scores for Radiation Therapy Compared With Conservative Management*

		Thong, 2010[161] Cohort (5-10 years)	Smith, 2009[159] (EBRT) Cohort (3.8 years)	Smith, 2009[159] (LD brachy) Cohort (3.8 years)	Smith, 2009[159] (HD brachy) Cohort (3.8 years)	Bacon, 2001[139] (EBRT) Cohort (5.0 years)	Bacon, 2001[139] (brachy) Cohort (5.0 years)	Schapira, 2001[156] Cohort (1.0 years)	Smith, 2000[160] Cohort (3.8 years)	Lubeck, 1999[152] Cohort (2.0 years)	Litwin, 1995[150] Cohort (6.0 years)	Median Difference (range)
Urinary Function	RT	82.0	92.6	93.5	89.8	89.0	87.0	89.4	89.0	84.9	82.0	-3.3 (-6.0 to7.2)
	CM	86.0	91.6	91.6	91.6	93.0	93.0	82.2	94.0	87.4	86.0	
	Diff	-4.0	1.0	1.9	-1.8	-4.0	-6.0	7.2	-5.0	-2.5	-4.0	
Urinary Bother	RT	75.0	81.4	84.4	76.7	83.0	75.0	81.3	81.0	65.1	77.0	-4.5 (-18.5 to 0.3)
	CM	78.0	84.1	84.1	84.1	89.0	89.0	84.0	88.0	83.6	80.0	
	Diff	-3.0	-2.7	0.3	-7.4	-6.0	-14.0	-2.7	-7.0	-18.5	-3.0	
Sexual Function	RT	NR	32.0	54.0	30.3	34.0	36.0	25.1	40.0	25.4	35.0	-12.1 (-20.0 to 9.9)
	CM	NR	44.1	44.1	44.1	54.0	54.0	36.1	60.0	29.1	41.0	
	Diff	NR	-12.1	9.9	-13.8	-20.0	-18.0	-11.0	-20.0	-3.7	-6.0	
Sexual Bother	RT	NR	57.6	66.8	60.5	51.0	54.0	60.1	51.0	32.4	29.0	-8.0 (-23.0 to 7.5)
	CM	NR	65.9	65.9	65.9	74.0	74.0	62.0	69.0	24.9	37.0	
	Diff	NR	-8.3	0.9	-5.4	-23.0	-20.0	-1.9	-18.0	7.5	-8.0	
Bowel Function	RT	87.0	84.5	88.8	87.8	81.0	80.0	79.4	NR	83.1	81.0	-6.0 (-11.0 to 2.1)
	CM	93.0	86.7	86.7	86.7	91.0	91.0	86.1	NR	89.1	84.0	
	Diff	-6.0	-2.2	2.1	1.1	-10.0	-11.0	-6.7	NR	-6.0	-3.0	
Bowel Bother	RT	85.0	79.8	91.1	84.3	78.0	72.0	76.6	NR	74.8	77.0	-8.3 (-17.0 to 3.0)
	CM	94.0	88.1	88.1	88.1	89.0	89.0	80.8	NR	90.0	85.0	
	Diff	-9.0	-8.3	3.0	-3.8	-11.0	-17.0	-4.2	NR	-15.2	-8.0	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: Brachy=brachytherapy; CM=conservative management; Diff=difference; HD=high dose; LD=low dose; RT=radiation therapy; NR-not reported

Appendix E Table 10. Raw SF-36 Scores for Androgen Deprivation Therapy Compared With Conservative Management*

