Systematic Evidence Review
Number 16

Screening for Prostate Cancer

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Systematic Evidence Review
Number 16

Screening for Prostate Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Context

More than 31,000 men were expected to die from prostate cancer in 2001. Researchers and the public have given most attention for controlling prostate cancer to screening. No well-conducted randomized controlled trial (RCT) of screening has been completed. We are thus left with examining indirect evidence to determine the efficacy of screening for reducing prostate cancer mortality.

Objective

To examine the evidence of the benefits and harms of screening and earlier treatment in reducing prostate cancer mortality and to assist the US Preventive Services Task Force in making recommendations on this topic.

Data Sources

We first developed an analytic framework and 9 key questions that represent the logical chain between screening and reduced mortality. We then systematically searched MEDLINE from January 1994 to September 15, 2002, using the Medical Subject Heading prostate neoplasms and combining this term with predefined strategies to identify English language studies concerning the 9 key questions. We also searched the Cochrane Library, contacted experts, and scanned review bibliographies.

Study Selection

We examined abstracts and full articles of all identified studies to determine whether they met preset inclusion and exclusion criteria for each key question. We selected studies that met the following inclusion criteria: (1) randomized controlled trials (RCTs), case-control studies, and ecologic studies that examined links between screening and reduced mortality, (2) studies that addressed the accuracy, reliability, and yield of screening tests by applying the test and a reference standard uniformly to a defined population; (3) RCTs with clinical outcomes for treatment questions; (4) studies of patient reports about their experience with screening or various treatments; and (5) studies that examined or modeled the costs and benefits of screening. For key questions about treatment, we required RCTs with clinical outcomes. We graded the quality of all included articles according to criteria established by the USPSTF.

Data Extraction

Members of the study team abstracted relevant information from included studies and entered it into established abstraction forms. The first author checked all abstractions against the original papers.

Data Synthesis

No conclusive direct evidence shows that screening reduces mortality from prostate cancer. Although we could not precisely determine the sensitivity and specificity of screening with prostate-specific antigen (PSA) and digital rectal examination (DRE), research is clear that these tests can detect prostate cancer at an earlier stage than clinical detection. Because of the

heterogeneity in the natural history of prostate cancer, we could not determine how many screen-detected cancers would eventually become clinically important. The efficacy of treatment for clinically localized prostate cancer detected by screening with any of the currently used approaches is unknown. Each treatment is associated with several well-documented potential harms. The cost of a national screening program is potentially large. Modeling studies show that men ages 50 to 69 years could receive benefit at reasonable cost from screening under favorable assumptions about the efficacy of earlier treatment. These studies do not adjust for the potential harms of screening. Given the current strategy for screening, men with a life expectancy of less than 10 years are unlikely to benefit even under favorable assumptions.

Conclusions

We are unable to determine the net benefit of screening because we cannot establish the presence and, if present, the magnitude of benefit from screening. We can establish the presence of potential harms.

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I. Introduction

Background

Prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer death in US men. Although several studies are exploring the potential of primary prevention of this disease, primary care clinical practice is currently dealing with great public interest in screening.

Screening for prostate cancer is a controversial topic. Those in favor of screening point to the lack of symptoms in early stage disease, the higher 5-year relative survival for localized (greater than 99%) compared with distant (less than 40%) cancer, and the fact that screening increases the proportion of cancers detected at an early stage.[1] Those opposed point to the lack of strong evidence that earlier treatment produces better health outcomes and the problem of harms arising from the various treatments for prostate cancer.[2]

Different medical groups make different recommendations about screening for prostate cancer. In 1996, the United States Preventive Services Task Force (USPSTF) recommended against screening for prostate cancer.[2] The American College of Physicians-American Society of Internal Medicine (ACP-ASIM) and the American Academy of Family Physicians have both recommended shared decisionmaking.[3,4] The American Urological Association and the American Cancer Society both have recommended offering screening to every eligible man with a life expectancy of more

than 10 years, but have also emphasized the importance of providing adequate information before testing.[5-7]

Since the earlier USPSTF review, investigators have completed new research bearing on the issue of screening for this disease. Among these studies are 2 case-control studies of the effectiveness of digital rectal examination (DRE) in reducing mortality from prostate cancer; analyses of changes in the incidence of and mortality from prostate cancer in various locations; randomized controlled trials (RCTs) of new approaches to its treatment; examinations of the operating characteristics of strategies for prostate cancer screening; and more research on the frequency of harms from treatment of the disease and ways to reduce those harms.

Given the continued controversy over this issue and the new evidence that has appeared since the previous review, the RTI-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) undertook this review for the use of the USPSTF in reconsidering its previous conclusions and recommendation.

Burden of Suffering

In 2001, the American Cancer Society predicted that 198,100 men would be diagnosed with prostate cancer and that 31,500 men will die from this disease.[7] Misattribution of cause of death on death certificates makes an exact counting of men dying as a result of prostate cancer difficult. Some studies show that misattribution of cause of death for this disease may be as high as 20% and that the misclassification may be higher among older men and may vary by aggressiveness of therapy.[8] What is clear is that, among cancers, only lung cancer kills more men each year.

I. Introduction

As discussed more fully in Chapter III (Results), the incidence of prostate cancer increased slowly from at least the 1970s to 1989, when it increased more dramatically, averaging a gain of 20% per year.[1,9] After 1992, the incidence of prostate cancer declined at a rate of 10% to 11% per year. These changes have been widely attributed to screening.

Prostate cancer mortality in the United States had been gradually increasing for many years until it began to increase more rapidly in the late 1980s and then to decline in 1991. The age-adjusted mortality rate for all men ages 65 years and older dropped from 243.8 deaths per 100,000 (2.9 per 100,000 among men younger than 65) in 1991 to 206.9 deaths per 100,000 (2.3 per 100,000 for men younger than 65) in 1997, a relative decrease of 15.1% (20.7% for men younger than 65).[1,9] Observers have attributed this decline in mortality to several different factors, as discussed later in this review.

The burden of prostate cancer falls disproportionately on older men and African-American men. The median age at diagnosis is about 71 years; the median age at death is 78.[1] More than 75% of all cases of prostate cancer are diagnosed in men more than 65 years of age, and 90% of deaths due to this disease are in this age group.[1,10] The average number of life years lost per person dying of prostate cancer is 9.0, compared with 19.3 years for breast cancer and 13.4 years from colorectal cancer.[11]

African-American men have about a 60% higher incidence rate and a 2-fold higher mortality rate than white men.[1] Five-year relative survival is 9% to 15% higher for white men than for African-American men, depending on the date of diagnosis.[1]

Epidemiology

Difference Between Incidence and Mortality

The incidence of prostate cancer in the United States is almost 5 times the mortality rate. This is a larger ratio than any of the other major cancers.[1,12] This implies that, although prostate cancer is a major cause of cancer death, many more men are diagnosed with this cancer than die from it.

Risk Factors

The etiology of prostate cancer is unknown. The best-documented risk factors are age, race-ethnicity, and family history. Some studies have also shown statistical associations between prostate cancer and dietary fat, androgen levels, and previous vasectomy, but the results have been neither consistent nor strong enough to recommend taking actions on the basis of these variables to reduce prostate cancer incidence or mortality. Benign prostatic hyperplasia (BPH), a common enlargement of the prostate gland often seen in older men, is not a risk factor for prostate cancer.

The age-specific incidence curve increases more rapidly for prostate cancer than for any other cancer. The incidence rate for men ages 45 to 49 years is 26.6 per 100,000; for men ages 55 to 59 years, 284.4 per 100,000; for men ages 65 to 69 years, 898.7 per 100,000; and for men ages 75 to 79 years, 1,118.5 per 100,000.[13-15] The lifetime risk of being diagnosed with prostate cancer is about 1 in 6.

Mortality increases with age in a similar fashion (1.0 per 100,000 for men ages 45 to 49; 258.8 per 100,000 for men ages 75 to 79). The lifetime risk of dying of prostate cancer is about 3.4% (about 1 in 29).

Incidence rates for African-Americans are among the highest in the world. Incidence rates for Asian-Americans are approximately one-third to one-half those of US whites. Asian-American and Hispanic men in the United States have rates somewhat lower than those of non-Hispanic white men in this country.[10]

Men with a first-degree relative with prostate cancer have an approximate 2-fold increase in risk for the disease, and much of this increased risk is expressed in men younger than age 50.[10,16] Although researchers have made advances in understanding the genetics of this disorder, the evidence is still insufficient to allow screening for specific genetic risk factors.

Screening Tools

Two basic tools are currently used in the United States to screen for prostate cancer: the DRE test and the blood test for prostate-specific antigen (PSA). With the DRE, the clinician inserts a gloved finger into the rectum to palpate the posterior aspect of the prostate gland for nodules or other abnormalities. The PSA test involves drawing a sample of blood that is tested for a glycoprotein produced primarily by epithelial cells in the prostate gland. Although blood levels of PSA often increase with prostate cancer, other conditions as BPH and prostatitis also may raise PSA levels.

Variations of the PSA test have been developed, primarily to improve the specificity of the test. These include PSA density (the ratio of the PSA level to the volume of the prostate as measured by transrectal ultrasound [TRUS]), PSA velocity (the rate at which the PSA increases over time), the percentage of free PSA (the ratio of the

portion of total PSA that is not bound to serum proteins [and thus is "free"] to total PSA), and the amount of PSA that is complexed with proteins.

Treatment Modalities

Clinicians have used 5 main types of therapies to treat patients with prostate cancer. These include surgery (radical prostatectomy), external beam radiation therapy (EBRT), brachytherapy (the implantation of small radioactive pellets within the prostate), hormonal manipulation (previously with estrogenic drugs or orchiectomy, now primarily with luteinizing hormone-releasing hormone agonists [LHRH agonists] or nonsteroidal antiandrogens, or both), and "watchful waiting" or expectant therapy (involving no treatment until symptoms arise or there is other evidence of progression).

Staging and Histologic Grading

Two important prognostic factors in prostate cancer are stage and histologic grade. One must understand these factors to appreciate fully the issues involved in screening.

Stage refers to the extent of the disease. Stage can be classified clinically, that is, estimated from clinical tests such as DRE, blood tests, computerized tomography (CT), radionuclide bone scan, or magnetic resonance imaging (MRI), or it can be classified pathologically by using information from histologic examination of the tumor and/or lymph nodes. Two staging systems are in current use – the Whitmore (A-D) approach and the Tumor-Nodes-Metastasis (TNM) approach. Their different stages and substages are defined in Table 1.

An important distinction is whether the cancer is confined within the prostate ("organ-confined" or "localized") or has spread to extracapsular (i.e., outside the prostate capsule) sites. Among neoplasms that have spread outside the capsule, some have spread only to contiguous structures (e.g., periprostatic tissue, seminal vesicles, local lymph nodes) and are termed "locally advanced"; others that have spread to distant structures (e.g., bone) are thus metastatic.

When it is first detected, prostate cancers can be categorized into "clinically localized" or "clinically advanced" disease. Clinically localized refers to the absence of any clinical evidence of spread beyond the prostate itself. If the patient undergoes surgery, the tumor can then be pathologically staged. As discussed later in this review, a number of clinically localized cancers are found at surgery to have spread beyond the capsule.

Histologic grade of the tumor refers to the degree of differentiation of the tumor cells. Pathologists use a standardized scoring system called the "Gleason score" to indicate the degree of differentiation.[17] It ranges from 2 to 10, with 2 to 4 indicating well-differentiated tumor cells, 5 to 7 indicating a moderate degree of differentiation, and 8 to 10 indicating poor differentiation.

Although the Gleason score is the standard grading system, studies have found problems with interobserver variability of this score. Aggregating scores into the 3 categories of well, moderate, and poor differentiation improves reliability.[17] Another problem is the agreement between Gleason scores based on biopsy specimens and scores based on larger amounts of tumor on surgical pathology specimens. One study found

74% agreement within a Gleason score of ± 1 between prostatectomy and biopsy specimens. The number of specimens overgraded and undergraded was similar.[18]

Focus of this Review

The purpose of this review is to update the USPSTF review appearing in the second *Guide to Clinical Preventive Services*.[2] As described more fully in Chapter II, we focus on evidence published since 1994 of the efficacy of screening in reducing mortality from prostate cancer, on the yield of screening tests and the potential harms of screening, on the benefits and harms of treatments for prostate cancer, and finally on the costs and cost-effectiveness of screening.

Table 1. Staging systems for prostate cancer

Clinical Stage		
A-D System	**TNM System***	**Definition**
1. Clinically nonpalpable cancers		
A_1	T_{1a}	Incidental finding of cancer in ≤ 5% resected (removed) tissue from TURP.
A_2	T_{1b}	Incidental cancer finding > 5% resected tissue. Moderately or poorly differentiated grade with < 5% resected tissue from TURP.
B_0	T_{1c}	Cancer detected by needle biopsy (e.g., following elevated PSA).
2. Palpable cancers apparently confined within prostate capsule		
B_1	T_{2a}	Involves one-half of one lobe of the prostate or less.
B_1	T_{2b}	Involves more than one-half of one lobe, but not both lobes.
B_2	T_{2c}	Involves both lobes of gland but apparently confined (B_2, but not T_{2c} cancers can be greater than 1.5 cm but still involve only one lobe.
3. Local extra-capsular penetration		
C_1	T_{3a-3b}	Penetration of the prostate capsule palpable without evidence of invasion of the seminal vesicles outside the prostate.
C_2	T_{3c}	
	T_{4a-4b}	Palpable invasion of seminal vesicle. Invasion of the bladder neck, external sphincter, rectum, or pelvic muscles.
4. Metastatic Disease		
D_1	N_x	Cannot assess; no apparent nodal involvement
	N_1 N_2 N_3	Metastasis in a single lymph node 2 cm, metastasis single nodes 2-5 cm, or multiple nodes (all ≥ 5 cm), metastasis in node ≥ 5 cm.
D_2	M_1	Distant metastasis.
	M_{1a}	Lymph nodes outside the region of the prostate
	M_{1b}	Bone.
	M_{1c}	Other site(s).

* In the TNM system, "T" refers to characteristics of the tumor, "N" refers to the extent cancerous cells are found in lymph nodes, and "M" refers to the extent of metastasis (spread of the cancer).

PSA indicates prostate-specific antigen blood test; TURP, Transurethral resection of the prostate, a procedure for treating benign prostatic hypertrophy (BPH), a noncancerous enlargement of the prostate, by surgically removing parts of the gland.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et.al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment.[13]

II. Methods

This chapter documents procedures that the RTI-UNC Evidence-based Practice Center (EPC) staff used to develop this report on screening for prostate cancer. During preparation of the evidence report, we collaborated with 2 current members of the US Preventive Services Task Force (USPSTF) who served as liaisons to the EPC topic team (see Acknowledgements). We first document the analytic framework and key questions developed at the beginning of the review. We then describe the inclusion and exclusion criteria for admissible evidence, our strategy for literature search and synthesis, and our approach to developing the final summary of the evidence.

Analytic Framework and Key Questions

The analytic framework (Figure 1) describes the relationship between screening and treating patients in a clinical setting and reduced morbidity and/or mortality from prostate cancer. The arrows with superscripts in the analytic framework represent steps in the chain of logic connecting screening with reduced morbidity and/or mortality from prostate cancer; the superscripts refer specifically to 9 key questions that guided our literature searches and synthesis of the evidence. We examined 1 overarching question (Key Question 1, linking screening and ultimate health outcomes) and 8 additional questions pertaining to specific links in the analytic framework.

Key Question 1: What are the health outcomes (both type and magnitude) of screening a defined population for prostate cancer compared to not screening?

Key Question 2: What is the yield of screening for prostate cancer (i.e., accuracy and reliability of screening tests, prevalence of undetected cancer in various populations)?

Key Question 3: What harms are associated with screening for prostate cancer?

Key Questions 4-7: What are the health outcomes associated with treating clinically localized prostate cancer with radical prostatectomy, external beam radiation therapy or brachytherapy, androgen deprivation, or watchful waiting?

Key Question 8: What harms are associated with treatment of clinically localized prostate cancer with the treatments above?

Key Question 9: What costs are associated with screening for and early treatment of prostate cancer? Have studies modeled the potential benefits of screening? What is the cost-effectiveness of screening for prostate cancer?

Eligibility Criteria for Admissible Evidence

The authors and Task Force liaisons developed eligibility criteria for selecting the evidence relevant to answer the key questions (Table 2). We first searched for evidence from randomized controlled trials (RCTs) for the efficacy of screening. As we found no well-conducted and well-analyzed RCT of screening, we then examined case-control and ecologic evidence regarding the overarching key question (Key Question 1).

For Key Question 2, concerning the operating characteristics of screening tests, we examined well-conducted systematic reviews and individual studies that started with a primary care or unselected population without prostate cancer and that compared the findings of 1 or more screening tests with an adequate reference standard. For Key

Questions 4 through 7, concerning the effectiveness of various therapies, we required evidence from RCTs with health outcomes. For Key Questions 3 and 8, concerning the harms of screening or treatment, we required either RCTs or well-controlled studies that included patient reports and, for treatment, at least 12 months of follow-up. Finally, for Key Question 9, we searched for evidence of the costs and cost-effectiveness of screening, including models of potential benefits, that considered all appropriate costs and estimates of effectiveness supported by reasonable assumptions based on good evidence.

Literature Search Strategy and Synthesis

The analytic framework and key questions guided our literature searches. We examined the critical literature described in the review by the USPSTF (published in 1996)[2] and searched the reference lists of systematic reviews (including Cochrane Library reviews) published since 1993. We then used our eligibility criteria to develop search terms and searched the MEDLINE database for relevant articles concerning humans in the English language published between January 1, 1994, and September 15, 2002. We especially looked for articles involving patients whose experience is clearly generalizable to a primary care US population.

The search strategy and results are given in Table 2. All searches started with the term "prostate neoplasm" and then proceeded by adding further terms as shown in the table.

The first author reviewed abstracts of all articles found in the searches to determine which met eligibility criteria. Other authors reviewed all abstracts excluded by

the first reviewer. We retrieved the full text of all articles not excluded by both reviewers (see next to last column in Table 2).

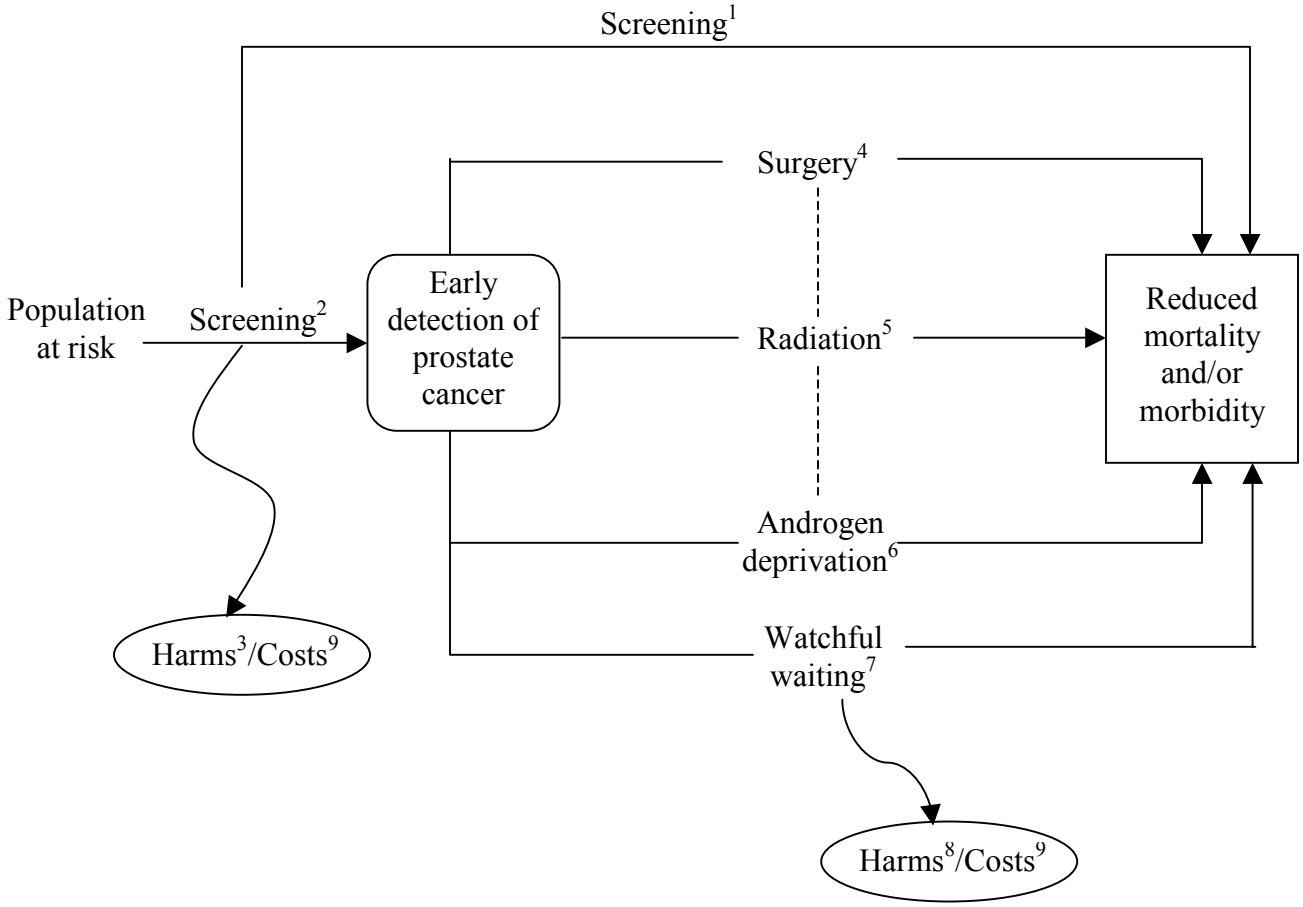
One reviewer then examined the full text of all retrieved articles against the inclusion/exclusion criteria and discussed all excluded articles with one of the other reviewers. We included any article that either reviewer judged had met inclusion criteria (see last column in Table 2). Three of the authors then divided the articles and abstracted data from them, entering the relevant data into predesigned evidence tables (see Appendix B). The abstracting author also graded the articles using the criteria established by the Methods Work Group of the USPSTF.[19] The first author read all articles, checked the grading, and discussed the crucial ones with a second author. The authors also discussed key articles with the Task Force liaisons.

