U.S. Preventive Services Task Force

Screening for Prostate Cancer: Recommendation Statement

▶ See related Putting Prevention into Practice on page 283.

This summary is one in a series excerpted from the Recommendation Statements released by the U.S. Preventive Services Task Force (USPSTF). These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

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Summary of Recommendation and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer *(Table 1)*. **D recommendation.**

Rationale

IMPORTANCE

Prostate cancer is the most commonly diagnosed non–skin cancer in men in the United States, with a lifetime risk of diagnosis currently estimated at 15.9 percent. Most cases of prostate cancer have a good prognosis even without treatment, but some cases are aggressive; the lifetime risk of dying of prostate cancer is 2.8 percent. Prostate cancer is rare before 50 years of age, and very few men die of prostate cancer before 60 years of age. Seventy percent of deaths due to prostate cancer occur after 75 years of age.[1]

DETECTION

Contemporary recommendations for prostate cancer screening all incorporate the measurement of serum PSA levels; other methods of detection, such as digital rectal examination or ultrasonography, may be included. There is convincing evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer. There is also convincing evidence that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime. The terms "overdiagnosis" and "pseudo-disease" are used to describe both situations. The rate of overdiagnosis of prostate cancer increases as the number of men subjected to biopsy increases. The number of cancer cases that could be detected in a screened population is large; a single study in which men eligible for PSA screening had biopsy regardless of PSA level detected cancer in nearly 25 percent of men.[2] The rate of overdiagnosis also depends on life expectancy at the time of diagnosis. A cancer diagnosis in men with shorter life expectancies because of chronic disease or age is much more likely to be overdiagnosis. The precise magnitude of overdiagnosis associated with any screening and treatment program is difficult to determine, but estimates from the two largest trials suggest overdiagnosis rates of 17 to 50 percent for prostate cancer screening.[3]

BENEFITS OF DETECTION AND EARLY TREATMENT

The primary goal of prostate cancer screening is to reduce deaths caused by prostate cancer and, thus, increase length of life. An additional important outcome would be a reduction in the development of symptomatic metastatic disease. Reduction in prostate cancer mortality was the primary outcome used in available randomized controlled trials of prostate cancer screening. Although one screening trial reported on the presence of metastatic disease at the time of prostate cancer diagnosis, no study reported on the effect of screening on the development of subsequent metastatic disease, making it difficult to assess the effect of lead-time bias on the reported rates.

Men with screen-detected cancer can potentially fall into one of three categories: those whose cancer will result in death despite early diagnosis and treatment, those who will have good outcomes in the absence of screening, and those for whom early diagnosis and treatment improve survival. Only randomized trials of screening allow an accurate estimate of the number of men who fall into the latter category. There is convincing evidence that the number of men

Table 1. Screening for Prostate Cancer: Clinical Summary of the USPSTF Recommendation

Population	Adult men
Recommendation	Do not use PSA-based screening for prostate cancer. Grade: D
Screening tests	Contemporary recommendations for prostate cancer screening all incorporate the measurement of serum PSA levels; other methods of detection, such as digital rectal examination or ultrasonography, may be included. There is convincing evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer, and that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime (i.e., PSA-based screening results in considerable overdiagnosis).
Interventions	Management strategies for localized prostate cancer include watchful waiting, active surveillance, surgery, and radiation therapy. There is no consensus regarding optimal treatment.
Balance of harms and benefits	The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years. The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis. Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic. The benefits of PSA-based screening for prostate cancer do not outweigh the harms.
Relevant recommendations from the USPSTF	Recommendations on screening for other types of cancer can be found at http://www.uspreventiveservicestaskforce.org/.

NOTE: *For the full recommendation statement and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

PSA = prostate-specific antigen; USPSTF = U.S. Preventive Services Task Force.

who avoid dying of prostate cancer because of screening after 10 to 14 years is, at best, very small. The USPSTF considered two major trials of PSA screening: the U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer). The U.S. trial did not demonstrate any prostate cancer mortality reduction. The European trial found a reduction in prostate cancer deaths of approximately one death per 1,000 men screened in a subgroup of men 55 to 69 years of age. This result was heavily influenced by the results of two countries; five of the seven countries reporting results did not have a statistically significant reduction. All-cause mortality in the European trial was nearly identical in the screened and nonscreened groups.

