Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2008 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for prostate cancer.

Methods: The USPSTF reviewed new evidence on the benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer, as well as the benefits and harms of treatment of localized prostate cancer.

Recommendation: The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.

The U.S. Preventive Services Task Force (USPSTF) makes *recommendations about the effectiveness of specific clinical preventive services for patients without related signs or symptoms.*

It bases its recommendations on the evidence of both the benefits and harms of the service, and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

SUMMARY OF RECOMMENDATION AND EVIDENCE

The USPSTF recommends against prostate-specific antigen (PSA)–based screening for prostate cancer (grade D recommendation).

See the Clinical Considerations section for a discussion about implementation of this recommendation.

See also:
Print
Related articles. 135, 137
Summary for Patients. I-44
Web-Only
CME quiz (preview on page I-23)

See **Figure 1** for a summary of the recommendation and suggestions for clinical practice. **Table 1** describes the USPSTF grades, and **Table 2** describes the USPSTF classification of levels of certainty about net benefit.

RATIONALE
Importance

Prostate cancer is the most commonly diagnosed non–skin cancer in men in the United States, with a lifetime risk for diagnosis currently estimated at 15.9%. Most cases of prostate cancer have a good prognosis even without treatment, but some cases are aggressive; the lifetime risk for dying of prostate cancer is 2.8%. Prostate cancer is rare before age 50 years, and very few men die of prostate cancer before age 60 years. Seventy percent of deaths due to prostate cancer occur after age 75 years (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" or "pseudo-disease" are used to describe both situations. The rate of overdiagnosis of prostate cancer increases as the number of men subjected to bi-

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TASK FORCE
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Figure 1. Screening for prostate cancer: clinical summary of U.S. Preventive Services Task Force recommendation.

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SCREENING FOR PROSTATE CANCER
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adult Males
Recommendation	Do not use prostate-specific antigen (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.
Other Relevant USPSTF Recommendations	Recommendations on screening for other types of cancer can be found at www.uspreventiveservicestaskforce.org.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

opsy 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% 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 diseases 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 2 largest trials suggest overdiagnosis rates of 17% to 50% for prostate cancer screening (3).

Benefits of Detection and Early Treatment

The primary goal of prostate cancer screening is to reduce deaths due to 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 1 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 1 of 3 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 last category. There is convincing evidence that the number of men who avoid dying of prostate cancer because of screening after 10 to 14 years is, at best, very small. Two major trials of PSA screening were considered by the USPSTF: the U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer). The

Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	*Note: The following statement is undergoing revision.* Clinicians may provide this service to selected patients depending on individual circumstances. However, for most persons without signs or symptoms there is likely to be only a small benefit from this service.	Offer/provide this service only if other considerations support offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

U.S. trial did not demonstrate any reduction of prostate cancer mortality. The European trial found a reduction in prostate cancer deaths of approximately 1 death per 1000 men screened in a subgroup aged 55 to 69 years. This result was heavily influenced by the results of 2 countries; 5 of the 7 countries reporting results did not find a statisti-

cally significant reduction. All-cause mortality in the European trial was nearly identical in the screened and non-screened groups.

There is adequate evidence that the benefit of PSA screening and early treatment ranges from 0 to 1 prostate cancer deaths avoided per 1000 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% of positive PSA test results are false-positive when cutoffs between 2.5 and 4.0 μg/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 1 or more biopsies, in the following year than those who have a negative test result (5). Over 10 years, approximately 15% to 20% 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% 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% 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 5 in 1000 men will die within 1 month of prostate cancer

Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.

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 1000 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 (FDA)–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 1000 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 an 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 later identified without screening, most experience the same outcome and are, therefore, subjected to the harms of treatment for a much longer period (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 for 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

Implementation

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 3** 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.

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 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 for 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 2- to 4-year screening interval (15). Other potential ways to reduce diagnostic- and treatment-related harms include in-

Table 3. 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 for harm. The USPSTF 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 1000 men aged 55–69 y† with a PSA test every 1–4 y for 10 y?