Development of the Final Systematic Evidence Review

The authors presented an initial work plan including a provisional analytic framework and key questions to the entire Task Force in September 2000; we also presented interim reports on results of the literature search and the early results of the synthesis of information in December 2000, March 2001, and September 2002. This draft Systematic Evidence Review was submitted for broad-based external peer review in May 2001; the peer review involved individual experts in the field, representatives of relevant professional organizations, and representatives of organizations and federal agencies that serve as liaisons to the USPSTF. After we received peer review comments and revised the evidence review accordingly, the Task Force voted on the recommendation at its June, 2001 meeting, and finalized the recommendation at its

September, 2002 meeting. Afterward, we revised the report for journal publication and made final revisions to this version for the AHRQ website.

Figure 1. Analytic framework for screening for prostate cancer



NOTE: Superscripts refer to Key Questions addressed by this review (see Table 2 and text).

Table 2. Inclusion criteria, search strategy, and results of searches

Key Question	Inclusion Criteria	Search Terms	Number of Articles	
			Identified for Abstract Review	Retained for Full Review
1. Efficacy of screening in reducing mortality from prostate cancer	RCT or case-control Screening test (PSA or DRE or other) Health outcomes ----- or ----- Surveillance (ecologic) study of PC incidence morbidity or mortality over time Defined population Associate mortality with screening	Prostate neoplasm Mass screening RCT Case-control ---------- Prostate neoplasm Incidence Mortality Trends Surveillance	100 1399	RCT, 1 Case-control, 2 Ecologic, 15
2. Yield of screening tests	Unselected population without PC Screening test used for all Result of screening test compared with a valid gold standard applied to all	Prostate neoplasm Mass screening DRE, PSA Diagnosis Sensitivity/ Specificity Predictive value Reproducibility	1905	35
3. Harms of screening	Unselected population Screened group compared with not screened group Either randomized or adjustment for confounders Reliable measure of adverse effects	Prostate neoplasm Mass screening Adverse effects Anxiety, depression Labeling Quality of Life	94	1

Table 2. Inclusion criteria, search strategy, and results of searches (continued)

Key Question	Inclusion Criteria	Search Terms	Number of Articles Identified for Abstract Review	Number of Articles Retained for Full Review
4 - 7. Health outcomes of treatment	RCT or large cohort with control group Follow-up at least 2 years At least 75% of patients followed Health outcomes	Prostate neoplasm Therapeutics Treatment Surgery, prostatectomy Radiation Brachytherapy	656	KQ4: 3 KQ5: 0 KQ6: 10 KQ7: 6
8. Harms of treatment	Unselected population with PC Treated group compared with valid comparison group Either randomized or adjustment for confounders Not metastatic cancer Valid measures of harms At least 75% of patients followed At least one year follow-up	Prostate neoplasm Therapeutics Treatment Surgery, prostatectomy Radiation Adverse effects Side effects Impotence Urinary incontinence Quality of life	923	32
9. Costs/cost-effectiveness of screening	Costs of screening Costs of treatment Cost-effectiveness, cost-utility Modeling studies	Prostate neoplasm Costs and cost analysis Cost-benefit Cost-effectiveness	84	2

III. Results

This chapter presents results from our review of the scientific literature pertaining to the 9 key questions listed in Chapter II and identified in the analytic framework. We divide the discussion into subsections as dictated by the topic. Evidence tables providing more details about the design, conduct, results, and quality of the studies reviewed for this report are found in Appendix B; the specific evidence tables are identified in the relevant sections below. Citations to specific publications in the evidence tables represent the articles from a given study that document specific information in the table itself; other papers from the same study that were not used for specific data in evidence tables are not cited there but may be used in the text and cited in this chapter.

Key Question 1: Efficacy of Screening in Reducing Mortality from Prostate Cancer

The first key question, indicated by the overarching arrow in the analytic framework (Figure 1), can be addressed in 2 ways: directly by data from randomized controlled trials (RCTs) or case-control studies of screening for prostate cancer, or indirectly by associating ecologic, population-level data regarding increases in prostate screening with reductions in mortality at the expected time in the expected population. Thus, we undertook 2 separate searches to examine these issues.

The earlier review by the USPSTF found no RCTs of screening and only a single case-control study (which showed no effect of screening by digital rectal examination [DRE] on prostate cancer mortality). No ecologic data were available at that time.[2]

For the first search, we accepted only RCTs or case-control studies examining the effect of screening on prostate cancer mortality. We found 1 RCT and 2 case-control studies. Details on these studies can be found in Evidence Tables 1A – 1C (Appendix B).

Randomized Controlled Trial

Labrie et al. completed the first RCT of prostate cancer screening.[20] In 1988, the investigators randomized 46,193 men ages 45 to 80 years registered in the electoral rolls of Quebec City and in the Quebec provincial health registries to 2 groups (ratio of 2:1 favoring invited group). One group was invited to be screened with a prostate-specific antigen (PSA) test (cutpoint = 3.0 ng/ml) and DRE. By the end of 1996, about 23% of the invited group and 6.5% of the not-invited group had actually been screened. This low adherence rate reduces the power of the study to detect a true difference that could be attributable to screening.

The authors analyzed the study by combining all men from both the invited and the not-invited groups who were actually screened, comparing their prostate cancer mortality with that for the men in both groups who had not been screened. They calculated a 69% reduction in prostate cancer mortality from screening.

Using data presented in the paper, an intention-to-treat analysis can be conducted. Among the 30,196 men in the invited group, 140 deaths from prostate cancer occurred (4.6 per 1,000); among the 15,237 men in the not-invited group, 73 deaths occurred (4.8 per 1,000). Because of low adherence to screening in the invited group, or because of lack of efficacy of screening, this study does not provide evidence to support the practice of prostate cancer screening.

Two other RCTs of screening for prostate cancer, both initiated in 1994, are ongoing. The National Cancer Institute's "Prostate, Lung, Colorectal, and Ovary" (PLCO) Trial is randomizing 74,000 men ages 60 to 74 years at 10 study sites to annual screening for 4 years with DRE and PSA compared with usual care. The European Randomized Study of Screening for Prostate Cancer (ERSPC) is randomizing 190,000 men ages 50 to 75 years in 7 countries to screening with PSA, DRE, and transrectal ultrasound (TRUS) or usual care. In 1998, the ERSPC investigators changed their screening approach to PSA alone, with a cutpoint of 3.0 ng/ml. Neither of these studies will have data on mortality from prostate cancer for several more years.

Case-Control Studies

The 1996 USPSTF review reported on a case-control study that found no evidence that DRE prevents late-stage prostate cancer (odds ratio [OR] = 0.90; 95% confidence interval [CI], 0.5-1.7).[21] Since that time, 2 additional nested case-control studies have provided mixed results. All 3 studies had similar designs and were well conducted.

Richert-Boe et al. conducted their case-control study among patients of a large health maintenance organization (Kaiser Permanente Northwest).[22] Cases were 150 patients who were 40 to 84 years of age when their prostate cancer was diagnosed and who died of the disease. Investigators selected 2 controls per case, matched for age and membership in the health plan. They then examined medical records to determine whether a previous DRE had been done and whether the DRE was performed for screening or diagnostic reasons. A similar number of cases and controls had had a screening DRE during the 10-year study period (OR = 0.84; 95% CI, 0.48-1.46).

Jacobsen et al. conducted a similar study among residents of Olmsted County, Minnesota, using the unified data system of the Rochester Epidemiology Project.[23] Investigators identified 173 patients who had died of prostate cancer as their cases and matched them to 346 patients as controls (2 per case). As in the previous studies, this research team used medical record reviews to determine whether each patient had had a DRE and whether it had been done for screening or diagnostic reasons. DREs performed during the year immediately before diagnosis were eliminated, because the investigators thought that these could well have been done for diagnostic rather than screening reasons. Control subjects had had more DREs between years 2 and 10 before diagnosis than case subjects (OR = 0.51; 95% CI, 0.31- 0.84), indicating a protective effect of DRE.

The Jacobsen et al. results were robust to a number of different analyses, such as excluding cases (and their matched controls) whose deaths may not have been due to prostate cancer, excluding DREs performed in the presence of symptoms that may have indicated prostate cancer, and adding a comorbidity index as a potential confounder. When they examined the data by year of most recent DRE, the investigators found the same odds ratio for every year up to 6 years before diagnosis but not for more distant DRE.

The reasons for the differences in the results from these otherwise similar studies are not clear. One group has suggested that eliminating DREs in the year before diagnosis in the Jacobsen et al. study adds bias,[24] but a major problem in all 3 studies is distinguishing between screening and diagnostic DRE.[25] We also note that all 3 studies are small, and all are consistent with an effect of DRE of up to 50% reduction in prostate cancer mortality.

We found no case-control studies of PSA screening. This can be explained at least in part by the fact that insufficient time has elapsed since the introduction of PSA as a screening test (late 1980s). Thus, its impact on prostate cancer mortality would be difficult to assess. Such studies are planned, however.[26]

Ecologic Data

For the second search, we accepted only studies of prostate cancer surveillance over time that associated indicators of screening with mortality. We found 7 such studies,[9,28,30,31,33,42,205] although only 2 actually relate screening and mortality in a quantitative manner. An eighth study used national data to model the effect of changes in screening on changes in mortality, given various assumptions about the natural history of prostate cancer.[33] Details can be found in Evidence Table 1C (Appendix B).

The 2 quantitative studies are from investigators at the National Cancer Institute (NCI), using incidence data from the Surveillance, Epidemiology, and End Results (SEER) system, together with mortality data from the National Center for Health Statistics.[9,27,28] They document several trends within the United States: a dramatic increase in age-adjusted prostate cancer incidence that accompanied increased screening in 1989, the peaking of incidence rates in 1992, and the subsequent decline. In 1991, the incidence of distant-stage disease began to decline (for all races and all SEER areas), with a decline in localized and regional disease beginning in 1992. The reduction in the incidence of distant-stage disease has been dramatic: an annual reduction of 17.9% since 1991 in white men.

With regard to prostate cancer mortality, between 1969 and 1987 the age-adjusted rates gradually increased for both whites and African Americans. Between 1987 and

1991, the mortality rates increased at an accelerating rate, 11% increase for white men and 14% increase for African American men. In 1991, mortality rates for whites began to decline and, in 1992, rates for African Americans followed suit: 16.1% decline for white men between 1991 and 1997 and 10.9% decrease for African American men from 1993 to 1997. (Preliminary data showed a continued decline in 1998.) Mortality rates declined in all age groups at about the same time.

The NCI investigators considered several potential factors to explain these trends. One possibility is screening with PSA. PSA testing began to increase at about the time of increasing prostate cancer incidence. A study of Medicare data found that the percentage of white men older than age 65 who had received a PSA test in the previous year increased from 1.2% in 1988 to about 40% in 1994.[34] The pattern of increased incidence followed by decreased incidence, decreasing late-stage disease, and then reduced mortality is what one would expect from the application of an effective screening program. In addition, the fact that mortality started to decline for all races and age groups at about the same time (i.e., calendar period effect) lends support to a global effect that affected all groups similarly.

One problem with ascribing the ecologic trends to screening is the timing of the decline in mortality. With cancers such as prostate, considered to be generally slow growing,[35,36] the time between the application of an effective screening program and an expected reduction in mortality is a matter of many years, whereas in this case a decline in mortality was seen only 2 to 3 years after widespread screening. Using an NCI model, investigators found that PSA screening could explain this trend only with several assumptions.[33] If one assumes that PSA screening reduces prostate cancer mortality by

20%, and if the mean lead-time is no longer than 3 years, then the fall in mortality can be explained largely by screening. Earlier estimates of the mean lead-time of screening for prostate cancer, however, had been 5 years or longer.[35]

The argument that the decline in mortality can be attributed to PSA screening would be stronger if one could show that the decline is largest in areas with more screening. To date, data are conflicting about this issue.[29,37,38]

Another problem with concluding from the ecologic data that screening is effective is the presence of alternative explanations for the trends. Investigators have offered 3 general hypotheses. The first 2 explanations agree that PSA likely accounts for the increased incidence of prostate cancer but offer different explanations for the decline in mortality. The third explanation postulates the existence of unknown factors.

The first alternative explanation (attribution bias) suggests that misattribution of deaths to prostate cancer that are actually caused by other conditions may account for the trends outlined above. This possibility is suggested by several facts: (1) death from prostate cancer often occurs in older men with multiple comorbid conditions; (2) studies have found inconsistencies between medical record review and death certificate causes of death in men with prostate cancer;[8,39] and (3) the mortality curve for prostate cancer closely parallels the incidence curve (both its rise and fall). If the percentage of deaths attributed mistakenly to prostate cancer is stable, then one would expect that the prostate cancer mortality rate would increase and decrease in close approximation with the prevalence (and thus with the incidence) of prostate cancer in the population.[28] Studies to investigate misclassification of prostate cancer deaths are under way.

The second alternative explanation is that improved treatment has reduced mortality. During the late 1980s and early 1990s, 3 major treatment changes emerged: (1) rates of radical prostatectomy increased; (2) luteinizing hormone-releasing hormone (LHRH) agonists and antiandrogen agents were developed, and this allowed for improved androgen deprivation without castration; and (3) refinements were made in radiation therapy, such as 3-D conformal radiation.

The third possible explanation for these puzzling trends is that changes in one or more unknown risk factors are increasing both the incidence and the mortality from prostate cancer. This alternative seems less plausible than the others for several reasons: the rates have later declined, the changes occurred so dramatically, and the trends affected all age groups at the same time (whereas risk factor changes typically affect some groups before others). Other experts have noted, however, that mortality from several cancers has been declining recently and that this trend is not completely understood.[40]

Further international analyses of reductions in prostate cancer mortality have been published. Quebec and Canada as a whole,[30] as well as England and Wales,[32] have experienced decreases in the mortality rate from this disease in a pattern similar to that seen in the US SEER data.[30] Within the United States, a population-based analysis from Olmsted County, Minnesota, also shows similar findings.[31]

A recent ecologic analysis from Austria found that prostate cancer mortality in Tyrol, an area with a free screening program, began to drop below that of the rest of the country a few years after screening began.[41,42] This finding could be attributed to the

screening program, changes in treatment that accompanied the program, attribution bias, or some combination of the three.

Summary of Results on Efficacy of Screening

We found a single RCT of PSA screening with low screening adherence and poor data analysis; 3 well-conducted nested case control studies (2 since the second *Guide to Clinical Preventive Services* appeared in 1996) of DRE screening with mixed results; and ecologic evidence that is suggestive but not conclusive of a benefit of screening, largely because of the timing of mortality trends and the presence of alternative explanations. If screening is effective, we are not able to determine to any degree of precision from these data the magnitude of the benefit.

Key Question 2: Yield of Screening for Prostate Cancer

The second key question, indicated by arrow No. 2 in the analytic framework (Figure 1), deals with the yield of screening for prostate cancer. Ideally, we would like to determine what type of prostate cancer is the most appropriate target for screening, the prevalence of this type of cancer, and the sensitivity and specificity of available screening tests for detecting this type of cancer. We first consider 2 methodologic issues involved in these questions: our knowledge about the appropriate target of screening and the optimal reference standard test for use in defining the sensitivity and specificity of screening tests. We then consider estimates of the sensitivity and specificity of PSA screening and, by comparison, the accuracy and reliability of other screening strategies.

Finally, we examine studies of the yield of large screening programs. (Evidence Tables 2A – 2B)

Methodologic Issues

Cancers to Target

Prostate cancer has a heterogeneous natural history. Autopsy studies have found occult prostate cancer in some 30% of men ages 50 and older who have died of other conditions.[13] Although the lifetime risk of being diagnosed with prostate cancer is about 16%, the lifetime risk of dying of this disease is about 3.4%.[14] The discrepancy between these numbers is similar to the discrepancy noted earlier between the annual number of men diagnosed with prostate cancer and the number dying from it. It shows that, although some prostate cancers cause suffering and death, others are clinically unimportant, i.e., they would never cause symptoms within the life span of a typical man.

Ideally, screening would target only those cancers that are destined to cause clinically important disease. What is not clear is how to distinguish clinically important from clinically unimportant prostate cancer.

Most clinicians and researchers have defined clinically important cancers as those that are localized (i.e., intracapsular or organ-confined) and have either a large enough volume or a high enough grade that they appear to have the potential to grow beyond the prostate. Theoretically, this type of cancer can be cured by prostatectomy or radiation therapy. For example, Schroder et al.,[43] in a population-based screening study, found that 62% of men with prostate cancer detected by having a PSA between 4.0 ng/ml and 9.9 ng/ml had cancer confined to the prostate gland, and 32% were both organ-confined and had a Gleason score of 7 or greater, indicating a high potential to grow.

In this model of screening, clinically unimportant cancers are both intracapsular and have no characteristics associated with further growth. In most screening studies, investigators find only a small percentage of cancers that meet these criteria. For example, in a screening study of volunteers utilizing PSA and DRE, Catalona et al.[44] found that only 8% of cancers detected by screening were organ confined, well differentiated, and involved 1 prostate quadrant.[45]

The size of the discrepancy between diagnoses and deaths indicates that this model cannot be exactly correct. Not everyone with clinically important cancers by these criteria dies of prostate cancer; the criteria for defining clinically unimportant cancers are too restrictive.

Statistically, the characteristics chosen by these researchers to define clinically important (or unimportant) cancer are correct. Pathologic stage at diagnosis, histologic grade of the tumor, tumor volume, patient age, and PSA level are associated with prognosis. Men with good combinations of all these factors have an excellent prognosis (and their cancers are likely not clinically important); men with bad combinations of all of these factors have a poor prognosis (and their cancers are likely clinically important).

Unfortunately, the great majority of men with screen-detected prostate cancer fall between these extremes; their prognosis remains uncertain.[46-50] Research has yet to define factors for this large "intermediate" group that discriminate well between those men with cancers that are destined to cause suffering and death and those men with cancers that will cause no or minimal symptoms.[51]

In addition to refining the above model with better criteria, we might consider another model. Although some organ-confined prostate cancers are clinically important,

a second group of cancers may also be important in the sense of being responsive to earlier treatment. These are tumors that have invaded locally beyond the capsule (i.e., "extracapsular" or "locally invasive"), with or without metastases to distant structures. If treatment of these cancers could delay their progression, even if the men were not cured, screening might still provide substantial benefit. Recent trials showing the effectiveness of androgen deprivation treatment for locally advanced cancers should at least raise the question of whether such cancers should be considered an appropriate target for screening. These points are taken up again in the discussion of Key Question 6, below.

Thus, the definition of clinically important prostate cancer, the target of screening, is not yet settled. Among the unresolved issues are which organ-confined cancers are most important to find and treat and whether some extracapsular tumors should be regarded as appropriate screening targets. The lack of a clear, evidence-based definition of clinically important cancer makes it impossible to determine the extent to which screening detects clinically unimportant cancer, a critical issue in the screening controversy, and this problem in turn complicates calculating the potential benefits and harms of screening.

Those who claim that screening detects only a small number of clinically unimportant cancers argue that PSA and DRE are sensitive enough to detect clinically important cancer, but *not* sensitive enough to detect clinically unimportant cancer. A retrospective analysis from the Physicians' Health Study has been cited in support of this idea.[35] In this study, conducted before widespread PSA screening, investigators drew blood and froze the sera at the beginning of the study. After the study, they analyzed the sera for PSA. The PSA results for men who had been diagnosed with prostate cancer (N

= 366) were compared with those of a matched control group. Using a PSA cutpoint equivalent to 4.0 ng/ml to define abnormal, the investigators found that the PSA test was more sensitive for cancers that were labeled "aggressive" (i.e., extracapsular or higher grade) than for those that were labeled "nonaggressive" (i.e., intracapsular and lower grade). Although provocative, this study still leaves unanswered the question of how many of these detectable prostate cancers were clinically important, as about 90% of men with prostate cancer did not die of this disease over the follow-up period.[35]

Further research is needed to define better the factors that discriminate between different prognostic types of prostate cancer. In the meantime, the percentage of prostate cancers detected by screening that would never cause serious clinical symptoms and the prevalence of cancers that would cause such symptoms are both unknown.

Reference Standard

To calculate the sensitivity and specificity of a screening test, ideally, one should compare the results of a screening test with a standard reference test that has been applied uniformly among all those screened. The usual reference standard used in prostate cancer screening studies is transrectal needle biopsy of the prostate, but this test is rarely done in the absence of a positive screening test.

Even if it were done uniformly in screening studies, prostate needle biopsy is an imperfect reference standard for 2 reasons. First, it misses some cancers; from 10% to 20% of men who had had a negative initial series of biopsies have cancer on repeat biopsy series.[52-56] Thus, some men categorized as not having cancer actually do have it, falsely lowering the measured sensitivity.

Second, in clinical practice and research, a "biopsy" is actually from 4 to 6 (or more) biopsies. Multiple biopsies are taken, most from normal-appearing areas of the prostate. An analysis of this practice concluded that up to 25% of apparently PSA-detected tumors and more than 25% of apparently DRE-detected tumors were likely in fact to have been detected by serendipity, that is, an incidental finding from a blind biopsy.[57] Thus, some men who are categorized as having cancer detected by screening actually have serendipity-detected cancer. This again falsely increases sensitivity.

Another possible reference standard is longitudinal follow-up. Men who do not develop clinical prostate cancer over an extended period of time did not have clinically important cancer. Other than the retrospective Physicians' Health Study described above, we found no study that used longitudinal follow-up of screened and nonscreened populations as a reference standard.

Accuracy of Screening

The most common screening tests for prostate cancer are PSA and DRE. TRUS has been largely abandoned as a primary screening modality because of its high cost, inadequate reproducibility, and inadequate sensitivity. We discuss here the operating characteristics of the PSA, the DRE, and proposed variations on the PSA test.

Because of the problems of an imperfect reference standard that is not uniformly applied and the lack of an evidence-based definition of what cancers should be the target of screening, the sensitivity and specificity of screening tests for prostate cancer cannot be determined with precision. Cancers that are actually present may be missed; cancers may be detected serendipitously and attributed to screening; and cancers that have no

clinical importance may be detected and counted as true positives rather than as false positives.

Screening with PSA

The Physicians' Health Study avoids some of the bias of the problematic reference standard by employing longitudinal follow-up as a reference standard.[35] Nevertheless, DRE screening may well have occurred (as this study involved a group of physicians with ready access to health care). The sensitivity of a PSA of 4.0 ng/ml or higher for detecting aggressive prostate cancers that appeared within 2 years of screening was about 91%; the sensitivity for detecting nonaggressive cancers within the same period was about 56%. The sensitivity for cancers appearing within 4 years was 87% for aggressive cancers and 53% for nonaggressive cancers. Among men who were not diagnosed with prostate cancer over 10 years, 9% had an initial PSA of 4.0 ng/ml or greater (i.e., specificity of 91%).