There is adequate evidence that the benefit of PSA screening and early treatment ranges from zero to one prostate cancer death avoided per 1,000 men screened.

HARMS OF DETECTION AND EARLY TREATMENT

Harms Related to Screening and Diagnostic Procedures. Convincing evidence demonstrates that the PSA test often produces false-positive results; approximately 80 percent of positive PSA test results are false-positive when cutoffs between 2.5 and 4.0 ng per mL (2.5 and 4.0 μg per L) are used.[4] There is adequate evidence that false-positive PSA test results are associated with negative psychological effects, including persistent worry about prostate cancer. Men who have a false-positive test result are more likely to have additional testing, including one or more biopsies, in the following year than those who have a negative test result.[5] Over 10 years, approximately 15 to 20 percent of men will have a PSA test result that triggers a biopsy, depending on the PSA threshold and testing interval used.[4] New evidence from a randomized trial of treatment of screen-detected cancer indicates that roughly one-third of men who have prostate biopsy experience pain, fever,

bleeding, infection, transient urinary difficulties, or other issues requiring clinician follow-up that the men consider a "moderate or major problem"; approximately 1 percent require hospitalization.[6]

The USPSTF considered the magnitude of these harms associated with screening and diagnostic procedures to be at least small.

Harms Related to Treatment of Screen-Detected Cancer. Adequate evidence shows that nearly 90 percent of men with PSA-detected prostate cancer in the United States have early treatment with surgery, radiation, or androgen deprivation therapy.[7,8] Adequate evidence shows that up to five in 1,000 men will die within one month of prostate cancer surgery, and between 10 and 70 men will have serious complications but survive. Radiotherapy and surgery result in long-term adverse effects, including urinary incontinence and erectile dysfunction in at least 200 to 300 of 1,000 men treated with these therapies. Radiotherapy is also associated with bowel dysfunction.[9,10]

Some clinicians have used androgen deprivation therapy as primary therapy for early-stage prostate cancer, particularly in older men, although this is not a U.S. Food and Drug Administration–approved indication, and it has not been shown to improve survival in localized prostate cancer. Adequate evidence shows that androgen deprivation therapy for localized prostate cancer is associated with erectile dysfunction (in approximately 400 of 1,000 men treated), as well as gynecomastia and hot flashes.[9,10]

There is convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors. The amount of overdiagnosis of prostate cancer is of important concern because a man with cancer that would remain asymptomatic for the remainder of his life cannot benefit from screening or treatment. There is a high propensity for physicians and patients to elect to treat most cases of screen-detected cancer, given our current inability to distinguish tumors that will remain indolent from those destined to be lethal.[7,11] Thus, many men are being subjected to the harms of treatment of prostate cancer that will never become symptomatic. Even for men whose screen-detected cancer would otherwise have been identified later without screening, most experience the same outcome and are, therefore, subjected to the harms of treatment for a much longer period of time.[12,13] There is convincing evidence that PSA-based screening for prostate cancer results in considerable overtreatment and its associated harms.

The USPSTF considered the magnitude of these treatment-associated harms to be at least moderate.

USPSTF ASSESSMENT

Although the precise, long-term effect of PSA screening on prostate cancer–specific mortality remains uncertain, existing studies adequately demonstrate that the reduction in prostate cancer mortality after 10 to 14 years is, at most, very small, even for men in what seems to be the optimal age range of 55 to 69 years. There is no apparent reduction in all-cause mortality. In contrast, the harms associated with the diagnosis and treatment of screen-detected cancer are common, occur early, often persist, and include a small but real risk of premature death. Many more men in a screened population will experience the harms of screening and treatment of screen-detected disease than will experience the benefit. The inevitability of overdiagnosis and overtreatment of prostate cancer as a result of screening means that many men will experience the adverse effects of diagnosis and treatment of a disease that would have remained asymptomatic throughout their lives. Assessing the balance of benefits and harms requires weighing a moderate to high probability of early and persistent harm from treatment against the very low probability of preventing a death from prostate cancer in the long term.

The USPSTF concludes that there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms.

