Screening for Prostate Cancer: Recommendations and Rationale

U.S. Preventive Services Task Force

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Corresponding Author: Alfred O. Berg, MD, MPH, Chair, U.S. Preventive Services Task Force, c/o David Atkins, MD, MPH, Scientific and Technical Editor, U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Center for Practice and Technology Assessment, 6010 Executive Boulevard, Suite 300, Rockville, MD 20852. (301) 594-4016, fax (301) 594-4027, Email uspstf@ahrq.gov.

Wood Johnson Generalist Physician Faculty Scholars Program, San Antonio, TX [member and affiliation at time recommendation was finalized]) C. Tracy Orleans, PhD (Senior Scientist and Senior Program Officer, The Robert Wood Johnson Foundation, Princeton, NJ); Jeffrey F. Peipert, MD, MPH (Director of Research, Women and Infants' Hospital, Providence, RI); Nola J. Pender, PhD, RN, FAAN (Professor Emeritus, University of Michigan, Ann Arbor, MI); Albert L. Siu, MD., MSPH (Professor of Medicine, Chief of Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY); Steven M. Teutsch, MD, MPH (Senior Director, Outcomes Research and Management, Merck & Company, Inc., West Point, PA); Carolyn Westhoff, MD, MSc (Professor, Department of Obstetrics and Gynecology, Columbia University, New York, NY); and Steven H. Woolf, MD, MPH (Professor, Department of Family Practice and Department of Preventive and Community Medicine, Virginia Commonwealth University, Fairfax, VA).

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendations on screening for prostate cancer and the supporting scientific evidence, and it updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services,* second edition.[1] Explanations of the ratings and of the strength of overall evidence are given in Appendix A and Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the accompanying article, "Screening for Prostate Cancer: An Update of the Evidence"[2] and in the Systematic Evidence Review[3] on this topic, which can be obtained through the USPSTF Web site (www.preventiveservices.ahrq.gov). The article and recommendation statement are also available in print through the AHRQ Publications Clearinghouse (call 1-800-358-9295 or e-mail ahrqpubs@ahrq.gov).

SUMMARY OF RECOMMENDATION

- The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate specific antigen (PSA) testing or digital rectal examination (DRE).

  I recommendation.

  The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.

Clinical Considerations

- Prostate specific antigen (PSA) testing and digital rectal examination (DRE) can effectively detect prostate cancer in its early pathologic stages. Recent evidence suggests that radical prostatectomy can reduce prostate cancer mortality in men whose cancer is detected clinically. The balance of potential benefits (the reduction of morbidity and mortality from prostate cancer) and harms (false-positive results, unnecessary biopsies, and possible complications) of early treatment of the types of cancers found by screening, however, remains uncertain. Therefore, the benefits of screening for early prostate cancer remain unknown. Ongoing screening trials, and

trials of treatment versus "watchful waiting" for cancers detected by screening, may help clarify the benefits of early detection of prostate cancer.

- Despite the absence of firm evidence of effectiveness, some clinicians may opt to perform prostate cancer screening for other reasons. Given the uncertainties and controversy surrounding prostate cancer screening, clinicians should not order the PSA test without first discussing with the patient the potential but uncertain benefits and the possible harms of prostate cancer screening. Men should be informed of the gaps in the evidence, and they should be assisted in considering their personal preferences and risk profile before deciding whether to be tested.
- If early detection improves health outcomes, the population most likely to benefit from screening will be men aged 50 to 70 who are at average risk, and men older than 45 who are at increased risk (African American men and men with a family history of a first-degree relative with prostate cancer).[2] Benefits may be smaller in Asian Americans, Hispanics, and other racial and ethnic groups that have a lower risk of prostate cancer. Older men and men with other significant medical problems who have a life expectancy of fewer than 10 years are unlikely to benefit from screening.[2]
- PSA testing is more sensitive than DRE for the detection of prostate cancer. PSA screening with the conventional cut-point of 4.0 ng/dl detects a large majority of prostate cancers; however, a significant percentage of early prostate cancers (10% to 20%) will be missed by PSA testing alone.[3] Using a lower threshold to define an abnormal PSA detects more cancers at the cost of more false positives and more biopsies.
- The yield of screening in terms of cancer detected declines rapidly with repeated annual testing.[2] If screening were to reduce mortality, biennial PSA screening could yield as much benefit as annual screening.