With the methodologic concerns above, other studies provide estimates of sensitivity for PSA with a cutpoint of 4.0 ng/ml of 63%[58] to 83%.[59] A recent population-based screening study estimated the sensitivity of this strategy to be 73%.[43]

Mettlin estimated the specificity of PSA (cutpoint of 4.0 ng/ml) to be about 90% for the first screening round,[58] and Jacobsen et al. found declining specificity with age: 98% for men in their 50s to 81% for men in their 70s.[59]

PSA has a lower specificity among men with larger prostate glands. This includes the large number of older men with BPH. One study of 4 carefully chosen populations found, for example, that the likelihood ratios for various PSA levels were much lower

among men with BPH than among men without BPH.[60] Thus, the PSA does not distinguish cancer as well among men with BPH as among those without BPH.

Because of the reduced specificity in older men with BPH, some experts have proposed that the PSA cutpoint be adjusted for age, with higher cutpoints for older men and lower cutpoints for younger men. [61] Age-adjusted cutpoints might be different in African American and white men.[62] Clearly, this change would increase cancer detection among men in their 50s (i.e., increase sensitivity and reduce specificity) and reduce detection among men in their 70s (i.e., decrease sensitivity and increase specificity). One study found that this strategy had little impact on overall specificity and missed more cancers than the non-age-adjusted PSA strategy.[63] Another multi-site study found that age-adjusted PSA cutpoints did improve specificity, but at the cost of a large reduction in sensitivity among older men. They found that other screening strategies (such as percent free PSA [%fPSA], see below) were superior in maintaining overall accuracy.[64] Oesterling argues, however, that improving sensitivity in younger men and specificity in older men actually improves the likelihood that the test will reduce prostate cancer mortality.[65]

To improve the detection of clinically important cancers, some have proposed decreasing the cutpoint for defining an abnormal PSA for all men from 4.0 ng/ml to 3.0 ng/ml (or even 2.6 ng/ml).[66,43,67] Studies of patients with PSA between 2.6 ng/ml or 3.0 ng/ml and 4.0 ng/ml who were screened with DRE or TRUS, or who were offered biopsy at this lower PSA value, have found that 12% to 23% of these patients have prostate cancer.[68] Decreasing the cutpoint for PSA from 4.0 ng/ml to 2.6 ng/ml or 3.0 ng/ml

would increase the percentage of men undergoing biopsy by an absolute 6% to 11%.[67,69-71]

Some have argued that many of these cancers are clinically important and thus need to be detected and treated.[69,72] The value of this increased detection, however, is unknown. In one study, 80% of the cancers detected among men who had PSA values between 2.6 ng/ml and 4.0 ng/ml (and who had surgery) were pathologically organ confined; 17% were low volume and low grade (the authors' definition for clinically unimportant).[68]

Screening with Variations on the PSA

PSA Density. Because of the problem of reduced specificity in older men with BPH, Benson proposed that the PSA be adjusted for prostate volume as measured by TRUS.[73,74] This test, called the PSA density (PSAD), is expressed in ng/ml PSA/cc prostate gland. Higher values indicate a higher probability of prostate cancer. Cutpoints from 0.078 to 0.15 have been used in the research literature.

Several research groups have tested the PSAD at various cutpoints; none found a large advantage beyond simple PSA testing.[64,75-78] Because the PSAD is more expensive and logistically difficult, and because some investigators have found that the TRUS lacks reproducibility,[79] the PSAD test has fallen out of favor as a primary screening test.

Percent free PSA (%fPSA). In the serum, PSA circulates in 2 forms: free and complexed with such molecules as alpha-1 antichymotrysin. Men with prostate cancer tend to have a lower percentage of their PSA in the free form compared with men without prostate cancer.[80,81] Thus, %fPSA (in which higher values are more "normal") has been proposed as a new test to improve the specificity of the total PSA assay. Various

cutpoints have been used; an abnormal test, indicating possible cancer, may be a value below 15%[82] to 30%.[83]

Several studies have examined the %fPSA test. Its major use in research has been to increase the specificity of screening by distinguishing between men with PSA between 4.0 ng/ml and 9.9 ng/ml who should be biopsied and those who should not. Using various cutpoints, from 20% to 40% of biopsies could potentially be avoided, although 2% to 15% of cancers would then be missed.[82,84-88]

Catalona et al.[44] proposed %fPSA as a second stage-screening test for men with PSA between 2.6 ng/ml and 4.0 ng/ml.[45,68] These investigators were able to define a cutpoint that would hypothetically detect 90% of cancers while avoiding 18% of biopsies.

Like lower total PSA, higher %fPSA has been associated with better stage and histologic markers of prognosis among men with prostate cancer.[64]

An important question with %fPSA, however, is how useful it actually is in clinical practice. To be useful, a negative %fPSA would have to reduce the probability of prostate cancer to a low enough level that men would be willing to forego biopsy.

A systematic review of studies examining %fPSA found that, using the authors' cutpoints for an abnormal test, a man with a PSA of between 4.0 ng/ml and 9.9 ng/ml would still have a probability of prostate cancer of 8% after a negative %fPSA test. Although this additional information represents a decrease in the man's probability of having prostate cancer, it is uncertain whether the reduction goes low enough for most men to forego biopsy. In practice, therefore, the test may or may not reduce the biopsy rate.[89]

A similar test, the amount of PSA complexed to alpha-1-antichymotrysin (complexed PSA) has also been shown to enhance specificity relative to total PSA, especially at lower levels of PSA.[90-93] Again, the issue remains whether this increased specificity is adequate to reduce the number of biopsies in actual practice.

PSA Velocity. In a small study, Carter noted that men with prostate cancer have a greater increase in their PSA over time than men without cancer.[94] Thus, he proposed that the annual rate of increase in PSA (PSA velocity) be considered as a way of increasing the specificity of the PSA test, using a cutpoint of PSA increase at or greater than 0.75 ng/ml per year. In other studies, this degree of change was neither sensitive nor specific for detecting cancers found by other screening tests.[63,95] Because of intraindividual variation, PSA velocity is most useful in men who have 3 or more PSA determinations each separated by a year.[63,96,97]

Screening with DRE

DRE has a lower ability to detect cancer than PSA. A meta-analysis of DRE studies of unselected populations screened by both PSA and DRE found a sensitivity of 59% (64% for the 4 best studies).[98] A recent study not included in the meta-analysis found that, although DRE found some cancers in men with PSA levels below 4.0 ng/ml or even 3.0 ng/ml, these cancers were usually small and well differentiated.[99] In another large screening study of volunteers, the overall cancer detection rates were as follows: DRE alone, 3.2%; PSA (cutpoint 4.0 ng/ml) alone, 4.6%; the combination, 5.8%.[44] A Canadian screening study found that about 90% of detected cancers would have been found by PSA screening alone. The investigators calculated that 344 men with a normal PSA would need to be screened to find a single prostate cancer.[100]

A final factor that dilutes the usefulness of DRE is its limited reproducibility. In 1 small study, the kappa of agreement among 8 urologists, fellows, and residents was 0.22.[101]

Studies of the Yield of Large Screening Programs

We found 6 screening studies of large populations using either PSA or a combination of PSA and DRE as the screening test followed by multiple-core prostate biopsy as the diagnostic standard.[20,43-45,67,102-106] Each study reported on a single screen among men, most of whom had not previously been screened. One study recruited volunteers from the areas around 6 medical centers;[45 44] the other 5 were population-based studies of men accepting an invitation to be screened. All studies included men beginning at age 45 to 55 and ending at age 67 to 80. Other studies have screened large populations but have used different screening strategies (e.g., American Cancer Society-Prostate Cancer Detection Project [ACS-PCDP]).[58] Using the results of these studies, we can estimate the yield of a screening program for men of different ages (Figures 2-4).

The percentage of participants with a PSA of 4.0 ng/ml or higher ranged from 6.5% (in a younger cohort from Spain) to 14.8% (in an older population of white volunteers from the United States); the percentage with PSA of 3.0 ng/ml or higher ranged from 14% (Finland) to about 20% (Quebec and Rotterdam). The additional percentage of men who had an abnormal DRE but a PSA less than 4.0 ng/ml ranged from 2.2% (Spain) to 11.0% (US volunteers). The total percentage of men with either a PSA greater than or equal to 4.0 ng/ml or a positive DRE is between 8.7% (Spain) and 25.8% (US volunteers).

***Figure 2*: Ages 50-59 - estimated yield of screening with PSA (or PSA and DRE) (prevalence screen)**

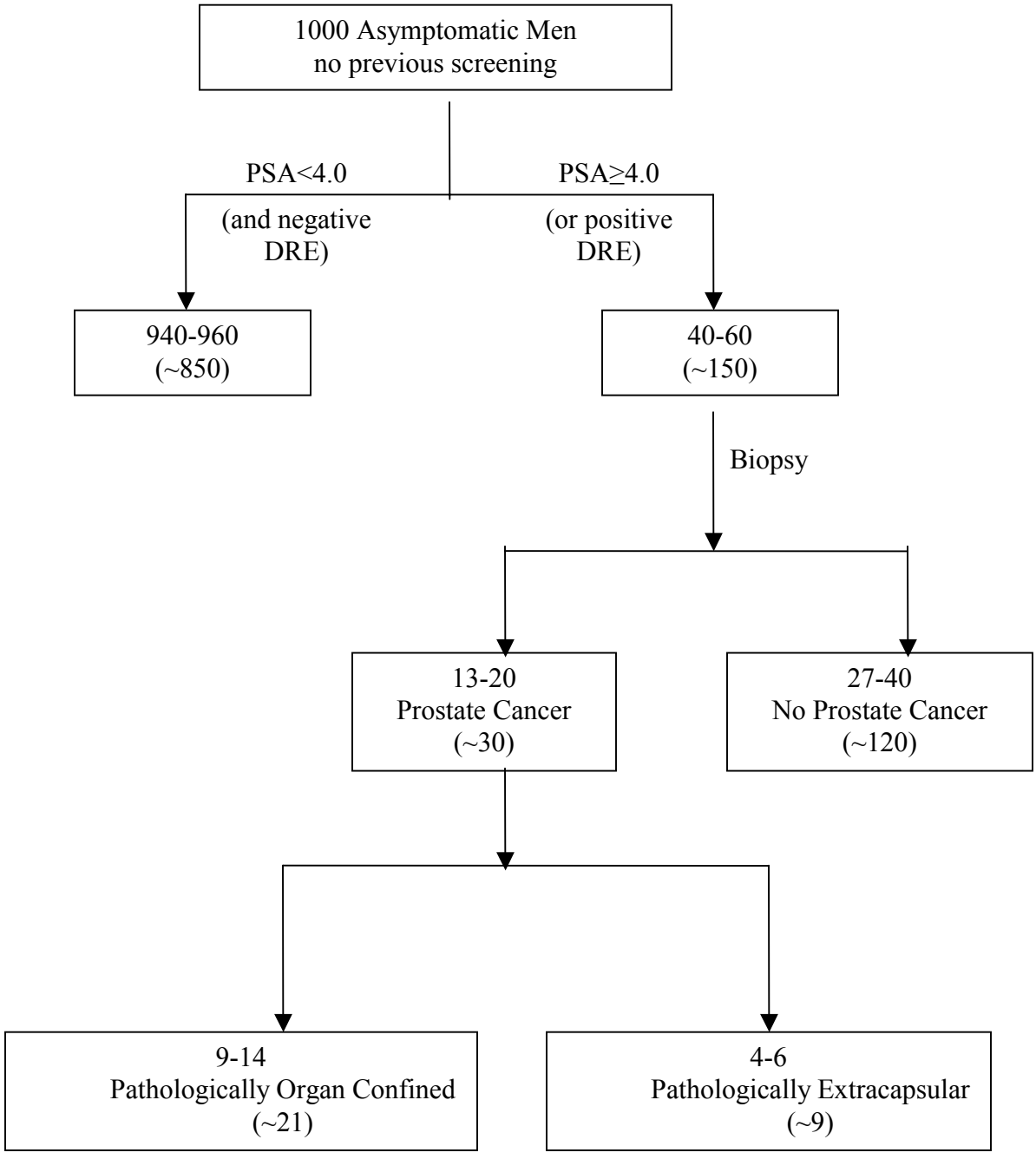


***Figure 3*: Ages 60-69 - estimated yield of screening with PSA (or PSA and DRE) (prevalence screen)**

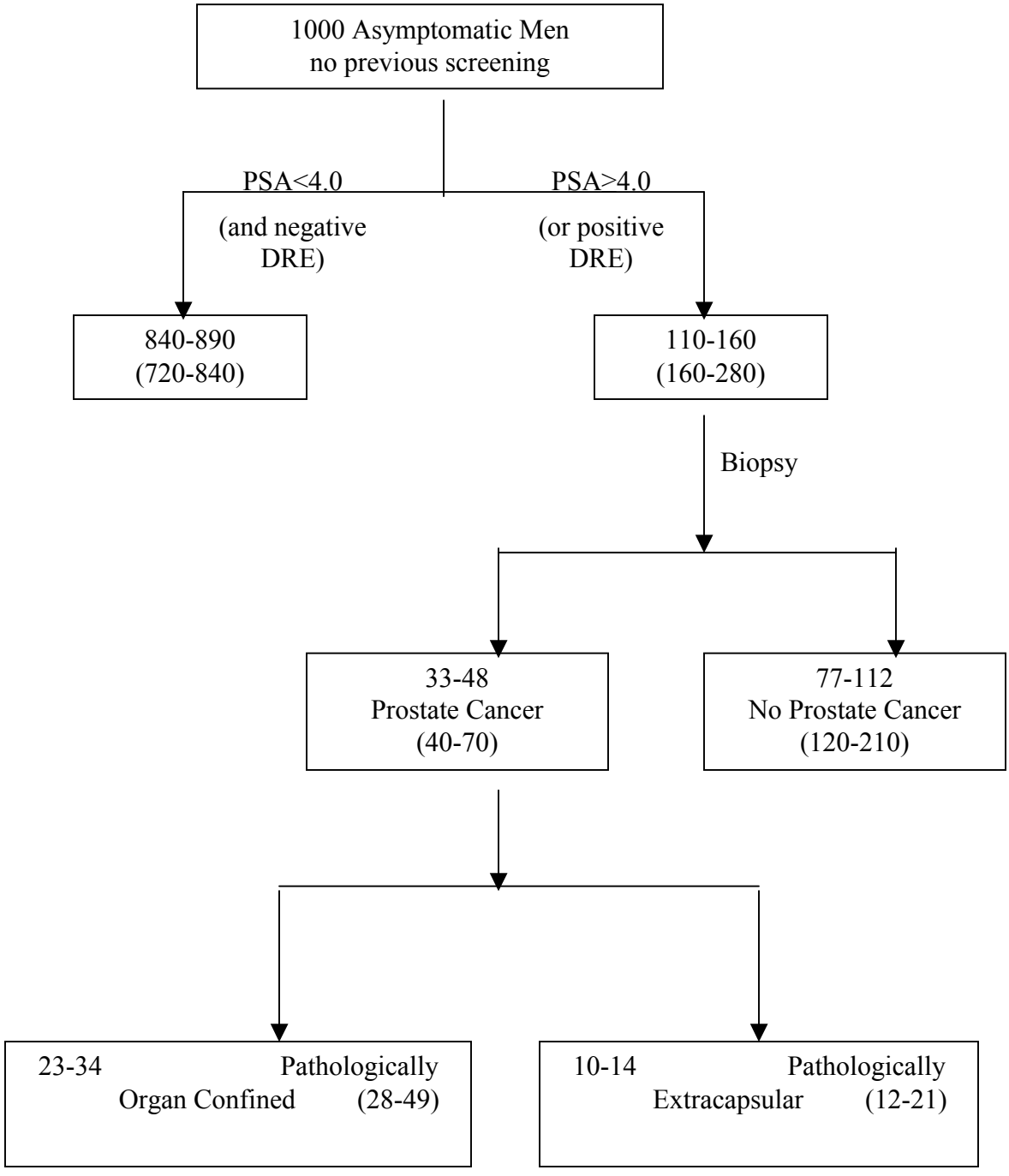
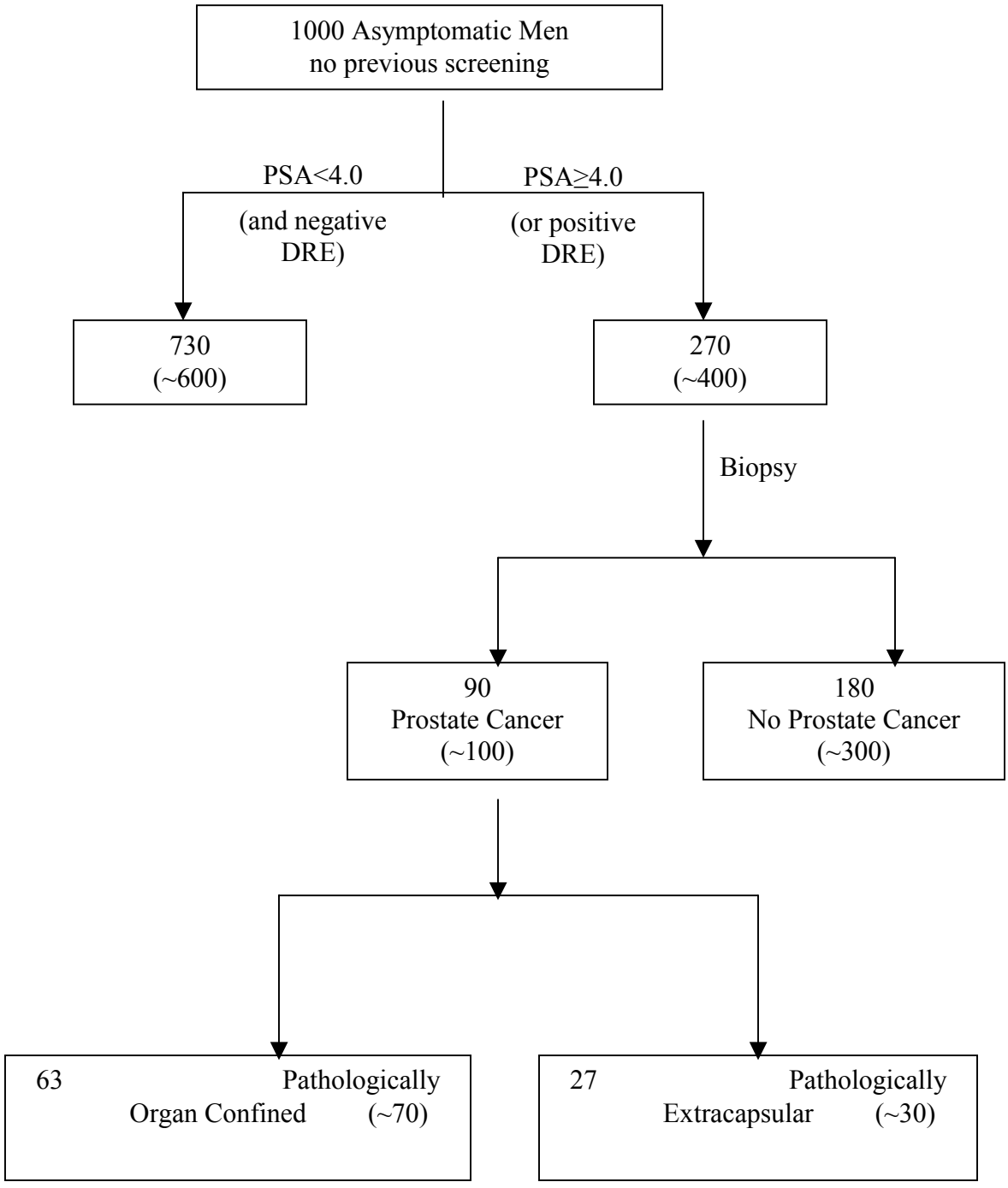


***Figure 4*: Ages 70-79 - estimated uield of screening with PSA (or PSA and DRE) (prevalence screen)**



These results varied by age group.[44,45,102,104,105] The percentage of men with a PSA of 4.0 ng/ml or more, for example, was about 3% for men in their 50s and rose to 11% to 17% for men in their 70s. Among the US volunteers, about 15% of men in their 50s and 40% of men in their 70s had either an abnormal PSA or positive DRE.[45]

Many men with abnormal screening tests had prostate biopsies; some had prostate cancer detected. The percentage of biopsies that detect cancer and the percentage of men screened who have cancer detected both depend on the prevalence of detectable cancer in the population screened, and thus these figures increase with age. The percentage of men screened who have cancer detected also depends on the percentage of men with an abnormal screening test who consent to having a prostate biopsy. Thus, studies of older, previously unscreened populations with high biopsy rates have a higher cancer detection rate.