Clinical Considerations

Although the USPSTF discourages the use of screening tests for which the benefits do not outweigh the harms in the target population, it recognizes the common use of PSA screening in practice today and understands that some men will continue to request screening and some physicians will continue to offer it. The decision to initiate or continue PSA screening should reflect an explicit understanding of the possible benefits and harms, and respect the patients' preferences. Physicians should not offer or order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by the patients. Similarly, patients requesting PSA screening should be provided with the opportunity to make informed choices to be screened that reflect their values about specific benefits and harms. Community- and employer-based screening should be discontinued. *Table 2* presents reasonable estimates of the likely outcomes of screening, given the current approach to screening and treatment of screen-detected prostate cancer in the United States.[6,9,10,14-18]

The treatment of some cases of clinically localized prostate cancer can change the natural history of the disease, and may reduce morbidity and mortality in a small percentage of men, although the prognosis for clinically localized cancer is generally good regardless of the method of detection, even in the absence of treatment. The primary goal of PSA-based screening is to find men for whom treatment would reduce morbidity and

Table 2. PSA-Based Screening for Prostate Cancer*

Why not screen for prostate cancer?

Screening may benefit a small number of men but will result in harm to many others. A person choosing to be screened should believe that the possibility of benefit is more important than the risk of harm. The U.S. Preventive Services Task Force assessment of the balance of benefits and harms in a screened population is that the benefits do not outweigh the harms.

What are the benefits and harms of screening 1,000 men 55 to 69 years of age† with a PSA test every one to four years for 10 years?

Possible benefit of screening	*Men, n*
Reduced 10-year risk of dying of prostate cancer	
Die of prostate cancer with no screening	5 in 1,000
Die of prostate cancer with screening	4 to 5 in 1,000
Do not die of prostate cancer because of screening	0 to 1 in 1,000
Harms of screening	*Men, n*
At least one false-positive screening PSA test result	100 to 120 in 1,000
Most positive test results lead to biopsy. Of men having biopsy, up to 33 percent will have moderate or major bothersome symptoms, including pain, fever, bleeding, infection, and temporary urinary difficulties; 1 percent will be hospitalized.	
Prostate cancer diagnosis	110 in 1,000
Although a diagnosis of prostate cancer may not be considered a harm, currently 90 percent of men with a diagnosis of prostate cancer are treated and, thus, are at risk of the harms of treatment. A large majority of the men who are being treated would do well without treatment. A substantial percentage of these men would have remained asymptomatic for life.	
Complications of treatment (of those who are screened)‡	
Develop serious cardiovascular events due to treatment	2 in 1,000
Develop deep venous thrombosis or pulmonary embolus due to treatment	1 in 1,000
Develop erectile dysfunction due to treatment	29 in 1,000
Develop urinary incontinence due to treatment	18 in 1,000
Die due to treatment	<1 in 1,000

PSA = prostate-specific antigen.

**—The table design is adapted from Woloshin and Schwartz.[14] Calculations of the estimated benefits and harms rely on assumptions and are, by nature, somewhat imprecise. Estimates should be considered in the full context of clinical decision making and used to stimulate shared decision making.*

†—*The best evidence of possible benefit of PSA screening is in men 55 to 69 years of age.*

‡—*The rate of complications depends on the proportion of men having treatment and the method of treatment. The table reflects a distribution of 60 percent surgical treatment, 30 percent radiation, and 10 percent observation (see below for more details about assumptions and references). Other harms of radiation, such as bowel damage, are not shown.*

NOTE: *Estimates of the number of prostate cancer deaths in screened and unscreened men are taken from the 11- and 13-year follow-up studies of the PLCO[15] and ERSPC[16] trials. False-positive rates for PSA tests are derived from the PLCO trial and the Finnish center of the ERSPC trial.[17,18] Information related to the harms of biopsy is derived from the work of Rosario and colleagues.[6] The incidence of prostate cancer in a screened population is derived from the incidence seen in the screened group of the PLCO trial.[15] Treatment rates for localized prostate cancer in the U.S. population are derived from the SEER program and the Cancer of the Prostate Strategic Urologic Research Endeavor registry.[9,10] Expected complication rates from prostatectomy and radiation therapy are derived from pooled estimates calculated in the evidence review done for the U.S. Preventive Services Task Force.[10]*