	Men, n
Possible benefit of screening	
Reduced 10 y risk for dying of prostate cancer	
Die of prostate cancer with no screening	5 in 1000
Die of prostate cancer with screening	4–5 in 1000
Do not die of prostate cancer because of screening	0–1 in 1000
Harms of screening	
At least 1 false-positive screening PSA test result	
Most positive test results lead to biopsy. Of men having biopsy, up to 33% will have moderate or major bothersome symptoms, including pain, fever, bleeding, infection, and temporary urinary difficulties; 1% will be hospitalized.	100–120 in 1000
Prostate cancer diagnosis	
Although a diagnosis of prostate cancer may not be considered a harm, currently 90% of diagnosed men are treated and, thus, are at risk for 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.	110 in 1000
Complications of treatment (among persons who are screened)‡	
Develop serious cardiovascular events due to treatment	2 in 1000
Develop deep venous thrombosis or pulmonary embolus due to treatment	1 in 1000
Develop erectile dysfunction due to treatment	29 in 1000
Develop urinary incontinence due to treatment	18 in 1000
Die due to treatment	<1 in 1000

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 aged 55–69 y.

‡ The rate of complications depends on the proportion of men having treatment and the method of treatment. The table reflects a distribution of 60% surgical treatment, 30% radiation, and 10% observation (see **Appendix 2**, available at www.annals.org, for more details about assumptions and references). Other harms of radiation, such as bowel damage, are not shown.

creasing the PSA threshold used to trigger the decision for biopsy or need for treatment (12, 16), 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 (17). 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 Under Consideration

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), and the reason for this disparity is unknown. Black men represented a small minority of participants in the randomized clinical trials of screening (4% 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 probably were predominately 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% 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 to be 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 quarter of 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 for prostate cancer among men with elevated PSA levels is lower in men with urinary symptoms than in men without symptoms (18).

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 for prostate cancer.

Screening Tests

Prostate-specific antigen–based screening in men aged 50 to 74 years has been evaluated in 5 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, 19–22). 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 (19, 23).

A prespecified subgroup analysis of men aged 55 to 69 years in the ERSPC trial demonstrated a prostate cancer mortality rate ratio (RR) of 0.80 (95% CI, 0.65 to 0.98) in screened men after a median follow-up of 9 years, with similar findings at 11 years (RR, 0.79 [CI, 0.68 to 0.91]) (4, 15). Of the 7 centers included in the ERSPC analysis, only 2 countries (Sweden and the Netherlands) reported statistically significant reductions in prostate cancer mortality after 11 years (5 did not), and these results seem to drive the overall benefit found in this trial (**Figure 2**) (15). No study reported any factors, including patient age, adherence to site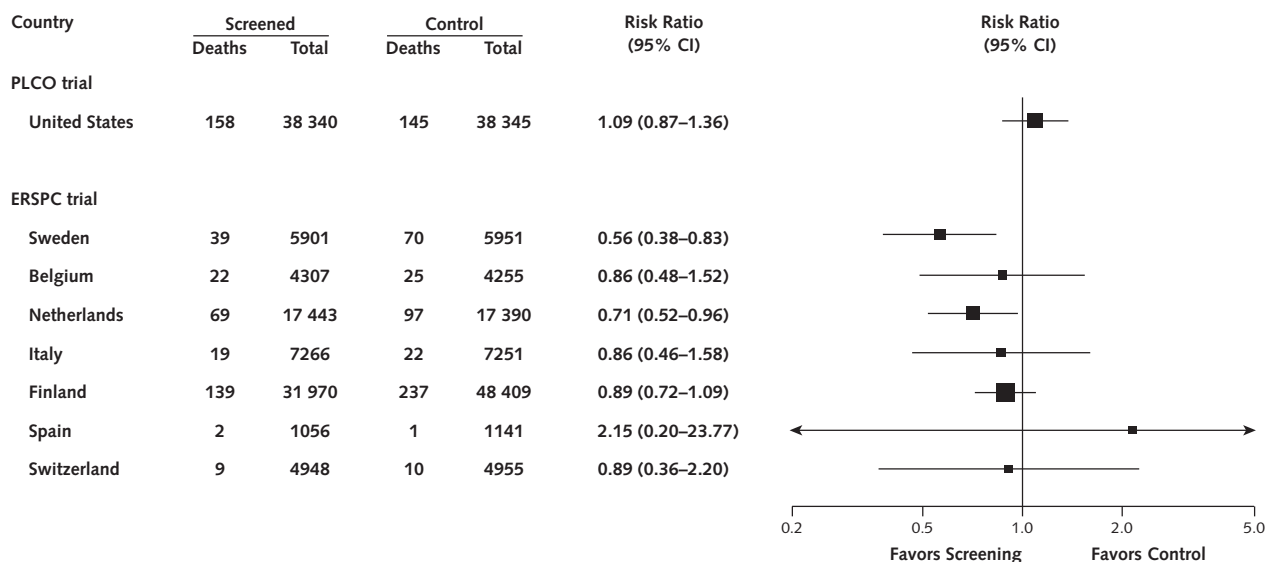 or study protocol, length of follow-up, PSA thresholds, or intervals between tests, that could clearly explain why mortality reductions were larger in Sweden or the Netherlands than in other European countries or the United States (PLCO trial). Combining the results through meta-analysis may be inappropriate due to clinical and methodological 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 (CI, 0.98 to 1.02) in all men randomly assigned to screening versus no screening. Results were similar in men aged 55 to 69 years (15). 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 (24). There is no consensus about the optimal treatment of localized disease. From