In these 6 studies, the percentage of biopsies that detected cancer ranged from about 10%[43] to about 30%.[20,67,102,103,106] For men in their 50s, this percentage ranged from about 6%[105] to about 20%;[104] for men in their 70s, to nearly 30%.[44,45,107]

The percentage of all men screened who were found to have prostate cancer ranged from about 1.2%[104,105] to 4.5%.[43] For men in their 50s, this percentage ranged from 0.2%[104,105] to 2.0%;[44,45] for men in their 70s the range was 3.0%[104] to 7.2%.[20,44,45,67,103,106]

All 6 studies reported some information on staging (either clinical or pathologic) or histologic grading of the tumors detected by screening PSA.[20,44,45,67,102-106,108] In 2 studies, screen-detected tumors were 60% to 70% clinically organ confined.[20,67,103,105,106] Three other studies found that, of those men who had prostatectomy after cancer

detection by screening, about 70% were pathologically organ confined.[44,45,109,110] Two studies[67,103,105,106] reported that 8.4% to 12.1% of screen-detected prostate cancers were metastatic at diagnosis; [20,67,103,106] 1 reported that less than 1% were found to be metastatic on later screening rounds.[20,106,67]

The percentages of screen-detected tumors that were well differentiated (i.e., Gleason score 2-4) varied widely, ranging from 1%[43,104] to 67%.[105] The percentage of screen-detected cancers that were poorly differentiated varied less: from 5%[43,104] to 10%.[20,67,103,106] Other center-based studies have found that a small percentage of screen-detected cancers are well differentiated and that the great majority (up to 95%) are moderately differentiated.[44,111,112]

Earlier series of newly diagnosed prostate cancer not detected by screening had shown that 50% or more were at the extracapsular stage and that a higher percentage of the tumors were poorly differentiated.[1,113]

Variation in Yield with Different Screening Intervals

Two studies provided information about how the rates of positive screening tests and cancer detection vary by repeated annual testing.[20,67,106,114] The percentage of men with a PSA of 4.0 ng/ml or greater was 10% to 12% on the initial screening round and dropped to about 6% to 10% on later rounds.[20,114] The cancer detection rate decreased from 3.4% to 4.0% on the initial screening round to between 0.6%[20,67,103,106] and 2.4%[114] in later rounds. A smaller percentage of cancers in later rounds than in earlier rounds was detected by DRE alone.[106] In 1 study, the percentage of men with a PSA of 4.0 ng/ml or greater who had prostate cancer was about 26% for the first screening round and about 6.2 % for subsequent rounds.[20]

Other studies provide information on testing strategies other than annual. Carter et al. used data from the Baltimore Longitudinal Study of Aging, including men ages 55 years and older, to examine the rate at which PSA increased to a level at which a cancer may become incurable (i.e., PSA of 5.0 ng/ml or greater).[115] They found that no man with an initial PSA of less than 2.0 ng/ml experienced an increase of PSA to 5.0 ng/ml or greater within 2 to 4 years. About 27% of men with a baseline PSA of 2.1 ng/ml to 3.0 ng/ml, and 36% of men with a baseline PSA of 3.1 ng/ml to 4.0 ng/ml, had increases in their PSA to 5.0 ng/ml or higher within 2 years. Thus, the authors reasoned that the 70% of the population with a PSA of less than 2.0 ng/ml need not have a PSA more often than every 2 years.

Similarly, a modeling study found that biennial screening of men after age 50 provided nearly the same potential benefit with many fewer biopsies.[15] The investigators also found a small potential benefit in doing 2 tests during the decade of the 40s. Finally, the Physicians' Health Study found that the sensitivity of PSA for prostate cancer appearing in the future did not decline appreciably for the first 4 years after screening.[35]

Summary: Yield of Screening

Many uncertainties cloud the yield of screening for prostate cancer. We are not clear about what type of cancer should be detected to have an impact on patient outcomes. Thus, we are not clear about the target for screening. The reference standard test for determining whether cancer is present may find some cancers that are not associated with the screening test and may miss others that may or may not be clinically important. Because of these problems, research has not been able to determine the operating characteristics of screening with precision.

PSA screening with a cutpoint of 4.0 ng/ml clearly detects many prostate cancers; lower thresholds detect more cancers at the cost of more false positives and more biopsies. False-positive screening tests are most common in the setting of men with BPH, a common condition among older men. At least 2 tests (e.g., %fPSA and complexed PSA) reduce the number of false-positive screening tests. Whether these tests can or will have a major impact on clinical decisionmaking remains uncertain. DRE detects some cancers missed by PSA.

In direct studies of the yield of screening programs using PSA and DRE, 10% to 25% of men above age 50 have a positive test. Older men have a larger percentage of positive tests. Overall, 1.2% to 4.5% of men have prostate cancer in an initial screening. In later annual screenings, from 1% to 2.5% have prostate cancer. Older men have higher cancer detection rates.

About 70% of cancers detected in the first round of screening are pathologically organ confined; this percentage increases with later annual rounds of screening. The extent to which the earlier detection of these cancers leads to improved outcomes is uncertain.

The yield of screening in terms of cancers detected declines with repeated annual testing. If screening for prostate cancer does reduce mortality, then biennial screening may give nearly as much benefit as annual screening, especially for those with baseline PSA of less than 2.0 ng/ml.

Key Question 3: Harms of Screening

The third key question, indicated by the first curving downward arrow on the analytic framework (Figure 1), deals with the harms of screening for prostate cancer. These harms can be considered in 2 categories: the psychological effects of the screening process and the physical effects of screening and the clinical evaluation for men with positive screening tests. (Evidence Table 3)

Psychological Effects of Screening

The Rotterdam section of the ERSPC trial, a well-conducted ongoing RCT of the effects of screening (with PSA, DRE, and TRUS) on prostate cancer mortality, examined the psychological effects of the screening process.[116] The investigators administered 3 general quality-of-life questionnaires (including the Medical Outcomes Study Short Form-36, or SF-36) to 600 participants and 235 nonrespondents at different times through the screening process and then compared pretest and posttest data for different groups.

Among men who had a negative screen (n = 381 usable responses), the investigators found a small improvement in mental health scores, a small decrease in anxiety, and no other differences on 3 validated general quality-of-life measures. After a negative biopsy, men who had had a false-positive screening test (n = 160 usable responses) reported small improvements in bodily pain and general health perceptions and a small decrease in anxiety.

For the entire group during the screening process, anxiety was highest among men who had an initially high "trait" anxiety score. After screening, anxiety decreased for men with an initially low trait anxiety score but remained high for men with an initially

high trait anxiety score. We do not know whether anxiety levels for these men decreased after a longer period after screening. We also do not know whether patients who had a negative biopsy were informed that they still had a 10% to 20% chance of having prostate cancer (see Key Question 2).

The authors concluded that they had documented little evidence of important psychological harms from the screening process. They noted that this could be because such problems are few or because their measures were not specific to the issue of prostate screening. Others have found that specific measures are best for documenting the psychological effects of screening.[117]

Physical Effects of Screening

Essink-Bot et al. also examined patient reports of physical problems encountered in the screening process and the clinical evaluation of positive tests.[116] Fifty-two percent of men experienced either discomfort or pain from the DRE, 29% from the TRUS. Among men who had a biopsy, 90% reported pain or discomfort from the procedure; 38% reported that the pain lasted after the biopsy, but only 2% said that the pain lasted longer than 1 week. Four percent had used painkillers. Four percent also had experienced a fever of 38 degrees Celsius or higher, and 3% had visited a physician because of complications from the biopsy. About 5% reported moderate to extreme interference with daily activities.

Rietbergen et al. used data from the Rotterdam screening program to examine the side effects of needle biopsy of the prostate.[118] Of 1,687 men who had had a biopsy, 7 (0.4%) had to be admitted to the hospital from complications, especially infection.

Summary: Harms of Screening

Evidence about the harms of screening is scant. The screening process is likely associated with some increase in anxiety, but the number of men affected and the magnitude of the increased anxiety are largely unknown. Some screening procedures cause transient discomfort; biopsy of men with positive screening tests is associated with discomfort lasting longer than 1 week in a small percentage of men. Less than 10% of men have ongoing interference with daily activities after biopsy, and less than 1% suffer more serious complications, including infections.

Key Question 4 to 7: Efficacy of Treatment

General Approach

The second edition of the *Guide to Clinical Preventive Services* found little evidence to support the effectiveness of any treatment, compared with no treatment, for clinically localized prostate cancer.[2] It cited a single RCT with multiple flaws comparing radical prostatectomy with expectant management, which had reported no difference in survival over 15 years of follow-up.[119,120] The previous *Guide* cited observational data showing a low prostate-cancer-specific mortality in untreated men with clinically localized cancer. Finally, it cited a structured literature review of nonrandomized studies that concluded that determining the efficacy of various treatments for clinically localized prostate cancer was not possible.[121]

To address various treatment efficacy questions, we reviewed the 23-year follow-up of the earlier RCT (for Key Question 4), searched for any other RCTs and for large, well-conducted observational studies that would provide relevant information on the

efficacy of treatment, and reviewed more recent observational data that might refine survival estimates (Key Question 7).

Key Question 4: Efficacy of Treatment with Radical Prostatectomy

Since 1991, radical prostatectomy (RP) has been the most commonly used treatment for clinically localized prostate cancer. It is the initial treatment for more than one-third of newly diagnosed patients.[1] The procedure is usually performed with curative intent on men who have a life expectancy of at least 10 years.

Randomized Controlled Trials

One older RCT, by Iverson et al., compared RP and expectant management for clinically localized prostate cancer;[122] another RCT, by Akakura et al., compared RP and external beam radiation therapy for locally advanced cancer, including some patients with clinically localized disease.[123] One more recent RCT compared RP with expectant management ("watchful waiting") in men with clinically localized but clinically detected prostate cancer.[124] We found no other RCTs comparing treatments for clinically localized prostate or locally advanced prostate cancer in which one arm received RP and the other did not. (Evidence Table 4)

In the Iverson et al. RCT, the research team randomized 142 men with newly diagnosed clinically localized prostate cancer being treated in 15 Veterans Administration hospitals in the United States between 1967 and 1975 to RP or expectant management.[122] Because of lack of funds, the study did not follow patients from 1978 to 1994, when the survival status of all patients was ascertained. Although vital status could be determined

for 111 participants (78%), the investigators could not accurately determine cause of death. Randomization had failed to balance several important prognostic factors, such as age and stage. After an average follow-up of 23 years, the investigators found no difference in overall survival between the RP and expectant management groups. Because of the high loss to follow-up, the problems with assessment of outcomes, and the relatively small size of the study, few consider these results definitive.

The Akakura et al. RCT included 95 men with prostate cancer that was palpable on DRE and that either involved both lobes or was palpably extracapsular.[123] Thus, some of the men likely had clinically localized cancer and some had extracapsular cancer. All men received 1 of several androgen deprivation therapies (including diethylstilbestrol, LHRH agonists, orchiectomy, or a nonsteroidal antiandrgen) before and after treatment and then were randomized to either RP or external beam radiation therapy. Five-year prostate-cancer-specific survival was 96.6% in the RP group and 84.6% in the radiation group ($p = 0.024$). The degree to which this trial represents results from treatment of clinically localized disease is not clear. The effect could well be attributed to an effect on locally advanced disease.

The more recent RCT, by Holmberg et al,[124] randomized 695 men with newly diagnosed prostate cancer to RP or watchful waiting. Only 5% of these cancers were detected by screening, and about 75% were palpable on rectal exam. Of the men assigned to RP, fewer then 8% had positive nodes at surgery. After a followup of 6.2 years, 4.6% of men assigned to RP had died of prostate cancer, compared with 8.9% of men assigned to watchful waiting (absolute difference: 4.3%; relative hazard 0.50; 95% CI 0.27-0.91). This difference in prostate cancer-specific mortality appeared only after 5

years of followup; there was a small trend favoring the RP group in all-cause mortality, but this difference was not statistically significant between groups.

Although this RCT was well-performed, it does not provide direct evidence concerning the efficacy of RP for those cancers detected by PSA screening. As these cancers are likely different from those detected clinically, one should be careful about extrapolating evidence from the cancers in this trial to screen-detected cancers. Also, the additional lead time from screening means that, even if RP is effective for screen-detected cancers, the benefit in prostate-specific mortality would only appear some years after it appeared in this trial (8 years in the trial). The effect of RP on all-cause mortality for any group of clinically localized cancers remains in doubt.

At least 1 RCT of RP compared with expectant management for clinically localized prostate cancer, mostly detected by screening, is ongoing. The U.S. Prostatectomy Intervention Versus Observation Trial (PIVOT) hopes to randomize 1,000 men up to 75 years of age with any histologic grade of localized prostate cancer and a life expectancy of at least 10 years. The trial started in 1994 and is scheduled to continue for 12 to 15 years of follow-up.

Observational Studies

We examined 6 case series of RP with at least 10-year survival data published since 1994. Three were from single institutions (Mayo Clinic,[125,126] Johns Hopkins,[50,127] and Duke University);[128] 2 were analyses of SEER data;[129,130] and 1 was a multi-institutional pooled analysis from 8 medical centers.[131] Overall, 10-to-15-year disease-specific survival was 80% to 97% for all analyses for men with well and moderately

differentiated tumors. For poorly differentiated cancers, 10-to-15-year disease-specific survival was 60% to 80%.

Lu-Yao and Yao analyzed SEER data together with an age-matched control group.[130] Overall 10-year survival for men who had had RP for well-differentiated prostate cancer was 77% (control group, 65%); for men with moderately differentiated cancers, survival 10 years after RP was 71% (control group, 64%); for men with poorly differentiated tumors, survival was 54% (control group, 62%). After adjustment for the younger age and lower stage of men receiving RP compared with radiation or watchful waiting, 10-year disease-specific survival for the RP group was not different from the radiation or the watchful-waiting groups for men with well-differentiated cancers. Disease-specific survival was only slightly higher for the RP group for moderately differentiated tumors (RP, 87%; radiation, 76%; watchful waiting, 77%); it was much higher for men with poorly differentiated cancers (RP, 67%; radiation, 53%; watchful waiting, 45%).

Summary of Efficacy of Treatment with Radical Prostatectomy

Three RCTs compared any other treatment with RP for clinically localized prostate cancer. One older trial, comparing RP with expectant management, had major methodologic flaws and does not provide definitive results. Another, comparing RP with radiation therapy, was small and included a large percentage of men with locally advanced rather than clinically localized cancer. The more recent RCT, comparing RP and watchful waiting, was larger and well-conducted, but the participants had clinically-detected rather than screen-detected prostate cancer. The results of this trial indicate that, after 8 years, RP reduces prostate cancer-specific mortality but not all-cause mortality. It

is likely that any benefit from RP in screen-detected cancer would take even longer to appear. Clearly, further studies are needed before we can draw valid conclusions about the efficacy of RP for screen-detected, clinically localized disease.

In the 6 large observational studies of outcomes after RP, 5 had no internal controls and the other had only age-matched controls. All studies found high (80% to 97%) long-term, 10-year disease-specific survival after RP for well or moderately differentiated cancers and somewhat lower (60% to 80%) disease-specific survival for men who had had RP for poorly differentiated tumors. The 1 study with an internal control group attempted to adjust for differences among the treated populations, finding a small advantage for RP compared with radiation or watchful waiting for men with moderately differentiated cancer and a larger advantage for men with poorly differentiated cancer.

All the observational studies have 2 important weaknesses: (1) the survival rates may be a reflection more of the patients and the tumors than the treatment;[132] and (2) none of these studies specifically included men whose prostate cancer had been detected by screening, so whether any results apply to a screened population remains unclear. With these weaknesses and the lack of convincing RCT evidence, we conclude that the efficacy of RP treatment for localized prostate cancer is unknown.

Key Question 5: Efficacy of Treatment with Radiation

Radiation therapy is the second most commonly used treatment for nonmetastatic prostate cancer; it is the most common treatment for men ages 70 years to 80 years.[1] Two types of radiation therapy are most commonly used and will be reviewed here:

external beam radiation therapy (EBRT) and brachytherapy, the insertion of radioactive pellets directly into prostate tissue.

External Beam Radiation Therapy

Research continues to examine the optimal manner of delivery and dose of EBRT for prostate cancer in various stages with various characteristics. Some evidence indicates that 3-dimensional (3-D) conformal radiation, in which computerized tomography is used to guide the radiation beam directly to the prostate rather than adjacent structures, may provide better cancer control with fewer side effects than standard EBRT. Using 3-D conformal techniques, clinicians may be able to deliver higher radiation doses that may be more effective, especially in higher risk patients.[133] Much of this research is not sufficiently mature, however, to determine the impact of these new approaches on patient health outcomes.

Randomized Controlled Trials

The Akakura et al. RCT (see Key Question 4 above) examined the efficacy of EBRT by comparing RP with EBRT in 95 men with either localized or locally advanced cancer. Prostate cancer-specific survival after 5 years was statistically significantly higher in the RP group (RP, 96.6%; EBRT, 84.6%, $p = 0.024$).[123] We found no other RCT with clinical outcomes comparing EBRT with any other therapy for clinically localized prostate cancer.

Observational Studies

Three large observational studies of men with clinically localized prostate cancer treated with EBRT provide some information about long-term clinical outcomes. The

largest study, from the Radiation Therapy Oncology Group (RTOG), included 1,557 men with various stages and grades of prostate cancer treated with EBRT. Prostate-cancer-specific survival after 15 years was 72% for men with clinically localized disease and Gleason score 2 to 6 (well to moderately differentiated), 61% for clinically localized disease and Gleason score 7, and 39% for clinically localized disease and Gleason score 8 to 10. A second large multi-institutional series of patients found a 72% prostate-cancer-specific survival after 12 years of follow-up.[134] Finally, an observational study mentioned earlier for Key Question 4 examined 10-year overall survival among men in the SEER registry who had received various treatments, comparing them to an age-matched control group. For EBRT, the age-matched control group had a 10-year survival of 54%. Survival rates for men with different stages of cancer were as follows: well-differentiated cancer, 63%; moderately differentiated cancer, 48%; and poorly differentiated cancer, 33%.[130]

Summary of Efficacy of External Beam Radiation Therapy

One small RCT comparing EBRT with any other therapy for clinically localized prostate cancer found a benefit for RP over EBRT in 5-year survival. Three large observational studies provide information about long-term survival among men treated with EBRT for clinically localized disease. As with the observational studies of RP, one can determine neither the independent effect of the treatment (as compared with the type of patient or the type of cancer) nor the extent to which these studies include patients who are comparable to those who would be detected by screening. With these weaknesses and the lack of convincing RCT evidence, we conclude that the efficacy of EBRT treatment for localized prostate cancer is unknown.

Brachytherapy

Although implantation of radioactive pellets directly into a cancer, or brachytherapy, has been used to treat gynecologic malignancies for some years, this technique has found widespread use in treating prostate cancer only in the past 10 to 15 years. It is most frequently used either alone in men with well differentiated cancer or in combination with EBRT in men with more aggressive cancer. The technique continues to evolve, and research to define its clinical efficacy is still in its infancy. Because it is a simple 1-time outpatient procedure for patients, and because some have the perception that it has fewer side effects, it has become a popular choice of treatment in some areas. The technique is, however, technically difficult and its applicability in community practice is as yet unknown.[135]

No RCT with clinical outcomes compared any treatment for prostate cancer with brachytherapy. Two observational studies with 100 patients or more reported clinical outcomes of treatment of clinically localized prostate cancer treated with brachytherapy. One study reported 90% to 100% 5-year survival for 157 patients treated with radioactive gold seeds.[136] Another study found that 15 years after treatment with radioactive iodine seeds, 43% of 126 patients had died of prostate cancer. [137] These investigators also observed that patients selected for this therapy more recently had less aggressive disease (i.e., lower stage and grade).

Summary of Efficacy of Brachytherapy

We found no RCT evidence on the efficacy of brachytherapy, and no large observational data provides useful information about this issue. As for EBRT, we

conclude that the efficacy of brachytherapy for clinically localized prostate cancer remains unknown.

Key Question 6: Efficacy of Treatment with Androgen Deprivation

Prostate cancer is often an androgen-dependent disease, and thus androgen deprivation has long been one approach to therapy. In the past, this treatment modality has taken the form of orchiectomy or estrogen therapy, primarily for men with metastatic disease. These therapies had a number of undesirable side effects, including psychological effects in the case of orchiectomy and cardiovascular effects in men given estrogen.

Newer approaches to androgen deprivation therapy (ADT) include drugs (e.g., flutamide or bicalutamide) that block peripheral androgen receptors and drugs that are LHRH analogues (LHRH agonists; e.g., goserelin or leuprolide). This latter group of drugs works by stimulating the release of luteinizing hormone from the pituitary gland, leading to a transient increase in testosterone production by the testes. Paradoxically, when used clinically, LHRH agonists result in a "down regulation" of pituitary receptors, thus markedly reducing testosterone production to the level of a castrate man. LHRH agonists have been used clinically since the late 1980s.

Randomized Controlled Trials

Three RCTs compared clinical outcomes among at least some men with clinically localized prostate cancer who were treated with either ADT or any other treatment. (Evidence Table 5) Lundgren et al., also discussed in conjunction with the efficacy of

watchful waiting (Key Question 7) below, compared outcomes among 228 men randomized to estrogen, estramustine (a nitrogen mustard derivative of estradiol with both cytotoxic and androgen deprivation properties), and watchful waiting. Among men followed for 10 years, about 12% of the estrogen group, 22% of the estramustine group, and 35% of the deferred therapy group had developed metastases. (read from Figure 2) During the followup period, about 12% of men in the estrogen group, 18% in the estramustine group, and 28% in the deferred treatment group died from prostate cancer (p = 0.03). Overall survival, however, was similar in all groups.[138]

Two other RCTs among men treated with EBRT found that ADT with either orchiectomy[139] or estramustine[140] either increased overall survival[139] or reduced clinical recurrence.[140] In both studies, improved outcomes occurred primarily among men who had positive lymph nodes.

We also examined RCTs comparing ADT with any other treatment for men with locally advanced prostate cancer (i.e., extracapsular but not metastatic disease). Four recent RCTs of ADT (using LHRH agonists) as adjuvant to EBRT or RP (compared with EBRT or RP alone) found statistically significantly improved overall survival (10% to 20% absolute difference) in men who received ADT.[141-146]

For example, in 1 study overall survival at 5-year follow-up was 79% in the group receiving an LHRH agonist plus EBRT and 62% in the group receiving EBRT alone (p = 0.001).[141] In the only study that added an LHRH agonist to RP, after 7 years 15% of men who received the LHRH agonist and 35% of the men treated only with RP had died.[146]

One further RCT of immediate versus deferred ADT (with either orchiectomy or LHRH agonists) without other treatment found improved survival (8% absolute

difference) for the immediate ADT group in men newly diagnosed with locally-advanced prostate cancer.[147]

Summary of ADT Efficacy

We found little evidence that ADT improves clinical outcomes among men with clinically localized prostate cancer. The studies performed to date on this issue, however, have included a large number of men with more advanced disease. Because the overall prognosis for men with clinically localized disease is often good (see Key Question 7 below), studies of any additive effect of ADT would necessarily require a large number of men followed for some years. We did find strong evidence that ADT, especially in the form of LHRH agonists, does improve clinical outcomes, including overall survival, among men with locally advanced prostate cancer who have already received either EBRT or RP.

Key Question 7: Efficacy of Treatment with Watchful Waiting

One critical issue in screening for prostate cancer is whether aggressive treatment of clinically localized prostate cancer with one of the modalities above produces better outcomes than does simple "watchful waiting." Watchful waiting, also termed "expectant" or "conservative" therapy, implies that no therapy is given initially but that the patient is followed for evidence of progressive or symptomatic disease. Treatment may then be offered only for men experiencing progressive disease. Evidence Table 6 provides details about the following studies.