		Smith, 2009[159] Cohort (3.8 years)	Potosky, 2002[154] Cohort (1.0 years)	Bacon, 2001[139] Cohort (5.0 years)	Smith, 2000[160] Cohort (3.8 years)	Median Difference (range)
Physical Component Summary Score	ADT	38.80	NR	46.0	NR	NA
	CM	46.90	NR	49.0	NR	(-8.1 to -3.0)
	Diff	-8.10	NR	-3.00	NR	
Mental Component Summary Score	ADT	53.20	NR	52.0	NR	NA
	CM	53.10	NR	55.0	NR	(-3.0 to 0.1)
	Diff	0.10	NR	-3.00	NR	
Physical Function	ADT	NR	NR	76.0	72.0	NA
	CM	NR	NR	79.0	85.0	(-13.0 to -3.0)
	Diff	NR	NR	-3.0	-13.0	
Physical Role Function	ADT	NR	50	62.0	69.0	-11.0
	CM	NR	61	85.0	80.0	(-23.0 to -11.0)
	Diff	NR	-11.0	-23.0	-11.0	
Bodily Pain	ADT	NR	73	75.0	79.0	-6.0
	CM	NR	74	81.0	87.0	(-8.0 to -1.0)
	Diff	NR	-1.0	-6.0	-8.0	
General Health	ADT	NR	NR	66.0	69.0	NA
	CM	NR	NR	71.0	71.0	(-5.0 to -2.0)
	Diff	NR	NR	-5.0	-2.0	
Vitality	ADT	NR	53	61.0	62.0	-7.0
	CM	NR	60	68.0	69.0	(-7.0 to -7.0)
	Diff	NR	-7.0	-7.0	-7.0	
Social Function	ADT	NR	NR	83.0	82.0	NA
	CM	NR	NR	87.0	92.0	(-10.0 to -4.0)
	Diff	NR	NR	-4.0	-10.0	
Emotional Role Function	ADT	NR	74	74.0	76.0	-15.0
	CM	NR	77	90.0	91.0	(-16.0 to -3.0)
	Diff	NR	-3.0	-16.0	-15.0	
Mental Health	ADT	NR	78	79.0	76.0	-4.0
	CM	NR	78	83.0	82.0	(-6.0 to 0.0)
	Diff	NR	0.0	-4.0	-6.0	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: ADT=androgen deprivation therapy; CM=conservative management; Diff=difference; NA=not applicable; NR=not reported

Appendix E Table 11. Raw PCI Scores for Androgen Deprivation Therapy Compared With Conservative Management*

		Smith, 2009[159] Cohort (3.8 years)	Bacon, 2001[139] Cohort (5.0 years)	Smith, 2000[160] Cohort (3.8 years)	Median Difference (range)
Urinary Function	ADT	92.80	84.0	90.0	-4.0 (-9.0 to 1.2)
	CM	91.60	93.0	94.0	
	Diff	1.2	-9.0	-4.0	
Urinary Bother	ADT	73.40	72.0	83.0	-10.7 (-17.0 to -5.0)
	CM	84.10	89.0	88.0	
	Diff	-10.7	-17.0	-5.0	
Sexual Function	ADT	8.30	25.0	29.0	-31.0 (-35.8 to -29.0)
	CM	44.1	54.0	60.0	
	Diff	-35.8	-29.0	-31.0	
Sexual Bother	ADT	66.50	59.0	49.0	-15.0 (-20.0 to 0.6)
	CM	65.90	74.0	69.0	
	Diff	0.6	-15.0	-20.0	
Bowel Function	ADT	82.10	81.0	NR	NA (-10.0 to -4.6)
	CM	86.70	91.0	NR	
	Diff	-4.6	-10.0	NR	
Bowel Bother	ADT	87.20	83.0	NR	NA (-6.0 to -0.9)
	CM	88.10	89.0	NR	
	Diff	-0.90	-6.0	NR	

*Conservative management is a general term used to describe management strategies (active surveillance, watchful waiting). Studies including men in observation, deferred treatment or no treatment groups were considered watchful waiting.

Abbreviations: ADT=androgen deprivation therapy; CM=conservative management; Diff=difference; NA=not applicable; NR=not reported

Adjunctive Testing Performed with PSA-Based Screening

National Comprehensive Cancer Network (NCCN) guidelines suggest one of the following tests as options to risk stratify men with PSA values from 3 to 10 ng/dL before biopsy with the potential benefit of reducing total biopsies and overtreatment of lower-risk cancers.[46] The tests can also be employed after negative biopsy to assist in decision-making regarding repeat biopsy.

Free PSA

The ratio of free PSA/total PSA is recommended by the NCCN as a reflex testing option for men with elevated PSA.[46] Lower levels of free PSA are associated with higher risk for high-grade prostate cancer. The percent free PSA is also a component of the 4kScore and the Prostate Health Index (see below). The Prostate Cancer Prevention Trial (PCPT) risk calculator has also been adapted to include free PSA, if available.