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Figure 2. **Relative risk of prostate cancer death for men screened with PSA versus control participants, by country.**

Country	Screened		Control		Risk Ratio (95% CI)	Risk Ratio (95% CI)
	Deaths	Total	Deaths	Total		
PLCO trial						
United States	158	38 340	145	38 345	1.09 (0.87–1.36)	
ERSPC trial						
Sweden	39	5901	70	5951	0.56 (0.38–0.83)	
Belgium	22	4307	25	4255	0.86 (0.48–1.52)	
Netherlands	69	17 443	97	17 390	0.71 (0.52–0.96)	
Italy	19	7266	22	7251	0.86 (0.46–1.58)	
Finland	139	31 970	237	48 409	0.89 (0.72–1.09)	
Spain	2	1056	1	1141	2.15 (0.20–23.77)	
Switzerland	9	4948	10	4955	0.89 (0.36–2.20)	

ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate-specific antigen.

1986 through 2005, PSA-based screening probably 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 1 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% 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% vs. 35%; $P = 0.26$). Prostate cancer mortality at 15 years was high in each group but did not differ between groups (23% vs. 19%; $P = 0.51$). External beam radiotherapy did reduce distant progression and recurrence-free survival (25). 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% 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 2000 men with PSA-detected prostate cancer. Results are expected in 2015 (26).

Up to 0.5% of men will die within 30 days of having radical prostatectomy, and 3% to 7% will have serious surgical complications. Compared with men who choose watchful waiting, an additional 20% to 30% or more of men treated with radical prostatectomy will experience erectile dysfunction, urinary incontinence, or both after 1 to 10 years. Radiation therapy is also associated with increases in erectile, bowel, and bladder dysfunction (9, 10).

OTHER CONSIDERATIONS

Research Needs and Gaps

Because the balance of benefits and harms of prostate cancer screening is heavily influenced by overdiagnosis and overtreatment, research is needed to identify ways to reduce the occurrence of these events, including evaluating the effect of altering PSA thresholds for an abnormal test or biopsy result on false-positive rates and the detection of indolent disease.

Similarly, research is urgently needed to identify new screening methods that can distinguish nonprogressive or slowly progressive disease from disease that is likely to affect quality or length of life, because this would reduce the number of men who require biopsy and subsequent treatment of disease that has a favorable prognosis without intervention. Additional research is also needed to evaluate the benefits and harms of modifying the use of existing prostate cancer screening tools. Research is needed to assess the effect of using higher PSA thresholds to trigger a diagnostic prostate biopsy, extending intervals between testing, and the role of periodic digital rectal examinations by trained clinicians. Although not well-studied, these strategies may reduce overdiagnosis and overtreatment, and evidence suggests that they may be associated with decreased mortality. Research is also needed to compare the long-term benefits and harms of immediate treatment versus observation with delayed intervention or active surveillance in men with screen-detected prostate cancer. Two randomized, controlled trials, PIVOT (27) and the ProtecT trial (28), are studying this issue. Preliminary results from PIVOT potentially support increasing the PSA threshold for recommending a biopsy or curative treatments in men subsequently diagnosed with prostate cancer.