Randomized Controlled Trials

Two RCTs compared watchful waiting to aggressive therapy for clinically localized prostate cancer: the VA study by Iverson et al described for Key Question 4[122] and an open-label RCT of hormonal therapy by Lundgren, described for Key Question 6.[138] Both studies were small and had methodological flaws.

Lundgren's RCT, begun in 1978, randomized 285 men (mean age 70 years) with clinically localized prostate cancer into 1 of 3 groups: estrogen, estramustine, or deferred treatment.[138] Some 24% of randomized patients were lost to follow-up or excluded for various reasons; randomization was unbalanced; and cardiovascular mortality in the estrogen group was high. During the observation period, prostate cancer-specific mortality was significantly worse in the deferred treatment group (28% compared with 12% and 18% for estrogen and estramustine, respectively, $p = 0.03$), although overall survival was not statistically different among the groups (40% versus 47% and 46%, respectively).

Observational Studies

Generic Issues. In the absence of compelling RCT evidence, we searched for large cohort studies dealing with the survival of men with clinically localized prostate cancer who were treated expectantly. Six such studies, published since 1994, provide information about the natural history of untreated clinically localized prostate cancer (see Evidence Table for Key Question 7). However, few or none of the prostate cancer cases in these studies had been detected by screening PSA; an unknown number had been detected by screening DRE. Thus, we do not know the extent to which these data are applicable to the screening-detected tumors of today.

Some cases had been detected by a surgical procedure, transurethral resection of the prostate (TURP), which was more commonly done in the past than it is now.[148] In performing this procedure, surgeons retrieved small "chips" of prostate tissue, some of which contained small foci of prostate cancer. Many experts suspect that a large percentage of such cancers are not clinically important. What is not clear is the extent to which current screening strategies detect these "minimal" cancers. If current screening does not detect such cancers, then some of the cancers in these older studies could have a better prognosis than screen-detected cancers of today, making the studies less applicable to today's situation. For example, while many of the prostate cancers detected by TURP were well-differentiated, many fewer cancers detected by PSA screening are well-differentiated.[149]

Imaging procedures used today (e.g., computerized tomography and magnetic resonance imaging scans) are much more sensitive in finding advanced disease than the examinations that were used when many of the cancers in these studies were detected. Thus, at least some of the cancers in these studies that had been denoted as clinically localized may instead have been locally advanced or even metastatic. This factor would tend to lower the survival of patients in these studies relative to the survival of patients with typical screen-detected cancers today.

In sum, competing selection biases in these studies may affect their results, although we cannot determine the net direction and magnitude of any bias.

Study-Specific Review. Five of the 6 studies were large, retrospective cohort studies, 1 using SEER data from the United States,[130] 1 using data from the Connecticut Tumor Registry,[47,150] and 3 using population-based data from Sweden or

Denmark.[48,151,152] The sixth study was a pooled analysis of individual data from 6 other nonrandomized studies of survival of untreated men with localized prostate cancer.[46]

With respect to disease-specific survival rates (i.e., survival rates in which men who die of other diseases are censored), the 5 studies with information on tumor grade show very favorable 10-year to 20-year rates for men with well differentiated, clinically localized prostate cancer who had been treated with watchful waiting.[46-48,130,150,152] Lu-Yao et al. for example, found that these men had the same survival as men without prostate cancer.[130] Men with moderately differentiated, clinically localized cancer had worse disease- specific survival than men with well-differentiated disease. Disease-specific survival at 15 years for men with moderately differentiated cancer was 74% to 83%, about 5%[46]to 15%[152] percentage points lower than men with well-differentiated disease. Lu-Yao found that 10-year overall survival was an absolute 11% lower (38% compared with 49%) for men with moderately differentiated prostate cancer than for age-matched controls without prostate cancer.[130]

Albertsen et al. found great heterogeneity within the group of moderately differentiated tumors, meaning Gleason score of 5 to 7.[47,150] Among men with Gleason score 5, from 6% (ages 50 to 59 years) to 11% (ages 70 to 74 years) had died of prostate cancer 15 years after diagnosis. Among men with Gleason score 6 cancer, 18% (ages 50 to 59 years) to 30% (ages 70 to 74 years) had died of prostate cancer. Among men with a Gleason score 7 cancer, 42% (ages 70 to 74 years) to 70% (ages 50 to 59 years) had died of prostate cancer. Thus, men with Gleason score 7 cancers had a greater probability of dying of prostate cancer than men with Gleason score 5 or 6 tumors. In addition, age had only a small effect on the probability of dying of prostate cancer for men with lower-

grade tumors (i.e., Gleason score 2 to 6), but older men had a lower probability of dying of cancers with Gleason score 7. This was also true for Gleason score 8 to 10 cancers (probability of death from prostate cancer was 60% for men ages 70 to 74 and 87% for men ages 50 to 59 years).

These data are particularly important, as most men with screen-detected cancers today have moderately differentiated histology. As noted earlier, some of these men have a good prognosis whereas others have a poor prognosis.

For poorly differentiated cancers, the studies agree that the prognosis for men with clinically localized cancer treated expectantly is grim: Lu-Yao et al. found that men with poorly differentiated but clinically localized tumors had a reduction in overall 10-year survival of an absolute 30% compared with age-matched controls without prostate cancer (17% compared with 47%).[130] Disease-specific survival after 15 years in the other studies for men with poorly differentiated cancer ranged from 13%[47,150] to 44%.[48]

Results from the Brasso et al. study are difficult to compare with the other studies.[151] These researchers selected only men who had survived for 10 years after their diagnosis, gave no disease-specific survival rates, and provided no information on tumor grade.

Summary: Efficacy of Treatment with Watchful Waiting

We found no convincing RCT evidence of the efficacy of watchful waiting compared with other treatments for clinically localized prostate cancer. Four retrospective cohort studies and a pooled analysis of 6 other cohort studies showed that men with well-differentiated, clinically localized prostate cancer have excellent long-term

survival, with little or no reduction in survival compared with similar men without prostate cancer.

With regard to moderately differentiated cancer, these cohort studies found a definite reduction in disease-specific and overall survival compared with the survival of men with well-differentiated cancers, although the magnitude of this reduction varied among groups and among studies. The most detailed analysis of this group found that men with Gleason 7 tumors had a substantially worse disease-specific survival than men with Gleason 5 tumors.[47] All studies agree that men with poorly differentiated cancers have low long-term disease-specific survival.

If the men in these studies are representative of contemporary men with screen-detected cancer, their data can be useful in determining the most appropriate target for screening. For example, one would not target well-differentiated, clinically localized prostate cancer for early detection and treatment. The major concern with these studies, however, is the extent to which selection biases of uncertain direction and magnitude limit their generalizability to the current population of men with screen-detected cancers.

A primary interest in reviewing these studies is to determine the outcomes for men with moderately differentiated prostate cancer, because this is the type of cancer most commonly detected by screening. The studies show that survival varies for this group of patients; some men have a good prognosis, others a poor prognosis. Clarifying this variation is an important research priority.

Summary: Efficacy of Treatment

No treatment has been shown to be effective in improving clinical outcomes for men with prostate cancer confined to the prostate. Among this group, outcomes are worst

for men with poorly differentiated tumors and best for men with well-differentiated tumors. The largest number of prostate cancers detected by screening is moderately differentiated; men with these tumors have a mixed prognosis.

Androgen deprivation therapy (ADT) is effective in prolonging survival among men with prostate cancer outside the capsule; this conclusion comes from studies in men who were (presumably) not detected by screening.

Key Question 8: Harms of Treatment

Because harms of treatment are experienced by the men themselves, we examined evidence that measured patients' perceptions of their function rather than assessments by physicians or investigators. Because it is difficult to interpret a proportion of men who are experiencing a dysfunction independent of some comparison, we examined evidence that provided some comparison of function, including control groups who had not had prostate cancer treatment, men with prostate cancer treated in a different way, or sequential studies comparing men's function before and after treatment. Because the frequency of harms changes over time after treatment, we examined evidence of harms at least 1 year after treatment. Details about the studies we found are provided in Evidence Table 7. Table 3 provides a summary of harms at least 1 year after different treatments.

Table 3. Harms of treatment*†

Treatment	Reduced Sexual Function	Urinary Problems	Bowel Problems	Other
Radical Prostatectomy	20%-70%	15%-50%		
External Beam Radiation Therapy	20%-45%	2%-16%	6%-25%	
Brachytherapy	36%?	6%-12%?	18%?	
Androgen Deprivation Therapy (LHRH agonists)	40%-70%			Breast Swelling: 5%-25% Hot Flashes: 50%-60%

* Percentage of men treated who had side effects at least 12 months after treatment.
† Entries with question marks are less certain than other entries because they are based on less, or less good, evidence.

Radical Prostatectomy

In 2 studies of acute adverse effects of RP relying on large databases, 30-day mortality was 0.7% (in a VA population ages 45 to 84 years)[153] to 1.0% (in a Medicare population, ages over 65 years);[154] the latter study found that men older than 80 had a 30-day mortality of 4.6%. Major cardiopulmonary complications occurred in 1.7% in the VA population[153] and in 7.4% in the Medicare population for men ages 70 to 74 years.[154]

The primary long-term adverse effects that have been associated with RP include erectile dysfunction, urinary incontinence, and bowel symptoms. Advances in the technique of performing RP, including delineation of the anatomy of the dorsal vein complex and pelvic plexus, enabled clinicians to spare important structures, which in turn might reduce complications following RP.[127] Thus, although most of the literature we found concerns standard RP, we especially examined articles that reported results of the newer "nerve-sparing" procedure.

Erectile Dysfunction

One meta-analysis of 40 studies through 1995 compared erectile dysfunction in men after RP or after EBRT.[155] The probability of maintaining erectile function was 0.42 after RP and 0.69 after EBRT ($p < 0.0001$). The RP probability was similar to that reported in a previous literature review.[121]

Twelve studies (some with several publications) published since the meta-analysis met our inclusion criteria.[156-172] Two studies compared sexual function among men treated by RP and age-matched population controls.[168,171] In 1, 79% of men who had had an RP and 46% of controls reported poor or very poor sexual function.[171] In the other,

82% of men who had had an RP and 63% of controls reported that they were distressed because of decreased sexual function.[168]

Seven studies gave the same men questionnaires before (or soon after) and 12 to 24 months after RP to assess the impact of the procedure.[157-172] One of these studies is the Prostate Cancer Outcomes Study (PCOS) in which patients with prostate cancer are ascertained from 6 SEER areas and sent questionnaires at various times after treatment. In this study, 41.9% of men at 24 months after RP reported that sexual function was a moderate to large problem. When asked about function before surgery, 17.9% said that sexual function had been a problem (difference about 24 percentage points). This difference in the negative impact of RP on sexual function varied by age. About 50% of men younger than age 60 years suffered a decline in sexual function (from 92.6% before surgery to 39% afterward), whereas about 30% of men ages 75 to 79 years suffered a decline (48.6% before RP to 19.1% afterward).

In a study that gave men questionnaires before and after RP, the percentage of men reporting that erections were usually inadequate for sex increased from 32% before the RP to 93% 12 months after surgery (difference about 60%).[163] In neither this study nor a similar one[162] did sexual function differ between men who had nerve-sparing surgery compared with men who had standard surgery.

In another study that followed men sequentially over time, from an academic center that helped develop the nerve-sparing RP,[156,172] Walsh found that 18 months after nerve-sparing surgery, 86% of men who had erections adequate for intercourse before surgery maintained their sexual function. Some of these men used drugs or other devices to assist potency, but 84% of these men reported little or no bother concerning sexual

function. Others have questioned whether such results are possible in community practice, or whether the patients were a selected subgroup.[156]

Three other studies published during 2001 compared erectile dysfunction in the same men before and after RP.[157-172] Sexual potency 1 to 2 years after surgery was impaired over baseline in 60% to 80% of men.

Steineck et al[173] conducted a survey of potential harms of RP about 4 years after randomization into Holmberg et al's RCT of RP versus watchful waiting for men with clinically-detected prostate cancer.[124] Erectile dysfunction (80% in RP group, 45% in watchful waiting group) was more frequent in the RP group.

Studies that have surveyed men a single time 12 to 24 months after having an RP, without controlling for prior function or function in the non-prostate cancer population, have generally attributed a higher level of sexual dysfunction to RP. For example studies by Fossa and Schrader-Bogen found 70% to 100% of men had erectile problems after having an RP.[166,167]

Summary: Erectile Dysfunction after Radical Prostatectomy

We found that at least 20%, and perhaps as many as 70%, of men who have had an RP in the general community suffer worsened sexual function 1 year later as a result. The evidence is mixed about whether the newer nerve-sparing RP reduces this burden outside of excellent academic centers. (Table 3)

Urinary Incontinence

Most of the same studies mentioned above that examined sexual function also considered urinary function. The 2 studies that compared function between men who had had an RP and an age-matched control group found that the difference in incontinence

potentially attributable to RP was 15% (frequent dribbling or no control: 21% in RP group compared with 6% in control group)[171] to 50% (leakage: 65% in RP group compared with 14% in control group).[174]

Four of the 5 studies that evaluated change in men's urinary function longitudinally found that an additional 25% to 37% of men were wearing pads for urinary incontinence 12 to 24 months after having an RP.[156-158,161] One of these studies, the PCOS, found that the effect on urinary function varied by age. The additional percentage of men who had incontinence more than twice each day 24 months after RP compared with before surgery was about 8% for men ages 60 years and younger, and about 36% for men ages 75 to 79 years.[161]

The fifth study was from an academic institution using the nerve-sparing surgery technique, finding that only 7% were wearing pads at 18 months after nerve-sparing RP.[156]

In the Steineck et al survey[173] within the Holmberg RCT of RP,[124] urinary leakage (49% in RP group, 21% in watchful waiting group) were more frequent in the RP group. Urinary obstructive symptoms, however, were more common in the watchful waiting group (44% in watchful waiting, 28% in RP group). Bowel function, anxiety, depression, and subjective quality of life were similar in the 2 groups.[172]

In 2 studies without a control group assessing urinary function only once after RP, 12% of men reported severe urinary leakage[167] and 19% reported that urinary problems affected their quality of life "quite a bit".[166]

Summary: Urinary Dysfunction after Radical Prostatectomy

In a variety of studies, we found that from 15% to 50% of men who had had an RP in the general community suffered substantial urinary problems afterward. We found little evidence about whether the newer nerve-sparing RP reduces this burden outside of excellent academic centers. (Table 3)

Harms of External Beam Radiation Therapy

We will first examine the evidence concerning the harms of EBRT followed by a review of the harms of brachytherapy. We will especially look for evidence concerning recent developments in these fields, especially conformal EBRT and TRUS-guided brachytherapy.

Erectile dysfunction

We found 1 meta-analysis of 40 studies, mentioned above,[155] that found that the probability of maintaining sexual function after EBRT is 0.69 (compared with RP, 0.42). None of these studies were published after 1995.

Three studies[168,169,171,175] examined sexual function among men treated with EBRT and age-matched controls without prostate cancer. [168,169,171,174,175] These studies found that 20% to 40% more men who had had EBRT suffered sexual dysfunction compared with the control group.

Seven studies examined sexual function over time after EBRT, either by repeated measures or by asking about previous function.[157,162,163,170,171,176-179] All 7 showed that 20% to 45% more men had erections inadequate for intercourse 12 to 24 months after

EBRT than at baseline. One of these studies found that more men older than 70 years suffered a decline in sexual function than men under age 70 (32% compared with 23%).

Two of these studies included men who had received conformal radiation therapy; 1 study found the same degree of decline in sexual function as other studies of conventional treatment[176] and the other found no decrease in sexual function over 12 months after conformal radiation.[178]

Two other studies used a single questionnaire after EBRT to assess sexual function. Each found that about 50% of men had erections inadequate for intercourse.[166,167]

Summary of Erectile Dysfunction from External Beam Radiation Therapy

From 20% to 40% of men who had no erectile dysfunction before EBRT developed dysfunction 12 to 24 months afterward. (Table 3)

Urinary Incontinence

Three studies[171,180] compared urinary function in a group of men who had had EBRT with a population control group. [168,171,180] One found no difference in urinary symptoms between men who had had EBRT and controls.[171] The other 2 studies found that the prevalence of severe urinary problems was 12%[180] to 16%[168] higher among men who had had EBRT than among controls.

Five studies examined urinary function over time among men who had had EBRT.[157,163,170,177-179] Among those men who had had no urinary symptoms at baseline, from 2% to 8% developed urinary incontinence severe enough to wear pads after EBRT.

Three studies surveyed men concerning urinary function at least 1 year after EBRT.[166,167,181] From 12%[167] to 36%[181] of men had frequent urinary incontinence. One of these studies compared standard EBRT with 3-D conformal EBRT, finding a statistically significantly lower prevalence of frequent urinary leakage (36% compared with 29%, p = 0.044).[181]

One RCT compared the side-effects of conformal and conventional EBRT.[182] This study does not actually meet our review criteria as it used physician rather than patient assessments of outcomes. It found no difference between the 2 approaches to EBRT in urinary function.

Summary of Urinary Dysfunction from External Beam Radiation Therapy

From 2% to 16% of men who had no urinary incontinence before EBRT developed dysfunction 12 to 24 months afterward. It is not clear whether conformal EBRT reduces the frequency of this side-effect. (Table 3)

Bowel Dysfunction

We found 3 studies[168,171,180] that compared bowel function in men who had had previous EBRT with a control population.[168,171,174,180] Compared with controls, about 10% to 25% more men who had had EBRT reported marked bowel problems, often increased frequency and urgency of bowel movements.

Five studies assessed bowel function over time in men who had had EBRT.[157,163,170,177-179] From 6% to 18% of men who had not had previous bowel problems reported substantially increased bowel problems from 12 to 24 months after

EBRT. One small study reported that men who had had conformal EBRT had fewer problems than men who had had conventional EBRT.[178]

Two studies surveyed men about bowel function at least 1 year after having EBRT. [166,168,171,180,181] They found that 11% to 17% had major problems with bowel function. One of these studies[181] also found that only 4% of men who had had conformal EBRT reported similar problems.

One RCT[182] using physician rather than patient assessment of outcomes found little difference between conventional and conformal EBRT in the development of severe bowel problems.[182]

Summary of Bowel Dysfunction from External Beam Radiation Therapy

From 6% to 25% of men who had no bowel dysfunction before EBRT reported marked problems 12 or more months afterward. The evidence is mixed about whether conformal EBRT reduces the frequency of this side effect. (Table 3)

Harms of Brachytherapy

We found 7 studies that assessed potential harms of brachytherapy by patient reports with a validated instrument. Four of these examined scores on validated measurement instruments longitudinally[183-186] while the other 3 were cross sectional in design.[160,187,188] The studies used one of 2 isotopes (iodine – 125 or palladium – 103) with a variety of doses.

Two longitudinal studies examined sexual function before and at least 1 year after brachytherapy treatment.[184,186] One study found that, among men who were potent before

treatment, about 21% were impotent and 36% had reduced erectile function 3 years after treatment.[184] The second study found that 35% of men treated with brachytherapy alone had not returned to pre-treatment sexual function 18 months after treatment.[186]

Three additional studies, all cross-sectional, assessed sexual function at 7 to 18 months after brachytherapy. One found that the percentage of men who reported erections adequate for intercourse declined from 73% before brachytherapy (measured by patient recall) to 55% after 12 months.[188] In the second study 43% of men reported adequate erections 9 months after brachytherapy.[160] In the third study,[187] investigators measured sexual function with a validated 100 point scale (UCLA-Prostate Cancer Index, higher numbers mean better function), finding that sexual function was 14 points lower than literature controls without prostate cancer, a statistically ($p = 0.05$) and clinically significant magnitude.

Four studies examined urinary function after brachytherapy.[160,185-187,189] Two used longitudinal designs.[185,186] These studies found that, although a majority of men will have distressing urinary symptoms in the first months after brachytherapy, from 6% to 12% will have such symptoms 1 year later. Men who had some urinary symptoms before brachytherapy had a higher probability of developing long-standing problems after treatment.[185] Perhaps 25% of men will have some loss of urinary control 1 year after brachytherapy.[186]

Two cross-sectional studies used validated scales to assess urinary function at 3 to 7 months after brachytherapy.[187,189] In one, the urinary score (I-PSS, lower numbers mean better function) more than doubled from the pre-treatment assessment to 3 months afterward.[189] In another study, urinary scores 7 months after treatment were more than 20

points worse than literature controls (p = 0.001).[187] In the third study, 57% of men had some degree of urinary incontinence 9 months after therapy.[160]

Two studies assessed bowel function after brachytherapy. In one, men who had had brachytherapy 7 months earlier were 8 points worse on a 100 point validated scale compared to literature controls (p = 0.05).[187] In the other, about 18% of men reported some degree of diarrhea at 12 months after treatment. [160] Another study found that 19% of men treated with brachytherapy had some persistent rectal bleeding 12 to 28 months after treatment.[190]

Summary of Harms from Brachytherapy

We found some evidence that brachytherapy has an impact on sexual, urinary, and bowel function, but insufficient evidence to determine precisely the magnitude of these harms. Our best estimates are that 36% of men will have some erectile dysfunction, 2% to 12% will have some urinary symptoms, and 18% will have some bowel dysfunction 1 year after treatment. (Table 3)

Although it did not meet our criteria (as it has no patient reports), we found 1 large study of procedures during 1991 to 1993 among men in the Medicare population who had had brachytherapy for prostate cancer in 1991.[191] Using claims data, these investigators found that 8.3% of 2,124 men underwent a surgical procedure for bladder outlet obstruction during the follow-up period. In addition, 0.3% underwent colostomy for complications of brachytherapy and 0.6% had a penile prosthesis. About 7% of men carried a diagnosis of urinary incontinence after the procedure.