mortality. Studies demonstrate that the number of men who experience this benefit is, at most, very small, and PSA-based screening as currently implemented in the United States produces more harms than benefits in the screened population. It is not known whether an alternative approach to screening and management of screen-detected disease could achieve the same or greater benefits while reducing the harms. Focusing screening on men at increased risk of prostate cancer mortality may improve the balance of benefits and harms, but existing studies do not allow conclusions about a greater absolute or relative benefit from screening in these populations. Lengthening the interval between screening tests may reduce harms without affecting cancer mortality; the only screening trial that demonstrated a prostate cancer–specific mortality benefit generally used a two- to four-year screening interval.[16] Other potential ways to reduce diagnostic- and treatment-related harms

include increasing the PSA threshold used to trigger the decision for biopsy or need for treatment,[12,19] or reducing the number of men having active treatment at the time of diagnosis through watchful waiting or active surveillance.[11] Periodic digital rectal examinations could also be an alternative strategy worthy of further study. In the only randomized trial demonstrating a mortality reduction from radical prostatectomy for clinically localized cancer, a high percentage of men had palpable cancer.[20] All of these approaches require additional research to better elucidate their merits and pitfalls, and more clearly define an approach to the diagnosis and management of prostate cancer that optimizes the benefits while minimizing the harms.

PATIENT POPULATION

This recommendation applies to men in the general U.S. population. Older age is the strongest risk factor for the development of prostate cancer. However, neither screening nor treatment trials show benefit in men older than 70 years. Across age ranges, black men and men with a family history of prostate cancer have an increased risk of developing and dying of prostate cancer. Black men are approximately twice as likely to die of prostate cancer than other men in the United States.[1] The reason for this disparity is unknown. Black men represented a small minority of participants in the randomized clinical trials of screening (4 percent of enrolled men in the PLCO trial were non-Hispanic black; although the ERSPC and other trials did not report the specific racial demographic characteristics of participants, they likely were predominantly white). Thus, no firm conclusions can be made about the balance of benefits and harms of PSA-based screening in this population. However, it is problematic to selectively recommend PSA-based screening for black men in the absence of data that support a more favorable balance of risks and benefits. A higher incidence of cancer will result in more diagnoses and treatments, but the increase may not be accompanied by a larger absolute reduction in mortality. Preliminary results from PIVOT (Prostate Cancer Intervention Versus Observation Trial), in which 30 percent of enrollees were black, have become available since the publication of the USPSTF's commissioned evidence reviews. Investigators found no difference in outcomes due to treatment of prostate cancer in black men compared with white men.[12]

Exposure to Agent Orange (a defoliant used in the Vietnam War) is considered a risk factor for prostate cancer, although few data exist on the outcomes or effect of PSA testing and treatment in these persons. Prostate cancer in Vietnam veterans who were exposed to Agent Orange is considered a service-connected condition by the Veterans Health Administration. The USPSTF did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms potentially suggestive of prostate cancer. However, the presence of urinary symptoms was not an inclusion or exclusion criterion in screening or treatment trials, and approximately one-fourth of the men in screening trials had bothersome lower urinary tract symptoms (nocturia, urgency, frequency, and poor stream). The presence of benign prostatic hyperplasia is not an established risk factor for prostate cancer, and the risk of prostate cancer among men with elevated PSA levels is lower in men with urinary symptoms than in men without symptoms.[21] This recommendation also does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer, and does not consider PSA-based testing in men with known *BRCA* gene mutations who may be at increased risk of prostate cancer.

SCREENING TESTS

PSA-based screening in men 50 to 74 years of age has been evaluated in five unique randomized controlled trials of single or interval PSA testing with various PSA cutoffs and screening intervals, along with other screening methods, such as digital rectal examination or transrectal ultrasonography.[4,22-25] Screening tests or programs that do not incorporate PSA testing, including digital rectal examination alone, have not been adequately evaluated in controlled studies.