4Kscore

The 4Kscore is generated by a prediction model original based on data from the ERSPC trial. It estimates the patient's risk of biopsy detectable prostate cancer with a Gleason score ≥ 7. The score includes both clinical variables (age, prior biopsy, and digital rectal exam results) with total and free PSA, intact PSA and Human kallikrein 2 (hK2). A recent prospective U.S. study of 1,012 men suggested that, compared to the PCPT risk calculator, the 4Kscore improved the area under the curve (AUC) from 0.74 to 0.82.[58]

Prostate Health Index (PHI)

The PHI is a blood test combining total PSA, free PSA and p2PSA (a precursor PSA isoform). It was approved by the FDA in 2012. A 2014 systematic review and meta-analysis of studies evaluating the diagnostic characteristics of PHI for detection of prostate cancer with a Gleason Score $>= 7$ found a pooled specificity of 0.45 and an AUC of 0.72.[221] A subsequently published retrospective cohort of 250 men found an AUC of 0.78 for PHI compared with an AUC of 0.70 for total PSA for detection of prostate cancer with a Gleason score ≥ 7.[222]

Adjunctive testing in conjunction with biopsy to decide on further treatment or follow up

These tests may be used to improve sensitivity of detection of prostate cancer in men with negative biopsies or biopsies showing high-grade prostatic intra-epithelial neoplasia. The free PSA, 4Kscore, and PHI are also sometimes used in this context. In addition, biomarkers are sometimes used to help inform decisions on treatment versus active surveillance for men with lower risk of prostate cancer.[223]

PCA3

PCA3 is a noncoding mRNA overexpressed in prostate cancer tissue. It can be detected in the urine following vigorous digital rectal exam and is used for men with previous negative prostate biopsies when repeat biopsy is being considered. The ratio of PCA3 to PSA transcripts yields the PCA3 score, which is used to predict the presence of prostate cancer. PCA3 is FDA-approved for the determination of the need for repeat biopsy among men with a prior negative biopsy. In men who are considered to be at elevated risk but who have a negative biopsy, the NCCN recommends consideration of PCA3 testing (or free PSA, 4Kscore, or PHI). [46]

Appendix F. New Adjunctive Testing Strategies

ConfirmMDx
Confirm MDx, a methylation marker genetic test performed on cells from a prostate biopsy sample, has been found in initial studies to have a high negative predictive value, providing decision support to reduce repeated prostate biopsies.[224]

Prolaris
A cell cycle suppression score, Prolaris is based on a 31-gene panel of cell cycle-related genes identified in prostate cancer tissue. It has been associated with the risk of subsequent metastatic disease. It has been approved by the FDA for use in treatment planning for low-risk men with a Gleason score of 6 on prostate biopsy, and for patients who are post-radical prostatectomy and are considered at high risk for prostate cancer recurrence.

Oncotype Dx Genomic Prostate Score (GPS)
Oncotype Dx GPS is a 17-gene RT-PCR-based panel, including 12 prostate cancer-related genes and 5 control genes. Oncotype Dx GPS is used to provide treatment decision support for men with a low- to intermediate-risk prostate cancer Gleason score on biopsy, or after radical prostatectomy.[223] While not FDA-approved, the test is covered by Medicare for men who meet specific criteria.

Imaging testing performed in conjunction with biopsy
When a prostate biopsy is planned to evaluate an abnormal PSA test, the standard method is a transrectal ultrasound (TRUS) guided series of core needle biopsies.[46] Multiparametric MRI is now used at some centers for evaluation of men with high clinical suspicion of prostate cancer and a negative biopsy. Multiparametric MRI of the prostate has been advocated as a preliminary test prior to initial biopsy to evaluate for suspicious lesions, with goals of improving both sensitivity (finding more prostate cancers with Gleason score ≥7) and improving specificity (reducing the rates of negative biopsies and biopsies identifying lower Gleason score cancers).[225] Using software, MRI is also increasingly combined with TRUS (MRI-TRUS "fusion") to allow targeted biopsy. Studies have yielded mixed results,[204-209] with MRI detecting some higher grade cancers missed by TRUS, but some have expressed concerns that MRI alone can miss Gleason 6 cancers.[46] An international multi-site randomized trial is currently in process,[226] recruiting men with clinical suspicion of prostate cancer and no previous prostate biopsy. The trial compares multiparametric MRI targeted biopsy (with no biopsy in the absence of suspicious lesion) to standard 12-core TRUS-guided prostate biopsy. Recruitment began in early 2016 and the trial is planned to be complete in fall of 2017.