Harms of Androgen Deprivation Therapy

LHRH agonists constitute the type of ADT that has been most recently studied for treatment efficacy and harms. One systematic review for AHCPR examined endocrine therapy in men with prostate cancer,[192] although whether it required studies to include patient reports of symptoms rather than or in addition to physician or investigator reports is not clear. The review found that 20.8% of men receiving LHRH agonists and 13.3% of men after orchiectomy had erectile dysfunction that prevented intercourse. One other study found that about 20% more men in a group treated with endocrine therapy (type not specified) for prostate cancer had fewer sexual thoughts and lower erectile capacity than a control group without prostate cancer.[168] According to the AHCPR systematic review, about 49% of men receiving LHRH agonists suffered from hot flushes, but less than 5% had gynecomastia.[192]

The Prostate Cancer Outcomes Study (PCOS), a national study of men with prostate cancer treated in various ways, has provided information about adverse health outcomes in two reports of men treated with ADT alone for at least the first 12 months after diagnosis. This study used patient reports, but did not include a pre-treatment assessment. The investigators did ask about pre-treatment function at the 6 months post-treatment assessment. They found that 70% to 80% of men who reported previous sexual activity ceased sexual activity after treatment; about the same percentage of men who were potent before treatment were impotent afterward. There were no differences between men who were treated with LHRH agonists and those men treated with surgical orchiectomy. About 25% of men treated with LHRH agonists and 10% treated with

orchiectomy reported breast swelling; hotflashes were similar between groups (56.5% for LHRH antagonists and 67.9% for orchiectomy).[193,194]

One other large national study used the Medicare database to identify men with prostate cancer who had had RP. The study compared self-reported quality of life 7 to 8 years after surgery in men in this group who had had androgen deprivation (some by orchiectomy and some by LHRH agonists) with those who had not. Although most men in both groups had poor sexual function, the androgen deprived group reported greater dysfunction, with only 2% having the ability to have sexual intercourse and 69% having any sexual drive in the previous 30 days. The androgen deprived group also reported lower function in 7 different indices of quality of life (e.g., mental health, activity, worries about cancer, energy, etc) compared to non-androgen deprived men.[195]

We found no other studies of 50 or more men taking LHRH agonists that provided patient reports of symptoms.

Anemia and osteoporosis have been reported as potential long-term complications of LHRH agonist therapy.[196,197] The frequency and severity of these complications is as yet unclear.

Summary of Harms from Androgen Deprivation Therapy

We found fair evidence that ADT with LHRH agonists reduces sexual function by 40% to 70%, and is associated with breast swelling in 5% to 25% of men. Hot flashes occur in 50% to 60% of men taking LHRH agonists. (Table 3)

Summary for Key Question 8: Harms of Therapy

The sections above have described our findings with respect to organ-specific function for each mode of therapy. All treatments are associated with definite harms, of varying severity and varying frequency. These are summarized in Table 3.

The impact of these symptoms on overall quality of life is complex, however. For example, Litwin et al[169] assessed overall quality of life in addition to individual symptoms in men with localized prostate cancer who had been treated in various ways. They compared quality of life scores among control men and men with prostate cancer within treatment groups. Although they found the same differences in symptoms as our review has found, they found no differences among groups (either among treatment groups or between men with and without prostate cancer) in overall quality of life.

On the other hand, Bokhour et al conducted focus groups with men who had been treated for early prostate cancer 12 to 24 months earlier. About 54% of participants had significant erectile dysfunction; the study documented the manifold effects of this problem on the men's lives, including their "experiences of intimacy with their partners, their relationships with women in social situations, and their self images as sexual beings."[198]

Key Question 9: Costs and Cost-Effectiveness of Screening

Several authors have estimated the costs of a screening program for prostate cancer. For example, in 1995 Barry et al.[199] estimated conservatively that first-year costs for a Medicare benefit for PSA screening (including only men ages 65 to 79 years) would

be $2.1 billion. Lubke et al. produced estimates of first-year costs of a national screening program using PSA and DRE for men ages 50 to 69 years between $17.6 billion and $25.7 billion[200] (see Evidence Table 8).

Given the uncertainties about the existence and magnitude of benefits, the cost-effectiveness of screening for prostate cancer has been difficult to calculate. A 1993 decision analysis, making optimistic assumptions about benefit from screening and early treatment, found little or no benefit for men with well-differentiated tumors.[201] For men with moderately or poorly differentiated cancers, screening and early treatment could offer as much as 3.5 years improvement in quality-adjusted life expectancy, again using the most optimistic assumptions of treatment efficacy. This model also concluded that, even with optimistic assumptions, men ages 75 years and older are not likely to benefit from screening and aggressive treatment. One major reason for this finding is that any benefits of screening are expected to accrue some years into the future, after many men of this age have died of some other condition. Two subsequent decision analyses have reached the same conclusions.[202,203]

In 1995, Barry et al. published a cost-effectiveness analysis using very favorable screening assumptions.[199] The marginal cost- effectiveness of screening men age 65 years with PSA and DRE, without adjustment for life quality and without discounting benefits, is between $12,500 and $15,000 per life-year saved. Changing only a few assumptions, however, quickly increased the marginal cost-effectiveness ratio to above $100,000 per life-year saved. Taking into account a decrement in the quality of life associated with the harms of treatment would make this ratio even less favorable. In

1997, these investigators updated their model with more recent data and further assumptions favorable to screening.[204] Their findings were similar.

A more recent model used inputs from US lifetables and prostate cancer mortality rates from the SEER registry to explore the relationship between increased PSA screening and the recent reduction in prostate cancer mortality (see Key Question 1).[33] Assuming that screening reduces prostate cancer mortality by 20% (the level used to calculate sample size in the PLCO trial), then PSA screening could explain the decline in mortality only with a lead time of 3 years or less, much shorter than the 5 years or longer previously thought likely.[35] If lead time is longer than 3 years, then PSA screening can provide at best a partial explanation for the reduction in mortality.

Thus, the cost-effectiveness of screening for prostate cancer depends largely on the efficacy of treatment for cancers detected by screening, and on the length of life of men detected with cancer. If one makes favorable assumptions about efficacy, screening may be cost-effective for men ages 50 to 69 and may have contributed to the recent decline in mortality. If reality is less favorable, then screening could easily result in net harm. The efficacy of treatment for screen-detected cancers is unknown, however, and will not be clear until high-quality RCTs of screening are completed. The models found that men over age 70 to 75 years, or who have a less than 10 year life expectancy, are unlikely to benefit substantially from screening quite apart from efficacy.

IV. Discussion

Context

Screening for prostate cancer is a controversial topic. National groups disagree about recommendations. An important reason for the disagreement is that no well-conducted randomized controlled trial (RCT) comparing screening with no screening has yet been completed, although 2 large RCTs are in progress (the National Cancer Institute Prostate, Lung, Colorectal, and Ovary [PLCO] trial and the European Randomized Study of Screening for Prostate Cancer [ERSPC]). This review considers the indirect evidence available now to guide the USPSTF in making a recommendation about screening while the field awaits the results of the 2 trials.

Major Findings and Limitations of the Literature

Prostate-specific antigen (PSA) and, to a lesser extent, digital rectal examination (DRE) can detect prostate cancer at an earlier stage than it would be detected clinically. Nevertheless, because some prostate cancers are clinically important and some are not, a major problem in considering the utility of screening is the heterogeneity of prostate cancer itself.

The large discrepancy between prostate cancer diagnoses and deaths indicates that at least some cancers detected by screening are unimportant clinically. Because of a lack of precision about the prognosis of prostate cancers of various types, research has not

defined well the most appropriate target of screening, i.e., those cancers that will cause clinical symptoms and death and can be treated better by earlier detection.

The efficacy of various types of treatment for clinically localized prostate cancer is largely unknown. We lack direct evidence that such treatments as radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, or androgen deprivation therapy (ADT) are effective for screen-detected clinically localized cancer. RP improves prostate cancer-specific mortality after 8 years in men with clinically-detected cancer, but its effect on all-cause mortality is uncertain. ADT is probably effective in prolonging survival in locally advanced cancer.

Each treatment for prostate cancer is associated with various potential harms, including sexual, urinary, and bowel dysfunction. The magnitude of harms is best documented for RP, EBRT, and ADT, and least well documented for brachytherapy.

The costs of a screening program for prostate cancer are potentially large. If treatment is highly efficacious, then for men ages 50 to 69 years the cost-effectiveness of screening may be reasonable; if treatment is less efficacious, the results may be net harm and high costs. Assuming that any potential benefit to screening accrues only after some years, men ages 70 to 75 years and older or with less than a 10 year life expectancy are unlikely to benefit.

Benefits and Harms

Ideally, we would present here an outcomes table, providing information about the estimated benefits and harms of screening 1000 men in different age groups. Although we could estimate the harms of various modalities of treatment (see key question 8) with reasonable certitude, the uncertainties about the benefits are too great.

Thus, completing such a table would necessarily be based on assumptions that have little basis in evidence, and we caution against attempting to do so at this juncture.

We can contrast the potential trade-off between benefits and harms for men by age. We know that older men (e.g., age 70 years or older) have a higher incidence (and, among men who have not been screened, a higher prevalence) of prostate cancer than younger men (e.g., ages 50 to 69 years). We also know that a higher percentage of older men will have an abnormal PSA or DRE screening test, partly because of an increased prevalence of BPH. Thus, the number of men offered a biopsy will be larger for older men. The percentage of biopsies that detect cancer after a positive PSA screening test does not differ a great deal by age.

Assuming that screening is beneficial in reducing mortality, and assuming that the benefit derives from detection of intracapsular tumors that would not have caused symptoms for some years, then older men would tend to benefit less as they are more likely to die of other causes before they would die of prostate cancer. Indeed, given 2 men with prostate cancer, both with a Gleason score of 7 or higher (i.e., more aggressive cancers), the older man is less likely to die of the cancer than the younger man. Finally, we also know that the harms of treatment for prostate cancer are at least as great for older men as younger men. Thus, if there is a benefit from screening, it seems likely that older men would have a smaller net benefit than younger men.

We do not have enough information to make these contrasts for African American men compared with white. We know that the incidence of prostate cancer among African Americans is nearly double that of white, and that mortality for African American men is more than double that for whites.[14] But most of the studies in this report primarily (or

exclusively) involve white men rather than any other ethnic or racial group. If screening is beneficial, then African American men could have a larger absolute benefit than white men. This may not mean screening at an earlier age (the age-incidence curve is as steep for African Americans as for whites) or screening at a different interval, but the total level of benefit could be higher. The same uncertainties about screening, however, apply to African Americans as they do to whites and other groups. Whether screening would result in benefit, and whether that benefit would outweigh the attendant harms, is unknown.

Future Research Needs

Successful completion of the PLCO and ERSPC screening trials is the most important research advance needed at this time. In addition, RCTs of various treatments for clinically localized prostate cancer, comparing standard treatments against watchful waiting (as in the Prostatectomy Intervention Versus Observation Trial [PIVOT]) and against each other, would be very useful.

Further research into identifying factors that would allow us to more precisely categorize prostate cancer into prognostic categories, better discriminating between clinically important and clinically unimportant cancers, would assist us to focus our efforts on those cancers that cause death and disability.

Finally, to date research concerning screening for prostate cancer has focused on detecting localized prostate cancer that might be cured by aggressive treatment. Several pieces of indirect evidence in this review suggest a different model for how screening might be able to impact mortality and morbidity from prostate cancer. This evidence includes these facts:

(1) prostate cancer mortality declined soon after the widespread introduction of screening (but if screening is contributing to this trend then the lead time must be short);

(2) reduction in the incidence of late-stage disease (with a short lead time) has been an impressive characteristic of this decline; and

(3) ADT has been shown in several RCTs to improve overall survival in men with locally advanced disease (which may be a subset of cancers with a shorter lead time). RP has been shown to improve prostate cancer-specific mortality for men with clinically detected prostate cancer.

If screening is responsible for at least some of the reduction in prostate cancer mortality, and if the cancers that are being better treated (e.g., by ADT or RP) as a result of screening are locally advanced (rather than localized), or advanced within the localized category (e.g., as shown by being clinically detected), then more research is needed in finding less expensive and more efficient means of detecting cancer at a stage intermediate between those detected by PSA and those that have already metastasized.

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Appendix A

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Appendix B. Evidence Tables

Appendix B. Evidence Tables

Appendix B. Evidence table glossary

Abbr.	Definition
+	Positive
ADT	Apparent diffusion tensor
Agg	Aggressive
APC	Annual percent change
AUC	Area under ROC curve
Av	Average
BPH	Benign prostatic hyperplasia
Bx	Biopsy
Ca	Cancer
CI	Confidence Interval
CT	Computerized tomography
DES	Diethylstilbestrol
Diff	Difference
DRE	Digital rectal examination
Dxed	Diagnosed
EBRT	External beam radiation therapy
Endpts	Endpoints
ERSPC	European Randomized Study of Screening for Prostate Cancer
F/U	Follow-up
Fxn	Function
Gy	Gray
HRQol	Health-related quality of life
IVP	Intravenous pyelogram
LHRH	Luteinizing hormone-releasing hormone
LR	Likelihood ratio
LUTS	Lower urinary tract symptoms
m-y	Months-years
MRI	Magnetic resonance imaging
Mos	Months
NCHS	National Center for Health Statistics
Nonagg	Non-aggressive
Ns	Not statistically significant
OR	Odds Ratio
PC	Prostate Cancer
PFS	Progression free survival
QALY	Quality adjusted life year
OR	Odds ratio
Qol	Quality of life
P	Probability
PC	Prostate cancer
PPV	Positive predictive value
PSA	Prostate specific antigen
Rad	Radiation
Rand	Randomization
RCT	Randomized controlled trial
ROC	Receiver operator characteristic
RP	Radical prostatectomy
SEER	Surveillance, Epidemiology, and End Results Program
Std	Standard
TRUS	Transrectal ultrasound

Appendix B. Evidence Tables

Abbr.	Definition
TURP	Transurethral resection of the prostate
Tx	Treatment
UCLA	University of California at Los Angeles
US	United States
WW	Watchful Waiting
XRT	Radiation therapy
Yrs	Years

Appendix B. Evidence Tables

Evidence Table 1A: Health outcomes of screening in reducing mortality RCTs (Key Question 1)

Citation Design	Study Population Selection	Study Population Description	Intervention	Results	Comments
Labrie F et al., 1999[20]	Men registered in the 1985 electoral rolls of Quebec City were randomized to screening or no screening Study conducted from 1/1/89 through 12/31/96	46,173 men aged 45-80 years 30,956 invited to be screened; 7,155 (23%) screened; Av age 60+/-7 Of 15,237 controls, 14,255 (93.6%) were not screened; Av age 58+/-9	Screening by PSA and DRE PSA cutpoint >3.0 ng/ml Screen test positive had TRUS and biopsy	Primary outcome was death from prostate cancer as recorded in the death registry of the province health dept. In the screened group, (including all screened men from both groups) the death rate was $13.7/10^5$ m-y. In the unscreened group, the death rate was $41.6/1010^5$ m-y The authors conclude that screening resulted in a 67% reduction in death rate incidence	No sociodemographic comparison of the two groups was presented Men in the screened group were followed an av 3.8 years; whereas men in the control group were followed an av 7.4 years The death rates from other causes for the two groups were not presented or compared No intention to treat analysis Quality: poor

Appendix B. Evidence Tables

Evidence Table 1B: Health outcomes of screening, case-control studies (Key Question 1)

Citation	Cases	Controls	Measurements (exposure, confounders)	Results	Comments
Jacobsen SJ et al., 1998[23] Population-based case-control Study of DRE and PC mortality Olmstead County, MN Study	N=173 Men with PC on death certificate between 1976 and 1991, verified by chart review (116 had PC listed as immediate or underlying cause of death)	N=346 2 men with registration numbers closest to **each** case, matched to date of birth and duration of medical record (all cases and controls in Olmsted County database)	Reviewed medical records for 10 years before index (diagnosis) date for evidence of DRE and findings from DRE Also abstracted obstructive urologic symptoms and comorbidity score (reliability high)	Controls more likely to have had DRE in years 2-10 before index year than cases: OR=0.51 (0.31-0.84) OR=0.53 (0.32-1.06) if cases restricted to those with PC as immediate or underlying cause of death OR=0.31 in men without urologic symptoms Results not changed by comorbidity score adjustment For only DRE in years 1-3, OR=0.76 If had DRE in years 4-6, no association for DRE in years 1-3 (OR=1.11)	Alternative explanation: "healthy screenee bias," men being screened may have had lower probability of dying of PC Could have missed DREs not recorded in medical record Study occurred before widespread PSA screening Disagreement about excluding DREs in the year before diagnosis Quality: good
Richert-Boe KE et al., 1998[22] Matched case-control study among patients at Kaiser Northwest	N=150 Men who died from PC between 1981-1990, age 40-84 when PC diagnosed, members of plan for at least 2 years, verified by chart review Excluded men whose death not due to PC	N=299 2 controls randomly selected from Kaiser members, matched according to age and entry into health plan	Medical record review of all DREs between enrollment in plan and index date (date of diagnosis of case) Findings of DRE and urologic symptoms also recorded Blinded reviewer categorized each DRE as screening or due to any of several symptoms Analyzed only screening DREs Reliability high	About half of fatal PCs were poorly differentiated, and half were stage D at diagnosis 77% of cases and 80% of controls had had a screening DRE during the 10yrs ending just before index date (OR=0.84; 0.48-1.46)	Study done before widespread PSA screening Could not adjust for family history No analysis reported for all DRE Only 58% of case subjects and 12% of controls with suspicious findings on DRE went on to have a biopsy Quality: good

Evidence Table 1C: Health outcomes for screening, ecologic studies (Key Question 1)

Citation	Study Population		Measurements	Results	Comments
Design	**Selection**	**Description**			
Etzioni R et al.. 1999[33] 7 year population-based cohort (computer simulation model)	US lifetables SEER data	Medicare population from 1988-1994[34]	Incidence data: Dissemination of PSA testing and prostate cancer detection in Medicare population from 1988-94 Mortality data: Allcause mortality rates from U.S. lifetables; prostate cancer specific rates from SEER Computer simulation model: PSA-tests and patients with early diagnosis; Identifying tested individuals; Identifying individuals with an early diagnosis; Lead time and survival; Prostate cancer deaths without PSA testing; same as previous with testing; Cancer deaths prevented because of PSA testing	Complete data only for 71-84 year old men Only very short lead times (time by which diagnosis is advanced by screening) of ≤ 3 years produce a decline in mortality in model and would explain the reduction in mortality rates after 1991 due to screening Projected mortality trends in the absence of PSA screening are not consistent with pre-1991 increasing trends for lead times of 5 or 7 years	Screening rates described as probabilities for the year 1998; no actual screening rates reported Cancer detection rate for first and consecutive tests as well as relative survival estimated; death rates from other causes and lead-time reported Study populations not described; information about clinical stage and histologic grade missing Problem of eliminating: a) clinically identified patients with cancer (whose diagnosis would have occurred regardless of use of test) b) patients with genuine early diagnosis Medicare did not reimburse for PSA testing in model years: possible underestimation of true PSA screening Study uses computer model; not substitute for RCT

Evidence Table 1C: Health outcomes for screening, ecologic studies (Key Question 1)(continued)

Citation	Study Population		Measurements	Results	Comments
Design	Selection	Description			
					Population of analysis is 71-84 years old; important data from younger men are missing Quality: good
Feuer, EJ et al., 1999[28]	SEER Data Death Certificate Data	Men newly diagnosed with PC living in 5 SEER areas from 1973-1995	PC incidence and mortality from 5 SEER areas from 1973-1995 Analyzed contribution to mortality rate changes of PC cases diagnosed since start of PSA testing (1987)	More than 50% of mortality rates come from men dying within 3 years of diagnosis Cases diagnosed after 1987 were major cause of rise and fall in PC mortality in late 1989s and early 1990s Attribution bias, due to attributing cause of death to PC in men who actually die of something else, may be partly responsible for rise and fall in PC mortality	Quality: good
Hankey BF et al., 1999[9] 23 year population-based cohort	Data from SEER and National Center for Health Statistics	229,556 PC cases as described in SEER (1973-95) Age: 50-85+	Incidence data: SEER Program; coding for age, stage, grade Mortality data: (1969-95) from NCHS represents overall prostate ca mortality in US APC for incidence and mortality measured	Increased incidence for whites and blacks from 1975-85 (2.35 APC); in 1989 APC ranged from 17.0 to 18.4; decreasing incidence from 1992 on with APC (–12.8 to –14.0) Increased mortality from 1969-80 (0.7 to 1.6); 1981-88 (3.1 to 3.2); decreased mortality from 1991 on (-1.9 to –1.7) Incidence/age: calendar period effect (all age groups started to decline in 1990) Incidence/stage: decrease of incidence for all 3 stages	Screening effect is proposed; decrease of incidence of distant stage disease since 1991, after not being perturbed by screening; calendar period effect (see Incidence results) No actual screening rates are reported for the study period Good confounder adjustment: age, race, grade, stage

Evidence Table 1C: Health outcomes for screening, ecologic studies (Key Question 1)(continued)

Citation	Study Population		Measurements	Results	Comments
Design	Selection	Description			
				Incidence/grade: decrease of incidence for all 3 grades; especially fast for well-differentiated tumors	Quality: good
Meyer, F et al. 1999[30] Ecologic Study	Population data	Men in Quebec who died of prostate cancer between 1976 and 1997 Men in Canada who died of prostate cancer between 1976 and 1996	PC incidence and mortality, 1976-1996/97	PC mortality increased 1.5%-1.7% per year until 1991 After 1991, mortality decreased moderately until 1995, when it decreased more rapidly Overall decline in mortality between 1991-1997 in Quebec was 23% (p=0.01) Overall decline in Canada was 9.6% (p=0.03) Larger decrease for men younger than 75 compared with older than 75	Because of short time interval between increased screening and decreased mortality, authors believe cause is better treatment Quality: good
Roberts, RO et al. 1999[31] Ecologic Study	Population data from computerized database	Men living in Olmsted County, Minnesota	PC mortality from 1980-1997 PC incidence since 1992	PC mortality increased from 25.8/100,000 men in 1980 to 34/100,000 in 1992 Mortality declined to 19.4/100,000 in 1997 (22% decline; 95% CI, 49% decline to 17% increase) Incidence peaked at 209/100,000 in 1992, declined to 108-132/100,000 in 1993-95	Mortality dropped to levels lower than in years before PSA testing Suggest that screening is playing a role Quality: good

Evidence Table 1C: Health outcomes for screening, ecologic studies (Key Question 1)(continued)

Citation	Study Population		Measurements	Results	Comments
Design	Selection	Description			
Bartsch, G et al. 2001[42] Ecologic Study	All residents in Tyrol, Austria compared with rest of country	65,123 men between 45-75 years	Mass PSA screening project initiated in Tyrol in 1993 Used age-referenced PSA cutpoints >80% of men with abnormal test had biopsy Treatments primarily RP or EBRT No mass screening program in rest of Austria	Dramatic increase in incidence of PC in Tyrol, 1988-92 No information on incidence in rest of country PC mortality decreased in Tyrol (1993-1999) more than rest of country (p=0.0004)	Because we have no information about screening in rest of country, and because we have no comparison of treatment Quality: fair
Oliver, SE et al. 2001[205] Ecologic Study	Population data	Male residents of England, Wales, and USA PSA screening is less common and even discouraged in UK	PC incidence and mortality from 1970-97 More screening in USA than UK	Much larger increase in incidence in USA compared to UK from 1989-92, then a larger decline in USA Mortality was higher in USA until 1985, when mortality was same in the 2 countries Since 1993, mortality higher in UK Decline in mortality in USA 1993-97 was 3.8% compared with 1.7% in UK (statistically significant)	Because mortality declined in both countries after 1993, authors suggest cause may be disease management Quality: good