Additional research is needed to determine whether the balance of benefits and harms of prostate cancer screening differs in men at higher risk of developing or dying of prostate cancer, including black men and those with a family history of the disease.

Accurately ascertaining cause of death in older persons can be problematic; as such, basing clinical recommendations on disease-specific mortality in the absence of an effect on all-cause mortality may not completely capture the health effect and goals of a screening and treatment program. Additional research is required to better assess and improve the reliability of prostate cancer mortality as a valid outcome measure in clinical trials, as well as the best application of the concomitant use of all-cause mortality.

Two large randomized, controlled trials of 5α-reductase inhibitors (finasteride and dutasteride) have shown that these drugs reduce the risk for prostate cancer in men receiving regular PSA tests. However, the observed reduction resulted from a decreased incidence of low-grade prostate cancer alone (Gleason score ≤6). The FDA has not approved finasteride or dutasteride for prevention of prostate cancer, concluding that the drugs do not possess a favorable risk–benefit profile for this indication. The FDA cited associated adverse effects, including loss of libido and erectile dysfunction, but most important it noted that there was an absolute increase in the incidence of high-grade prostate cancer in men randomly assigned to finasteride or dutasteride compared with control participants in both trials (29). Additional research would be useful to better understand whether these drugs are associated with the development of high-grade prostatic lesions, determine the effect of 5α-reductase inhibitors (or other potential preventive agents) on prostate cancer mortality, and identify the population that may benefit most from prostate

cancer prevention (with these or other chemoprevention strategies).

Research is needed to better understand patient and provider knowledge and values about the known risks and benefits of prostate cancer screening and treatment, as well as to develop and implement effective informed decision-making materials that accurately convey the best evidence and can be instituted in primary care settings across varied patient groups (for example, by race, age, or family history).

RESPONSE TO PUBLIC COMMENTS

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 11 October to 13 December 2011. Commenters expressed concern that a grade D recommendation from the USPSTF would preclude the opportunity for discussion between men and their personal health care providers, interfere with the clinician–patient relationship, and prevent men from being able to make their own decisions about whether to be screened for prostate cancer. Some commenters asked that the USPSTF change its recommendation to a grade C to allow men to continue to make informed decisions about screening. Recommendations from the USPSTF are chosen on the basis of the risk–benefit ratio of the intervention: A grade D recommendation means that the USPSTF has concluded that there is at least moderate certainty that the harms of doing the intervention equal or outweigh the benefits in the target population, whereas a grade C recommendation means that the USPSTF has concluded that there is at least moderate certainty that the overall net benefit of the service is small. The USPSTF could not assign a grade C recommendation for PSA screening because it did not conclude that the benefits outweigh the harms. In the Implementation section, the USPSTF has clarified that a D recommendation does not preclude discussions between clinicians and patients to promote informed decision making that supports personal values and preferences.

Some commenters requested that the USPSTF provide more information about the consequences of avoiding PSA screening. A summary of the benefits and harms of screening can be found in **Table 3**. In summary, the USPSTF concluded that choosing not to have PSA testing will result in a patient living a similar length of life, with little to no difference in prostate cancer–specific mortality, while avoiding harms associated with PSA testing and subsequent diagnostic procedures and treatments.

Commenters were concerned that the USPSTF did not adequately consider a separate recommendation for black men. Additional information about this population can be found in the Patient Population Under Consideration section.