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Consequences

Prostate cancer is the second leading cause of cancer-related death among men in the U.S. (second to lung cancer).[2] In 2002, an estimated 189,000 new cases of prostate cancer will be diagnosed in American men, and approximately 30,200 men will die from the disease.[4] The risk of developing prostate cancer increases beginning at age 40 . The probability of developing prostate cancer over the next 10 years is 0.17% for men aged 40, 2.01% for men aged 50, and 6.46% for men aged 60.[5]

The burden of prostate cancer varies among different racial and ethnic groups. African American men have about a 60% higher incidence rate and a 2-fold higher mortality rate from prostate cancer than white men.[2] Compared to white men, mortality from prostate cancer is 35% lower in Non-white Hispanics and 40% lower in Asian Americans and Pacific Islanders.[6]

Although prostate cancer is a major cause of cancer death, many more men are diagnosed with this cancer than die from it. Men in the U.S. have a 15% lifetime risk of being diagnosed with prostate cancer but only a 3% lifetime risk of dying from the disease.[5] More than 75% of all cases of prostate cancer are diagnosed in men older than 65, and 90% of prostate cancer deaths occur among men in this age group.[2] The prostate cancer mortality rate declined 19.4% between 1991 and 1998, but the causes of this decline are uncertain.[5]

Tumor grade appears to be a stronger predictor of prognosis than stage of disease. In studies of untreated prostate cancer, well-differentiated tumors had low rates of metastasis or mortality over 10 years. Progression and mortality were high for poorly differentiated cancers.[3]

Accuracy and Reliability of Screening Tests

DRE and PSA are the 2 principal tests currently used in the U.S. to screen for prostate cancer. Determining test characteristics of any screening test for prostate cancer is difficult because clinicians disagree on which cancers are "clinically important," and thus disagree on an appropriate target for early detection. The gold standard often used in screening studies--needle biopsy--may miss cancers that are present. Conversely, needle biopsy may serendipitously detect cancers unrelated to abnormal screening results. Especially in asymptomatic older men, screening with DRE and PSA may detect cancers that appear clinically significant based on size and tumor grade, but which would not have progressed to clinical symptoms during the patient's lifetime.

DRE is limited by the fact that only the posterior and lateral aspects of the gland can be palpated and the fact that different examiners often disagree about whether a DRE is abnormal. An overview of studies of screening suggests that DRE alone detects less than 60% of prevalent prostate cancers.[3] Adding DRE to PSA does appear to increase the yield of screening; in a large study of volunteers, the combination of DRE and PSA detected 26% more cancers than PSA alone.[7] However, combining DRE and PSA also increases the rate of false positive results.

Sensitivity and specificity of PSA screening depend on the value used to define an abnormal PSA result. If a cut-point of 4.0 ng/dl is used, PSA screening has an estimated sensitivity of 63% to 83% for "clinically significant" disease using pathological criteria.[3] In a retrospective study of clinically diagnosed cancers prior to widespread screening, PSA levels were above 4 ng/dl in 91% of patients who were diagnosed with "aggressive" cancers over the 2 years following the test.[8] Specificity of a cut-point of 4.0 ng/dl has been estimated at around 90% on the first screening round but declines with increasing age and the presence of benign prostatic hypertrophy (BPH).[3,9] One study reported specificity of 98% for men in

their 50s but specificity of only 81% for men in their 70s.[10] Even lower specificity rates have been found in men with documented BPH.[3] Conditions such as prostatitis may also raise PSA levels.[3]

Variations of the PSA test have been developed, primarily to improve the specificity of the test (ie, to reduce false positives). These include PSA density (the ratio of the PSA level to the volume of the prostate as measured by trans-rectal ultrasound (TRUS), PSA velocity (the rate at which the PSA increases over time), age- and race- adjusted reference ranges, and percentage of free PSA (the proportion of total PSA that is not bound to serum proteins).[3] There is insufficient evidence that these variations will improve the accuracy of screening in practice, however.

The yield of screening varies with the age of the population, screening history, and screening protocol. In studies of generally unscreened populations of men aged 45 to 80, 7% to 13% had a PSA $\geq$4ng/dl; of these, 10% to 30% had cancer on biopsy.[3] Overall, initial screening detects cancer in 0.2% to 2% of men in their 50s and 3% to 7% of men in their 70s.[3] Yield of screening declines substantially with subsequent annual screenings, especially among men who have low PSA values on initial screening.[2]

About 70% of cancers detected in the first round of screening are pathologically organ confined; this percentage increases with subsequent annual rounds of screening.[3,7] Between 5% and 10% of cancers detected by screening are poorly differentiated[3]; the proportion of cancers that are well-differentiated varies among studies, but most cancers detected by screening are moderately differentiated. The extent to which earlier detection of these cancers leads to improved outcomes is uncertain. The yield of screening in terms of cancers detected declines rapidly with repeated annual testing.[3,11]

Effectiveness of Early Detection

The USPSTF found 1 randomized controlled trial (RCT) and 3 case-control studies examining the effect of screening on prostate cancer mortality. The single RCT of PSA and DRE screening, which reported a benefit from screening, was hampered by a low rate of acceptance of screening in the intervention group (23%) and by flaws in the published analysis[11]; no difference in the number of prostate cancer deaths was observed between the groups randomized to screening versus usual care using "intention to treat" analysis.[3] Three case-control studies of screening DRE produced mixed results.[12,13,14] A number of RCTs of PSA screening for prostate cancer are underway in both the U.S. and Europe, but they are not expected to report results for several years.