Appendix B. Evidence Tables

Evidence Table 2A: Yield of screening (Key Question 2)

Citation	Participants	Screening Test and Gold Standard	Results	Comments
Gann PH et al., 1995[35]	Nested case-control study 22,071 physicians between ages 40 and 84 in 1982 520 cases of PC were reported by 1992 366 of the cases of PC and supplied a blood sample For each PC case, selected 3 controls	PSA (≥4.0) Gold std: follow-up x10 yrs.	Follow-up / Sensitivity / Specificity 1 yr. — 83% 2-3 yrs. — 100%- — 86% 3-4 yrs. — 56% — 98% Agg.-nonagg — 92%-67% Agg.-nonagg — 73%-33% Overall detected in 0-5 yrs. 73% — 50% — 88% Area under ROC curve for cancers diagnosed in 5 yrs: 0.85 Av lead time: 5.5 yrs.	"Aggressive Cancers" = stage C or D (i.e., extracapsular) + Gleason 7 or higher Of 366 total PCs, 183 (50%) classified as aggressive Quality: good
Meigs, JB, Barry MJ et al., 1996[60]	Men with organ-confined PC (N=276) Unselected men from the community who were not found to have PC by screening and biopsy of positive screens (N=305) Men with LUTS and BPH coming to prostatectomy (and were found not to have PC) (N=173) Men with BPH enrolled in the North American finasteride trial (N=770)	PSA test Biopsy is gold standard	Overall LR+ for men with PSA 4.1-6.0 = 3.4 for unselected men and 1.4 for men with BPH Men with LUTS had lower LR+ than men without LUTS In cancer group, 39.2% of men with organ-confined PC and PSA < 4.0	Quality: good

Evidence Table 2B: Yield of screening, studies of screening programs (Key Question 2)

Citation	Population Screened, Participation Rate, Age	Test Abnormals (% of Screened)	Biopsies % Screened	Cancers % Screened % Biopsies	Staging, Grading
Martin E et al., 1999[105]	N=2,576 screened 18% participation Men ages 50+ City in Spain	DRE: (3.6%) PSA>4: (6.5%) One or other: (8.7%) % abnormal screens: Ages 50-55 (3.3%) Ages 66-70 (17.0%)	225 (8.7%) Ages 50-54: 3.3% Ages 66-70: 17.0%	Overall 33: Screened: 1.3% Biopsies: 14.7% Ages 50-54: Screened: 0-2% Biopsies: 6.1% Ages 66-70: Screened: 2.4% Biopsies: 14.3%	Clinically: 60.6% organ confined 12.1% Metastatic Histologically: 67% Well differentiated 27% Moderate 6% Poor Quality: good
Horninger W et al., 2000[104]	N=21,078 screened 32% participation Men 45-75 Living in Tyrol	PSA, age referenced standard: 1618 abnormal (7.7%) PSA>4: 8.9%	778 (48.1% of positive test) (3.7% of screened) Biopsies/screened: Ages 50-59: 1.5% Ages 70-75: 11%	197 Screened: 1.2% Biopsies: 25.3% Ages 50-59: Screened: 0.3% Biopsies: 19.7% Ages 70-75: Screened: 3.0% Biopsies: 27.5%	135 (68.5%) of all cancers had RP 95 (70.4%) path organ confined Quality: good

Evidence Table 2B: Yield of screening, studies of screening programs (Key Question 2) (continued)

Citation	Population Screened, Participation Rate, Age	Test Abnormals (% of Screened)	Biopsies (% Screened)	Cancers (% Screened) (% Biopsies)	Staging, Grading
Maattanen L et al., 1999[102]	N=15,685 screened (69% participation) Ages 55-67	PSA ≥4.0: 1342 (8.6%) PSA 3-3.9: ~15% had +DRE (DRE only given to men with PSA 3-3.9) PSA 3-3.9: 801 (5.1%) of all men	1,236 biopsies (7.9% screened) from abnormal PSA	PSA ≥4.0: 386 cancers Screened: (2.5%) Biopsies: (29%) 22 additional cancers from DRE in men with PSA 3-3.9: Screened: (2.7%) Biopsies: (~18%)	84% of cancers Gleason 2-6 16% Gleason 7-10 No staging data given Quality: good
Schroder, F et al., 2000[43]	N=10,523 screened (uncertain participation) Ages 55-74 Living in Rotterdam	PSA ≥4.0: 1312 (12.5%) PSA ≥4.0 +DRE+TRUS: biopsied any abnormality	2,499 total biopsies (23.7%) PSA ≥ 4.0: 1,184 (47%) PSA< 4.0: 1,315 (52.6%) due to DRE or TRUS	478 total cancers found: Screened: (4.5%) Biopsies: (19%) 351 due to PSA ≥ 4.0 Screened: (3.3%) Biopsies: (29.6%) PSA<4.0: 127 due to DRE/TRUS: Screened with PSA<4.0: (1.4%) Biopsies: (9.7%)	166 (34.7%) patients with cancers had RP PSA ≥ 4.0: 116 cancers 44% Gleason 4-6 51.7% Gleason 7 4.3% Gleason 8-10 68% organ confined 9.7% overall pathologically metastatic Quality: good

Evidence Table 2B: Yield of screening, studies of screening programs (Key Question 2) (continued)

Citation	Population Screened, Age, Participation Rate	Test Abnormals (% of Screened)	Biopsies (% Screened)	Cancers (% Screened) (% Biopsies)	Staging, Grading
Labrie F et al., 1992[67] Labrie F et al., 1993[106] Labrie F et al., 1999[20] Labrie F et al., 1996[103] (1st visit data) Quebec	N=7,350 screened (23.1% participation) Ages 45-80 Living in Quebec City	PSA (>3.0) and DRE 1451 PSA >3.0 19.7% of screened	761 biopsies (10.4% of screened)	252 Cancers 222 (88%)found by PSA >3.0 and 119 (47%) by DRE Screened: 3.4% Biopsies: 33% (17.4% of abnormal tests) Of 222 cancers found by PSA > 3.0 Screened: 3.0% (2.5% age 55-60; 6.9% age 65-70) Of 119 found by DRE Screened: 1.6% 196 cancers found in men with PSA >4.0 Screened: 2.7%	Of 228 cancers clinically staged, 70% organ confined; 10.5% metastatic Quality: good
Catalona, WJ et al., 1994[44] Richie JP et al., 1993[45]	N= 6,630 men Ages 50+ from advertisements in 6 communities	PSA>4.0: 983 Screened: 14.8% +DRE: 982 Screened: 14.8% Positive on at least one test: 1,710 (25.8%)	1,167 biopsies: Screened: (17.6%) Abnormal: (68.2%) 686 biopsies due to PSA and 683 due to DRE	264 cancers: Screened: (4.0%) Biopsies: (2.3%) Screened for PSA > 4.0: (3.3%) Screened for +DRE: (2.2%)	Clinically, 99% cancers were organ confined 162 (61%) cancer patients had RP 71% pathologically organ confined No distant metastases beyond pelvic lymph nodes PSA>4.0 found 75% of organ confined cancers DRE found 56% of organ confined cancers Quality: good

Evidence Table 3: Harms of screening (Key Question 3)

Citation	Participants	Measurements	Results	Comments
Essink-Bot, ML et al., 1998[116]	Men ages 55-74 Initially: 600 participants in Rotterdam ERSPC, group invited to be screened Attrition to 541 after screening 235 of 500 non-participants	SF-36 EQ-5D, European quality of life instrument STAI to measure state and trait anxiety Visual analogue scale for overall health Pain and physical discomfort of screening DRE, TRUS, biopsy Limitations in week after biopsy	Negative screening test group (pre to post test): Small improvement in mental health on SF-36 Decrease in anxiety False positive screening test group (pretest to post biopsy) Small improvements in bodily pain and general health perceptions Small decrease in anxiety Entire group Anxiety increased mostly in those with high trait anxiety DRE: 52% some discomfort/pain TRUS 39% some discomfort/pain Biopsy: 98% some discomfort/pain 4% used pain killers 4-6% interfered with function	High response rate from participant group Quality: good

Appendix B. Evidence Tables

Evidence Table 4: Efficacy of treatment with radical prostatectomy (Key Question 4)

Citation	Participants Number/Description	Measurements	Intervention	Results	Comments
Akakura et al., 1999[123]	100 of 243 eligible men aged less than 75 years without obvious enlargement of pelvic nodes by CT or MR with newly diagnosed Stage B or C prostate cancer enrolled Between 1989 and 1993, eligible men recruited from 6 Japanese hospitals 5 of 100 excluded before randomization for other reasons	Outcomes were progression (local growth of tumor and/or appearance of distal metastasis) and cause-specific survival (death after progression was considered as cancer death)	All participants received endocrine therapy for 8 weeks before RP or EBRT and were continued on it 46 men were randomized to receive RP with pelvic lymph node dissection; 49 men received EBRT	4 (9%) in RP group and 12 (25%) in EBRT group developed disease progression. 5-year progression free survival was 91% in the RP group and 81% in the EBRT group (p=0.044); at 5 years, cause-specific survival was 97% in the surgery group and 85% in the XRT group (p=0.024) 5-year overall survival rate was 86% in the RP group and 76% in the EBRT group (p=Ns)	Only 41% of those eligible enrolled Rising PSA not included as disease progression Patients were only followed for approximately 5 years Quality: good but small
Iversen P et al., 1995[122] RCT comparing RP plus oral placebo to oral placebo alone (i.e. expectant treatment).	76 men aged 50-84 years (mean 65.9) with Stage A PC and 66 men aged 44-78 years (mean 62.3) with Stage B disease were enrolled From 15 VA hospitals between 1967-1975 18 men randomized to placebo only and 13 men randomized to RP not evaluable for follow up because they refused treatment, were misstaged, or violated the protocol	The main endpoint was overall survival, including all causes of death Survival status updated by contacting the participating hospitals, patients or their relatives, or by Vital Records offices Could not ascertain cause of death	39 men with Stage A and 29 men with Stage B disease randomized to oral placebo only; other 74 men randomized to RP and placebo Median length of follow up was 23 years	For all patients, the median survival in the RP group was 10.6 years compared to 8 years in the placebo group (p=Ns) Within each stage, age adjusted survival comparison by treatment was not significant	How these patients specifically recruited not reported Major loss to follow-up Quality: poor
Holmberg L et al., 2002[124] RCT of RP versus watchful waiting	695 men with newly diagnosed clinically localized prostate cancer; mean age 64-65 5.2% detected by screening > 45% initial PSA > 10	Prostate cancer specific mortality All-cause mortality Independent endpoint committee	RP with lymph node dissection WW no treatment until symptoms or signs of progression	Prostate cancer specific mortality: no difference at 5 years (4.6% WW vs 2.6% RP); 8 years (13.6% WW vs 7.1% RP); Relative hazard 0.50 (0.27-0.91) No difference in all cause mortality	About 75% of men had palpable prostate cancer. Quality: good

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Granfors et al., 1998[139] RCT comparing XRT with and without orchiectomy in men with and without lymph node disease	400 men expected to be enrolled, but study terminated due to an interim analysis revealing high rate of progression in group treated with XRT alone 91 men with Stage B and C enrolled; mean patient age 68.8 years (49.2-75.3) Patients with early stage and well or moderately well differentiated lymph node negative tumors were excluded	Men with newly diagnosed PC between 1986 and 1991 in three urologic clinics were invited to participate	Patients were followed for 3 years with history and DRE; bone scans done when clinical progression or suspicion of metastatic disease Progression defined as occurrence of clinically evident local tumor growth or bone or other metastases	All patients underwent bilateral staging pelvic lymphadenectomy and were randomized to XRT with or without orchiectomy with stratification for tumor and nodal status 45 patients were in the XRT and orchiectomy (combined) group and 46 in the XRT alone group. XRT was begun a few weeks after orchiectomy. All patients received XRT to pelvis and a boost to the prostatic area	Patient characteristics of groups similar; patients followed for median of 9.3 years (6.0-11.4) XRT alone group, progression occurred in 61% (44% of node negative and 84% of node postive) patients for combined group, progression occurred in 31% (32% of node negative and 30% of node positive) patients 44% of XRT alone group and 27% of combined group died of PC (p=0.06); overall, 61% of XRT alone group and 38% of combined group died (p=0.02) (statistically significant for node + but not for node - disease)	Immediate androgen deprivation is better than deferred endocine treatment for clinically localized PC, particularly in patients with positive lymph nodes Lymph node staging for clinically localized PC is extremely important	Unclear how men were recruited, but once enrolled there was good follow up Diagnosing disease progression was subjective, and criteria for attributing death to prostate cancer were not described One of a few studies to clearly stratify, analyze, and report results regarding nodal status Quality: good

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Schmidt et al., 1996[207] RCT composing adjuvant therapy (cyclophosphamide estramustine or observation) in two protocols, as part of the National Prostate Cancer Project, clinically localized PC	184 men enrolled in Protocol 900 and 235 enrolled in Protocol 1000 Follow up information was available for 170 and 233 men respectively No description of participants, 29% of those in Protocol 900 and 63% of those in Protocol 1000 had positive pelvic lymph nodes	Recruitment was not described	Outcomes: recurrence rates (metastatic disease, increases in serum acid phosphatase, and increases in PSA), median PFS (not defined), and overall survival.	Protocol assignment at the discretion of the investigator Protocol 900 included patients receiving radical surgery or cryosurgery; Protocol 1000 included patients receiving XRT Men in both protocols randomized to cyclophosphamide for up to 2 yrs (C), estramustine phophate for up to 2 yrs (E), or observation (O)	Follow up information available for 403 patients (92%) for an average 11 years For Protocol 900 (prostatectomy), overall recurrence rate 53%, (71% in those with positive nodes); differences among adjuvant treatments not statistically significant for with and without nodal disease For Protocol 1000 (XRT), overall recurrence rate 66%, (82% in those with positive nodes); differences among adjuvant treatments not statistically significant in negative node group; in positive node group rates of recurrence for C, E, and O were 75%, 57%, and 66% respectively, and were significantly different In Protocol 900, the PFS for Groups C, E, and O were 79, 155, and 104 months (p=0.13); in Protocol 1000, the PFS for Groups C, E, and O were 35, 52, and 46 months (p=0.18)	Overall survival and PFS greater in Protocol 900 (prostatectomy) compared to Protocol 1000 (XRT) A beneficial effect of estramustine observed	Entry into one protocol versus the other was not randomized Groups had different rates of positive nodes, but no other comparison between the two groups upon entry was presented, so comparing the two groups is of little value Randomization to aduvant therapy within the protocols and follow up appears well done, but the evaluators do not appear to have been blinded to the treatment received Paper essentially two studies: one to compare adjuvant treatments in men having prostatectomy, and one comparing adjuvant treatments in men receiving XRT Paper does not evaluate or discuss the primary treatment (prostatectomy versus XRT) Quality: fair

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Lundgren et al., 1995[138] RCT comparing immediate to deferred endocrine treatment of clinically localized PC	285 men previously untreated PC; Mean age 70 years; 99 men had Stage A, 107 had Stage B; 22 Stage C 57 excluded after randomization (mostly for protocal violations and incorrect randomization)	Patients from 5 urological or surgical clinics in Sweden were eligible	Patients followed with DRE, blood work, bone scan, and prostate biopsy	Diagnosis and tumor differentiation determined by TURP or by prostate biopsy 81 patients to receive polyestradiol plus ethinylestradiol (PE); 93 patients to receive estramustine (E); and 98 patients deferred endocrine treatment D Progression defined as appearance of metastases, poorly differentiated cancer, local progression with pain and/or ureteral dilitation remaining after TURP. (D)	More Stage B tumors in the E group and more Stage C tumors in the D group. Overall 125 (55%) had disease progression Metastasis in 22%: 17% in group PE, 20% in group E, and 28% in group 46 (20%) died from PC: 12% in PE group, 18% in E group, and 28% in D group (p=0.03) Overall, 128 patients (56%) died from any cause: 53% in PE group, 54% in E group, and 60% in D group (p=0.48).	More people died from PC in the deferred group than in the immediate treatment groups After 10 years of follow up, the probability in the deferred treatment group of dying of PC was 26% and that of dying of intercurrent disease was 25% The probability of dying from PC is higher than that previously reported, and men with at least 10 years life expectancy should receive early treatment	57 patients regarded as nonevaluable, created dissimilarities among treatment groups Unclear how cause of death determined or attributed PC Study provides good information on natural history of PC. Although deferred treatment group had higher rates of death from PC, overall survival rates not different Quality: fair

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Pilepich, M.V., et al., 1995[144] RCT	203 patients assessed Median f/u time of 107.8 mos. Actual median f/u of alive pts. was 78.9 mos. March 1983-June 1986 198 pts. total randomized to Megestrol Acetate (n=100) or DES (n=98) Eligible if had locally advanced prostate CA, stage B (42 Megace group, 45 DES group) or stage C (58 Megace, 53 DES) 90% compliance in Megestrol, 82% in DES arm	No mention of recruitment specifics	Endpts = tumor clearance rate (rand. To 1st tumor-free assess.), effect of rx on serum testosterone levels, evaluation of loco-regional control (prog. Of clinc. Detectable disease or + biopsy after 2nd post-rad. year), incidence of distant mestastases (end pt. of metast=occurrence of disease outside pelvic region), survival (failure=death from any cause), and assessment of effects of tx on sexual fxn	Megestrol 40 mg 3x daily po DES 1 mg 3x daily po All received radiotherapy 44-46 Gy, 1.8-2 Gy daily to regional lymphatics, followed by boost to prostatic are of 20-25 Gy, 1.8-2 Gy daily, to a total of 65-70 Gy Tumor response assessed clinically and by CT Serum test. levels recorded: "throughout trial"	Median increase in test. levels higher in DES (94.5% vs. 77%, p<0.0001) No difference in tumor clearance No diff. in loco-regional occurrence (no p value from Fig. 2) Difference in metastatic rate not significant (p= 0.73) Survival rates not different and appear to be insignificant from Fig. 4, but no p values Return of sexual potency @ 1 year= 81% Megestrol arm, 58% DES arm	Comparable efficacy in tx using Megestrol or DES DES appears more effective @ suppressing testosterone, but also associated with higher incidnce of drug-related toxicity	No mention of blinding, in either randomization or assessment of results Need p values or CI's for several figures Survival as death from any cause suspect No median age of subjects (or age range) Quality: fair

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Bolla, Michel, et al., 1997[141] Prospective RCT	415 men Median age of 71 years. (51-80) Recruited from may 1987-september 1995 14 subjects lost to follow-up (10 from radiotherapy group, 4 from combined tx group) 208 rand to external irrad. Only 207 to ext. irrad & goserelin tx 99% irradiation only compliance; -96% combined therapy compliance	Specific recruitment methods Not mentioned; patients referred from various Institutions by dx of locally advanced prostate CA (T1 or T2) and WHO grade 3	Median follow-up: 45 mos Main outcome: overall survival @ date of death or most recent f/u Disease free interval from date of randomization to date of local or regional failure PSA progression: PSA level increase of 1.5 ng/ml in 2 successive observations	Irradiation groups: Planning target vol. 1 received 50 Gy once daily 5 times/week for 5 weeks (whole pelvis) Planning target vol. 2 received 20 Gy once daily 5x/week for 2 weeks (prostate and seminal vesicles) Goserelin administered 3.6 mg SQ every 4 weeks starting on 1st irradiation day through 3 years	Kaplan-Meier estimates of overall survival @ 5 years=79% (combined tx group, 95% CI 72-86%); 62% in radiotherapy (95% CI 52-72%) 85% disease free @five years in combined tx (95% CI 78-92%); in radiotherapy group 48% (95% CI 38-58%) P<0.001 in all results	Adjunctive therapy with goserelin @ beginning of external irradiation through 3 years can improve 5 year overall survival of patients with locally advanced PC	Impressive attention to instrument calibration Use of a run-in period to assess future compliance Data analysed according to intention to treat principle Unclear about "minimization technique" of randomization Specific characteristics re: CA stage good, but other confounders Not addressed in much detail Quality: good

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Messing, Edward, et al., 1999[146] Prospective RCT	100 men enrolled (1988-1993) who had undergone radical prostatectomy and pelvic lymphadenectomy @ no more than stage T2 100 men randomized (2 ineligible after randomization) Initial accrual goal of 220 subjects Median age=65.6 Median follow-up of 7.1 years	Recruited from various institutions by dx (specific recruitment methods not mentioned)	Observation of immediate antiandrogen therapy; followed subjects until signs of elevated serum PSA levels noted	Immediate group given 3.6 mg goserelin SQ every 28 days Observation group followed until signs of progression CA noted other than elevated serum PSA levels	Overall survival @7.1 years Immediate group vs observation: 89% in immediate group 62% in observation only group (p=0.02) PC specific survival was 97% vs. 63% (immediate vs. observation) [p=0.001] Progression-free survival rate was 84% vs. 37% (immediate vs. observation) [p<0.001] Unable to determine 95% CI from tables	Early, immediate hormonal therapy significantly increases the chances of survival	Temporal issues re: not using PSA levels as part of inclusion criteria interesting, but addressed lack of centralized review of pathologic findings undermines internal validity Cox model used to manage confounders Needs more discussion of consequences of falling short of initial accrual goal No blinded assessment of outcome Quality: good