The PLCO trial found a nonstatistically significant increase in prostate cancer mortality in the annual screening group at 11.5 and 13 years, with results consistently favoring the usual care group.[15,22]

A prespecified subgroup analysis of men 55 to 69 years of age in the ERSPC trial demonstrated a prostate cancer mortality rate ratio (RR) of 0.80 (95% confidence interval [CI], 0.65 to 0.98) in screened men after a median follow-up of nine years, with similar findings at 11 years (RR = 0.79; 95% CI, 0.68 to 0.91).[4,16] Of the seven centers included in the ERSPC analysis, only two countries (Sweden and the Netherlands) reported statistically significant reductions in prostate cancer mortality after 11 years (five did not), and these results seem to drive the overall benefit found in this trial (see figure at http://www.uspreventiveservicestaskforce.org/prostatecancerscreening/prostatefinalrsfig.htm).[16] No study reported any factors, including patient age, adherence to site or study protocol, length of follow-up, PSA thresholds, or intervals between tests, that could clearly explain why mortality reductions were larger in Sweden or the Netherlands than in other European countries or the United States (PLCO trial). Combining the results through meta-analysis may be inappropriate due to clinical and methodologic differences across trials.

No study found a difference in overall or all-cause mortality. This probably reflects the high rates of competing mortality in this age group, because these men are more likely to die of prostate cancer, as well as the limited power of prostate cancer screening trials to detect differences in all-cause mortality, should they exist. Even in the "core" age group of 55 to 69 years in the ERSPC trial, only 462 of 17,256 deaths were due to prostate cancer. The all-cause mortality RR was 1.00 (95% CI, 0.98 to 1.02) in all men randomly assigned to screening versus no screening. Results were similar in men 55 to 69 years of age.[16] The absence of any trend toward a reduction in all-cause mortality is particularly important in the context of the difficulty of attributing death to a specific cause in this age group.

TREATMENT

Primary management strategies for PSA-detected prostate cancer include watchful waiting (observation and physical examination with palliative treatment of symptoms), active surveillance (periodic monitoring with PSA tests, physical examinations, and repeated prostate biopsy) with conversion to potentially curative treatment at the sign of disease progression or worsening prognosis, and surgery or radiation therapy.[26] There is no consensus about the optimal treatment of localized disease. From 1986 through 2005, PSA-based screening likely resulted in approximately 1 million additional U.S. men being treated with surgery, radiation therapy, or both, compared with the time before the test was introduced.[7]

At the time of the USPSTF's commissioned evidence review, only one recent randomized controlled trial of surgical treatment versus observation for clinically localized prostate cancer was available.[13] In the Scandinavian Prostate Cancer Group Study-4 trial, surgical management of localized, primarily clinically detected prostate cancer was associated with an approximate 6 percent absolute reduction in prostate cancer and all-cause mortality at 12 to 15 years of follow-up; benefit seemed to be limited to men younger than 65 years.[13] Subsequently, preliminary results were reported from another randomized trial that compared external beam radiotherapy (EBRT) with watchful waiting in 214 men with localized prostate cancer detected before initiation of PSA screening. At 20 years, survival did not differ between men randomly assigned to watchful waiting or EBRT (31 versus 35 percent; $P = .26$). Prostate cancer mortality at 15 years was high in each group but did not differ between groups (23 versus 19 percent; $P = .51$). EBRT did reduce distant progression and recurrence-free survival.[27] In men with localized prostate cancer detected in the early PSA screening era, preliminary findings from PIVOT show that, after 12 years, intention to treat with radical prostatectomy did not reduce disease-specific or all-cause mortality compared with observation; absolute differences were less than 3 percent and not statistically different.[12] An ongoing trial in the United Kingdom (ProtecT [Prostate Testing for Cancer and Treatment]) comparing radical prostatectomy with EBRT or active surveillance has enrolled nearly 2,000 men with PSA-detected prostate cancer. Results are expected in 2015.[28]

Up to 0.5 percent of men will die within 30 days of having radical prostatectomy, and 3 to 7 percent will have serious surgical complications. Compared with men who choose watchful waiting, an additional 20 to 30 percent or more of men treated with radical prostatectomy will experience erectile dysfunction, urinary incontinence, or both after one to 10 years. Radiation therapy is also associated with increases in erectile, bowel, and bladder dysfunction.[9,10]

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The "Other Considerations," "Response to Public Comments," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm.

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