Data are also limited to determine whether and how much treatment of screening-detected cancers improves outcomes. Radical prostatectomy and radiation are the most commonly used treatments for localized prostate cancer, yet few well-conducted randomized controlled trials have been completed to determine whether these treatments reduce mortality or are more effective than "watchful waiting" (deferring treatment until symptoms or disease progression is evident) for organ-confined prostate cancer. A recent large, good quality RCT[15] reported that prostatectomy, compared with watchful waiting, significantly lowered the probabilities of dying of prostate cancer (4.6% vs 8.9%) and of developing distant metastases (13.4% vs 27.3%) after 8 years for men with clinically detected, organ-confined cancer that was well- or moderately differentiated; reduction in total mortality was smaller and not significant (20% vs 28%). Although important, this study does not establish a benefit of screening due to several factors: screening-detected cancers (only 5% of the cases in this study) may have a less aggressive course than clinically detected cancers, and the delay between treatment and benefit (5 years in this study) is likely to be even longer due to

"lead time" from screening (ie, PSA screening may detect cancers 4 or more years earlier than they would be detected clinically). Finally, this study cannot address how much better outcomes would have been if treatments were begun earlier as a result of screening. A similar ongoing study in the U.S., where most cases of prostate cancer are detected by screening, may provide information more relevant to the benefits of early detection through screening. In observational studies, outcomes are worst, and the potential impact of aggressive treatment are greatest, for poorly differentiated cancers.[3] In the absence of better data about which treatments are effective for which tumors, the USPSTF could not determine whether the increased detection of prostate cancer from screening would reduce mortality and morbidity.

The USPSTF also examined a variety of ecologic data, including studies of secular trends in prostate cancer mortality, after the introduction of PSA screening and comparisons of prostate cancer mortality rates in communities with and without screening.[2] Prostate cancer mortality rates in the U.S. have declined since 1991.[5] However, the available ecologic studies have not provided sufficient evidence that the decline in prostate cancer in the U.S. or other countries are attributable to screening; differences in prostate cancer treatment, underlying risk factors, and how deaths are classified can all introduce bias into ecological comparisons.

Potential Adverse Effects of Screening

Evidence about the harms of screening per se 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. Fewer than 10% of men have ongoing interference with daily activities after

biopsy, and fewer than 1% suffer more serious complications, including infections.[3]

Screening may result in harm if it leads to treatments that have side effects without improving outcomes from prostate cancer, especially for cancers that have a lower chance of progressing. Erectile dysfunction, urinary incontinence, and bowel dysfunction are well-recognized and relatively common adverse effects of treatment with surgery, radiation or androgen ablation, but men differ in their responses to these symptoms.[2,16] In a recent trial, patients undergoing prostatectomy were more likely to have erectile dysfunction (80% vs 45%) and urinary leakage (49% vs 21%) than patients receiving watchful waiting, but both groups reported similar outcomes on measures of quality of life and psychological and physical well-being.[17]

Cost and Cost-effectiveness

Given uncertainties about the effectiveness of screening and the balance of benefits and harms, the cost-effectiveness of screening for prostate cancer is impossible to determine. If one makes favorable assumptions about efficacy of screening, PSA screening may be cost-effective for men aged 50 to 69.[2] If efficacy of early treatment is lower, harms could exceed benefits and PSA screening would not be cost-effective. Current models show that men older than 70 to 75 are unlikely to benefit substantially from screening because of their shorter life-expectancy and higher false-positive rates.[2] Cost-effectiveness of different screening intervals or variations of PSA measurement is unknown.

RECOMMENDATIONS OF OTHERS

Most major U.S. medical organizations recommend that clinicians discuss with patients the potential benefits and possible harms of PSA screening, consider patient

preferences, and individualize the decision to screen. They generally agree that the most appropriate candidates for screening include men older than 50 and younger men at increased risk of prostate cancer, but that screening is unlikely to benefit men who have a life expectancy of less than 10 years. These organizations include the American Academy of Family Physicians, American Cancer Society, American College of Physicians-American Society of Internal Medicine, American Medical Association, and the American Urologic Association.[18-22] None of these organizations endorses universal or mass screening for any group of men. In 1994, the Canadian Task Force on Preventive Health Care recommended against the routine use of PSA or TRUS as part of the periodic health examination[23]; while recognizing the limitations of DRE, they concluded that the evidence was insufficient to recommend that physicians discontinue use of DRE in men aged 50 to 70. The Canadian Task Force is in the process of updating their recommendations.

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APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians routinely provide [this service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE
STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.