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Pilepich MV et al., 1997[145] RCT comparing adjuvant hormonal treatment with XRT to XRT alone	977 patients with locally advanced PC were enrolled Patients who had either a perineal or retropublic prostatectomy were eligible if there were positive surgical margins or seminal vesicle involvement In both groups, about 15% had Gleason score 2-5, 54% 6-7 and 31% 8-10 29% of the immediate hormonal treatment group and 26% of the hormones at relapse had positive nodes About 15% in both groups had prostatectomies 32 patients were deemed ineligible Median follow up was 4.5 yrs (range 0.2 to 8.8 yrs)	Between 1987-1992, patients were entered by a telephone call to the study headquarters within the first week of starting XRT Multicenter study of the Radiation Therapy Oncology Group	Disease free survival was defined as survival in the absence of local or regional failure, or distant metastasis Local failure was defined as persistence of the palpable tumor beyond 24 months after study entry, reappearance or progression of palpable tumor, or biopsy proven disease 2 or more years after study entry Regional failure required clinical or radiographic Evidence or tumor in the pelvis Time to local recurrence or to distant metastasis was measured from the date of randomization to the occurrence of either event	Patients were randomized to receive XRT alone (488) or with adjuvant hormonal treatment (489) For all, the prostatic bed received 44-46 Gy in 1.8-2.0 Gy fractions with a prostatic target volume boost of 20-25 Gy using a multiple field technique. Goserelin 3.6 mg SQ was begun during the last week of XRT in the intervention group and upon relapse in the control group	16% of the combined group and 29% of the hormones at relapse group had local failure at 5 yrs ($p<0.01$). 17% of the combined group and 30% of the hormones at relapse group had metastatic disease at 5 yrs ($p<0.01$). 60% of the combined group and 44% of the hormones at relapse group were disease free at 5 yrs ($p<0.01$). Survival for patients with Gleason score 2-7 was 76% at 5 years and not different between the groups. Survival at 5 years for patients with Gleason score 8-10 was 65% in the combined treatment group and 55% in the hormone at relapse group ($p=0.03$).	Adjuvant goserelin is associated with a remarkable improvement in local control and disease free survival The beneficial adjuvant effect appears to be more prominent in patients with high grade lesions An improvement in overall survival was observed only in patients with the most unfavorable lesions (Gleason 8-10), and is most prominent in those patients who did not undergo prostatectomy before radiotherapy	Potential bias in how patients were selected to participate in study Potential bias in identification of clinical failure Unclear if an intention to treat analysis was done, or how many in the treatment upon relapse group received treatment Quality: fair

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Pilepich MV et al. con't			Absolute survival was measured from the date of randomization to the date of death or most recent follow-up evaluation				

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Medical Research Council Prostate Cancer Working Party Investigators Group.[147]	934 patients with local disease considered too advanced for curative treatment or asymptomatic metastatic disease who had not previously received hormonal treatment. 10 men were younger than 60 years and 82 men were older than 80 years.	From an unknown number of urologists' clinics in the UK. How participating urologists were selected was not described.	Survival, disease progression (as measured by need for TURP), and complications (spinal cord compression, pathologic fracture, ureteric obstruction, extra-skeletal metastasis) Annual survey forms were sent to those enrolled Information on cause of death was obtained from National Health Service records Used intention to treat analysis	469 men were randomized to immediate treatment (orchiectomy or LHRH analogue) and 465 men to deferred treatment (same treatment once clinician detected indication) 55% of the immediate group and 52% of the deferred group had non-metastatic disease confirmed by bone scan	347 men in the deferred group subsequently received treatment Indications for treatment included pain (52%), local progression (46%), and increasing tumor marker level (7%) Of the 244 patients in the deferred group with non-metastatic disease, 169 were later treated, 50% of whom began treatment within 27 months For those with non-metastatic disease, 38% of the immediate group and 59% of the deferred group developed metastases or died from PC ($p<0.01$); 18% of the immediate group and 26% of the deferred group developed complications; and 62% of deaths in the immediate group and 70% in the deferred group were from prostate cancer ($p<0.01$) 14% of the immediate group and 58% of the deferred group underwent TURP	Those most likely to benefit from deferred treatment are elderly men with non-metastatic disease Progression of disease will be arrested or slowed in patients treated immediately The data presented provide consistent support for the benefits of immediate treatment	Length of follow-up wasn't reported There was no protocol for management of the patient other than hormonal treatment, nor guidelines for indications for treatment in the deferred group Patients were stratified based only on metastasis, and no information on tumor grade or stage was included There was no blinding of clinicians. The need for TURP may not be the optimal method of evaluating progression Quality: fair

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Corn BW et al. 1999[143]	139 patients with locally advanced disease who had either a perineal or retropublic prostatectomy Mean age was 66 years In the immediate hormone treatment group, 65% had Gleason 2-7 and 35% 8-10, and median PSA was 3.2 Hormone treatment in relapse group, 58% had Gleason 2-7, 42%had Gleason 8-10, and median PSA 1.6 31% had positive nodes in both groups	Between 1987-1992, patients were entered by a telephone call to the study headquarters within the first week of starting XRT Multicenter study of the Radiation Therapy Oncology Group	Disease free survival was defined as survival in the absence of local or regional failure, or distant metastasis Local failure was defined as persistence of the palpable tumor beyond 24 months after study entry, reappearance or progression of palpable tumor, or biopsy proven disease 2 or more years after study entry Regional failure required clinical or radiographic evidence or tumor in the pelvis. Time to local recurrence or to distant metastasis was measured from the date of randomization to the occurrence of either event.	Patients were randomized to receive XRT alone or with adjuvant hormonal treatment For all, the prostatic bed received 60-65 Gy in 1.8-2.0 Gy fractions using a multiple field technique Goserelin 3.6 mg SQ was begun during the last week of XRT in the intervention group and upon relapse in the control group	Using a PSA threshold of 0.5 ng/ml at 5 years, the FFBR was 65% for men who received combination therapy compared to 42% for men receiving XRT alone (p<0.01) In a multivariate model, combined treatment was an independent predictor of remaining FFBR with an endpoint PSA <4 ng/ml (p=0.05), <1 ng/ml (p<0.01), or <0.5 ng/ml (p<0.01) No differences evident between the two groups in rates or clinically diagnosed local progression, distant relapse, or absolute survival	The benefit of combination treatment after surgery was evident after evaluating a spectrum of biochemical outcomes No benefit was seen, among those patients treated with combination therapy after surgery, relative to other classic oncologic end points Experimental arm of the study, although tolerable and biochemically beneficial, cannot be viewed as standard of care	Potential bias in how patients were selected to participate in study Potential bias in identification of clinical failure Unclear if an intention to treat analysis was done, or how many in the treatment upon relapse group received treatment Quality: good

Evidence Table 5A: Efficacy of treatment with androgen deprivation therapy (Key Question 6) (continued)

Citation Design	Description	How recruited?	Measurements	Interventions/co-Interventions	Results	Conclusions (by authors)	Quality comments
Corn BW et al con't			Freedom from biochemical relapse (FFBR) was also computed for various PSA thresholds				

Evidence Table 5B: Efficacy of treatment with androgen deprivation therapy (Key Question 6): systematic review

Citation	Studies	Results	Comments
Aronson N et al., 1999[192]	Systematic literature review from 1966-March, 1998 Only accepted RCTs Meta-analysis Studied men with advanced cancer (both metastatic and locally advanced)	No difference for patients treated by LHRH agonist vs. orchiectomy or DES No difference in survival among patients treated with different LHRH agonists Trend toward lower survival in patients treated with nonsteroidal anti-androgens compared with LHRH agonists, orchiectomy, or DES Adverse effects: Withdrawals: 0-4%% LHRH agonists nonsteroidal anti-androgens: 4-10% Erectile dysfunction more common with LHRH agonists and orchiectomy then nonsteroidal anti-androgens, but can't quantify differences Hot flashes more common and Gynecomastia less common among patients treated with LHRH agonists	Quality: good (doesn't include most recent articles on ADT efficacy in locally advanced PC)

Evidence Table 6: Efficacy of watchful waiting (Key Question 7)

Citation	Participants	Evaluation	Initial Treatment	Results	Comments
Chodak, GW et al., 1994[46]	Pooled analysis from 6 cohort studies of 828 men with clinically localized PC treated conservatively	Clinical evaluation at baseline Histologic grading	Watchful waiting for all	Relative disease-specific survival at 10years: Grade 1 or 2: 87% Grade 3: 34% Metastasis-free survival among those who hadn't died of other causes: Grade 1: 81% Grade 2: 58% Grade 3: 26%	Unclear if these patients are comparable to screen-detected Quality: good
Albertsen, PC et al., 1998[47]	N=767 men Ages 55-74 at diagnosis from CT tumor registry, diagnosed from 1971-1984 and not tested 26% diagnosed by needle biopsy 71% diagnosed by TURP or open prostatectomy Excluded men with missing data	Clinical evaluation at baseline Histologic grading Evaluation did not include CT or MRI	Watchful waiting or immediate/deferred hormonal	Probability of dying of PC at 15 years: Gleason / Ages 55-59 / Ages 70-74 2-4: 4% / 7% 5: 6% / 11% 6: 18% / 30% 7: 70% / 42% 8-10: 87% / 60% 33% of men had Gleason 2-5 56% had Gleason 6-7 10% had Gleason 8-10 10% of men with Gleason 8-10 accounted for 25% of PC deaths Over 10 years, 23 died from PC and 39% from competing hazards No difference in survival between those detected by needle biopsy and those detected by TURP or prostatectomy	Unclear if these patients are comparable to screen-detected Uncertain why these men chose watchful waiting Quality: good

Evidence Table 6: Efficacy of watchful waiting (Key Question 7) (continued)

Citation	Participants	Evaluation	Initial Treatment	Results	Comments
Johansson, JE, 1997[48]	N=648 consecutive men diagnosed with PC from March 1977-February 1984 at medical center in Sweden: 84% diagnosed by palpable nodules 16% by surgery for BPH Only 6 lost to follow-up Mean age=72 years	Physical Exam Chest x-ray IVP Bone scan Bone x-rays for abnormal bone scan No nodal staging Baseline Evaluation found: 47% localized 28% locally advanced 25% metastatic Mean follow-up=14 years Patients reassessed at 2-12 month intervals	Of localized cancers (n=300): 0.7% had RP 25% had radiation or hormonal treatment 74% had no treatment Of locally advanced and metastatic cancers (n=342) All treated hormonally	At the end of study, 84% of participants had died: 31.3% of all participants had died of Additional participants, PC a contributing cause of death: 5.5% of participants 6.5% of deaths % of deaths due to PC: 44% participants younger than 61 25% older than 80 at diagnosis Overall corrected 15-year survival: 71.8% without initial metastasis 5.7% with initial metastasis Of men with initial localized cancers: 12% developed metastasis 11% died of PC Corrected 15-year survival: 80.9% No difference in survival between treated and untreated	Excellent prognosis for men with localized cancer with well/moderately differentiation Quality: good

Evidence Table 6: Efficacy of watchful waiting (Key Question 7) (continued)

Citation	Participants	Evaluation	Initial Treatment	Results	Comments
Brasso K et al., 1999[151]	All men ages 84 or younger at diagnosis (1943-1986) Used data only for those men who survived 10 or more years 4.5%-9.3% survived 10+ years Median age 68	Data from Danish Cancer Registry Information on stage but not grade	Usual care for localized PC in Demark is deferred hormonal treatment	Mean survival=14.1 years Patients with clinically localized PC at diagnosis: mean survival=15.3 years Overall mortality=69.2% Death directly due to PC=42.7% PC as contributing cause of death=19.1% PC was direct or contributing cause of death in 61.3% of deaths among men with clinically localized cancer and 75.9% of men with advanced PC Annual risk of death from PC remained stable at about 3%	Data totally depends on accuracy of stage and death certificate data Unclear if these patients are comparable to screen-detected Quality: good
Sandblom, G et al., 2000[152]	N=813 Population-based cohort of men diagnosed with PC between 1974-1986 No screening done Excluded cases diagnosed at autopsy Mean age at diagnosis: 73 years (296 men younger than age 70)	Bone scan Physical exam and history 47% had localized tumors	RP or radiation given in selected patients under age 70 with localized tumors Most asymptomatic localized tumors treated with watchful waiting	94% died before December 1997 39% of all men died of PC 42% of all deaths were due to PC (includes deaths thought due to PC by either death certificate or research team) At 15 years, survival of those treated with watchful waiting was better than men treated in any other way At 20 years, survival of watchful waiting group slightly less than men treated definitively 10-year disease-specific survival for men with localized PC treated with watchful waiting: Grade 1: 90% Grade 2: 74% Grade 3: 59%	Uncertain if these patients are similar to those found by screening Quality: good

Evidence Table 6: Efficacy of watchful waiting (Key Question 7) (continued)

Citation	Participants	Evaluation	Initial Treatment	Results	Comments
Lu-Yao, GL and Yao, SL, 1997[130]	Data from 59,876 SEER registry patients Ages 50-70 with clinically localized PC diagnosed between 1983-1992, and accompanying death certificate data from the states (previously validated for prostate cancer deaths) Mean length of follow-up=44.5 mos.	Cancers classified into 4 histologic grades: 1 (Gleason 2-4) 2 (Gleason 5-7) 3 (Gleason 8-10) Unknown; pathologically staging for men with RP and clinical staging for others	RP, radiation, or conservative management from SEER program	10-year mortality for men with grade 1 PC who received conservative treatment was about the same as an age-matched control croup For men with grade 2 disease, 10-year relative survival (relative to age-matched controls) for mean treated conservatively was 0.78, while the prostatectomy and radiation-treated groups were about the same as the age matched control group For men treated conservatively with grade 3 disease, the 10-year relative survival was 0.35 (radiation group 0.63 and prostatectomy group 0.87)	Uncertain if these patients are similar to screening-detected Quality: good

Appendix B. Evidence Tables

Evidence Table 7: Harms of treatment (Key Question 8)

Citation	Participants	Measurements	Results	Comments
Robinson, JW et al., 1997[155]	Comprehensive literature review and meta-analysis of rates of erectile dysfunction associated with RP and EBRT 40 articles found Pretreatment sexual function must be known	18 studies used chart reviews Questionnaires used in 5 studies, interviews in 8 studies Physiologic measures used in 2 studies	Logistic regression model Probability of maintaining normal erectile function: RP: 0.42 EBRT: 0.69 (p<0.0001)	Quality: fair (included some studies with measurements of uncertain validity)
Fowler, FJ et al., 1996[179]	N=373 Sample of Medicare beneficiaries who had RP for PC Patients treated with EBRT from SEER registries	Self-administered mailed questionnaire several years after treatment	91% response rate for RP patients 83% response rate for EBRT patients Sexual function (% inadequate erection for intercourse) Age < 70 RP: 89% EBRT: 67% Age ≥ 70 RP: 88% EBRT: 73% Urinary function (% wearing pads) RP: 32% EBRT: 7% Bowel function (% medium/big problem with frequent bowel movements) RP: 3% EBRT: 10%	Quality: good

Evidence Table 7: Harms of treatment (Key Question 8) (continued)

Citation	Participants	Measurements	Results	Comments
Widmark, A et al., 1994[180] Fransson, P. and Widmark, A., 1996[175]	Umea, Sweden N=200 patients with PC treated by EBRT N=200 age-matched controls	Pre-tested mailed questionnaire, some linear-analog and some multiple responses	93% response rate in PC group 71% response rate in control group Sexual function: (% failure to achieve erection) EBRT+ADT: 87% Control: 12% EBRT: 56% Urinary function (% leakage quite a bit/very much) Control: 4% EBRT: 15% Bowel function (% have problems with intestine quite a bit/very much) Control: 5% EBRT: 30%	Quality: good
Helgason, AR et al., 1996[168] Helgason, AR et al., 1997[165] Adolfsson, Jet al., 1998[174]	Stockholm area N=431 men with PC treated in various ways N=435 age-matched controls	Self-administered questionnaire assessing urinary, bowel, sexual function	Response rate 79% in PC group and 73% in control group Sexual function: (% distressed with erection capacity) Control: 63% RP: 82% EBRT: 81% ADT: 63% Urinary function (% with any leakage) Control: 14% RP: 65% EBRT: 33% No Rx: 30% Bowel function (% urgency) Control: 10% RP: 10% EBRT: 35% No Rx: 18%	Quality: fair (uncertain validation of questionnaire)

Evidence Table 7: Harms of treatment (Key Question 8) (continued)

Citation	Participants	Measurements	Results	Comments
Litwin, MS et al., 1995[169] Litwin MS, 2000[171]	N=214 with clinically localized PC treated in different ways N=273 aged-matched controls without PC Retrospective cross-sectional study Patients from large managed-care population	HRQol surveys Self-administered mailed questionnaires Prostate-targeted functional items	79% response rate among PC patients 46% responses rate in control group No group differences in potential confounders Sexual function (% poor/very poor) Control: 46% Watchful waiting: 49% RP: 79% EBRT: 71% Urinary function (% frequent dribbling/no control) Control: 6% Watchful waiting: 9% RP: 21% EBRT: 8% Bowel function (% rectal urgency 1+times/day) Control: 13% Watching waiting: 18% RP: 13% EBRT: 23% No differences among groups in overall Qol measures	Quality: fair (low response rate in control group)

Evidence Table 7: Harms of treatment (Key Question 8) (continued)

Citation	Participants	Measurements	Results	Comments
Stanford, JL et al., 2000[161] Potosky AL et al., 2000[170]	Patients diagnosed with PC in 6 SEER areas, random sample of 5,672 patients 83.5% contacted and invited to participate 62.3% completed 6 and/or 12-month survey (N=3,533) 2nd study reports on subset of 1,591 patients given 6,12 and/or 24-month surveys	Mailed, self-administered questionnaire at 6, 12, and 24 months after diagnosis Patients asked to recall baseline (before treatment) function	Sexual function (% sexual function moderate to big problem) Baseline / 24 Months All RP ages: 17.9% / 41.9% % erections not firm enough for intercourse) Baseline / 24 Months All RP ages: 15.8% / 59.9% Age < 60: 7.4% / 61% 75-79: 51.4% / 80.9% Urinary function (% frequency of incontinence > 2/day) Baseline / 24 Months All RP ages: 2.6% / 11.9% Age < 60: 1.7% / 10.0% 75-79: 4.1% / 40.8% 2nd study: (24-month survey) (% wore pads to stay dry) RP: 28.3% EBRT: 2.5% % erection insufficient for intercourse RP: 82.1% EBRT: 50.3% % bowel urgency) RP: 16.1% EBRT: 30.5%	Quality: fair (low response rate)

Evidence Table 7: Harms of treatment (Key Question 8) (continued)

Citation	Participants	Measurements	Results	Comments
Talcott, JA et al., 1998[163] Talcott, JA et al., 1997[164]	Men with newly diagnosed PC, nonmetastatic; 398 approached; 80 refused and 29 did not complete baseline questionnaire Final N=287 (72%) 48.4% had EBRT 44.8% had RP 6.5% no Tx	Previously validated self-administered questionnaire before treatment and at 3 and 12 months afterward	Sexual function (% erections inadequate for intercourse) Baseline / 12 Months RP: 32% / 93% EBRT: 45% / 67% Urinary function (% wearing pads) Baseline / 12 Months RP: 3% / 35% EBRT: 1% / 5% Bowel function (% bowel urgency or tenderness) Baseline / 12 Months RP: 7% / 6% EBRT: 1% / 19% Nerve-sparing RP resulted in same amount of sexual or urinary dysfunction as non-nerve sparing RP	Quality: good

Evidence Table 7: Harms of treatment (Key Question 8) (continued)

Citation	Participants	Measurements	Results	Comments
Brandeis, JM et al., 2000[187]	N=48 men with clinically localized PC treated at UCLA with brachytherapy N=74 similar men treated with RP Retrospective cross-sectional study Literature controls	Self-administered mailed questionnaires 3-17 months after treatment 86% response rate from brachytherapy patients 73% response rate from RP patients General quality of life questionnaires and symptom specific questionnaires	RP patients younger RP and brachytherapy patients similar in general quality of life measures Urinary bother scores (higher scores=better outcomes): RP: 74 Brachy: 65 Controls: 86 Bowel bother: RP: 90 Brachy: 81 Controls: 89 Sexual bother: RP: 34 Brachy: 39 Controls: 53	Quality: good
Lee, W R et al., 1999[189]	46 men with clinically localized PC consecutively treated with brachytherapy Complete information on 44	Self-administered questionnaire, validated Completed before treatment and at 1 and 3 months after treatment	Modest decrease in quality of life at 1 month, returning to baseline at 3 months Score of lower urinary tract symptoms (I-PSS) mean at: T_0: 8.3 T_1: 19.7 T_3: 15.4 indicating an increase in symptoms	Quality: fair (no absolute percentage of patients having various degrees of problems given)
Steineck, G et al., 2002[173] One point survey of men in an RCT comparing RP and WW	326 of 376 eligible men (87%) responses from survey about 4 years after randomization Mean age 64-65	Validated scales, some disease-specific and some general	Erectile dysfunction: 80% RP 45% WW Urinary Leakage: 49% RP 21% WW Weak urinary stream: 28% RP 44% WW No difference in anxiety, bowel function, depression, subjective quality of life	No pre-treatment measure Quality: good

Evidence Table 8: Cost-effectiveness of screening (Key Question 9)

Citation	Methods	Results	Comments
Barry MJ et al., 1995[210] Coley CM et al., 1997[204]	MEDLINE search for studies of efficacy of treatment Developed decision analysis for one-time PSA and DRE screening of men ages 50 years and older Markov models Efficacy assumptions favorable for screening	With favorable assumptions, one-time screening would increase discounted average life-expectancy by 7-11 days for screened men ages 50-69 and 3 days for men ages 70-79, but with considerable iatrogenic morbidity With favorable assumptions, dollars per life-year saved (no adjustment for iatrogenic morbidity): Age 50-59: $12,491 Age 60-69: $18,769 Age 70-79: $65,909 Relaxation of favorable assumptions about treatment efficacy and cancer-specific mortality lead to dramatically increased cost-effectiveness ratios, still without adjusting for iatrogenic morbidity	Quality: good
Kattan MW et al., 1997[211]	Built on Barry and Coley model after analysis showed it to be accurate Markov model All patients begin with localized PC, compares RP with watchful waiting Utilities come from small interview study of men without PC using time trade-off concerning relevant health states Secondary Monte-Carlo sensitivity analysis	Quality of life adjustment downgrades watchful waiting benefit because of concern about living with cancer QALY benefit of RP over watchful waiting for men with PC: Age / Grade / Benefit 60 / poor / 2.43 years 60 / moderate / 1.16 years 60 / well / 0.90 years 75 / poor / 1.05 years 75 / moderate / .042 years 75 / well / 0.28 years These numbers are not discounted; with discounting, RP benefit is reduced If more recent morbidity figures are used, RP benefit is reduced	Authors conclude that men under 70 do better with RP, but that men ages 70 and over face a toss-up (unless higher co-morbidity, in which watchful waiting is superior) Quality: good