Many commenters mistakenly believed that the USPSTF either relied solely on the PLCO trial or published meta-analyses or did its own meta-analysis to reach its conclusions about the efficacy of PSA-based screening. Although the commissioned systematic evidence review summarized the findings of 2 previously published meta-analyses because they met the minimum inclusion requirements for the report, neither the authors of that review nor the USPSTF did a new meta-analysis. The USPSTF is aware of the heterogeneity in the available randomized trials of prostate cancer screening and the limitations of meta-analysis in this situation. Both the ERSPC and PLCO trials were heavily weighted by the USPSTF in its considerations, because they had the largest populations and were of the highest quality, although both had important—but different—methodological limitations. The screening intervals, PSA thresholds, use of digital rectal examinations, enrollee characteristics, and follow-up diagnostic and treatment strategies used in the PLCO trial are most applicable to current U.S. settings and practice patterns.

Commenters asked the USPSTF to consider evidence from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, showing that prostate cancer mortality decreased by 40% in the United States between 1992 and 2007 (30). Many suggested that the decline must be attributable to the effect of screening, because PSA-based screening was introduced in the United States in the early 1990s and became widespread by the mid-1990s to late 1990s. The challenge of ecologic data is that it is impossible to reliably separate out the relative effects of any changes in screening, diagnosis, or treatment practices (or fundamental changes in the underlying risk of developing or dying of the disease in the population due to a multiplicity of other causes) that may have been occurring simultaneously over a given period. All of these, including screening, may have played some role in the decline seen in mortality; however, only a randomized trial can determine with confidence the magnitude of effect that can be attributable to a given intervention. According to the SEER database, in the 1970s and 1980s, before the introduction of widespread PSA screening, prostate cancer mortality rates started at 29.9 cases per 100 000 men and showed a slow but constant increase over time. The reason for this increase is unknown. Mortality from prostate cancer peaked between 1991 and 1993—roughly the same time when PSA tests became a common clinical practice—at 39.3 cases per 100 000 men, and began to decline by approximately 1 to 2 cases per 100 000 men per year after this point (2007 rate, 24.0 cases per 100 000 men). Information from randomized trials suggests that any potential mortality benefit from screening will not occur for 7 to 10 years. As such, it would be very unlikely that any decline in mortality rates from 1990 to 2000 would be related to screening.

Some commenters believed that the USPSTF should have considered a reduction in morbidity due to prostate cancer as an outcome, not just mortality. The rate of met-

astatic disease should roughly parallel the rate of deaths; if a large difference in metastatic disease was present between the intervention and control groups of the ERSPC and PLCO trials at 11 and 13 years of follow-up, a larger effect on the reduction in mortality would have been expected. Although the USPSTF agrees that a demonstrated effect of PSA-based screening on long-term quality of life or functional status would be an important outcome to consider, insufficient data are available from screening trials to draw such a conclusion. The ERSPC trial provides information about the incidence of metastatic disease only at the time of diagnosis, rather than longitudinal follow-up for the development of such disease in screened versus unscreened populations. Data on quality of life are available from randomized treatment trials of early-stage prostate cancer and suggest that treatment with observation or watchful waiting provides similar long-term quality of life as early intervention, with marked reduction in treatment-related adverse effects (31, 32).

Many commenters asked the USPSTF to review a publication reporting that the efficacy of PSA-based screening in the PLCO trial was affected by comorbidity status (33); they believed that this provided evidence that PSA-based screening could be recommended for very healthy men. In the article, Crawford and colleagues (33) reported that the hazard ratio for death in men without comorbid conditions in the annual screening versus the usual care group was 0.56 (CI, 0.33 to 0.95). However, the PLCO investigators later reported, as part of their extended follow-up of the trial, that this finding was sensitive to the definition of comorbidity used (23). Crawford and colleagues chose an expanded definition of comorbidity that included both "standard" Charlson comorbidity index conditions and hypertension (even if it was well-controlled), diverticulosis, gallbladder disease, and obesity. When the analysis was repeated by using only validated measures of comorbidity (that is, Charlson comorbidity index conditions only), an interaction was no longer seen. Several researchers (including PLCO investigators) have questioned the biological plausibility of this finding by Crawford and colleagues, noting, among other reasons, that the positive interaction seems to be largely driven by the inclusion of hypertension and obesity, conditions that seem to convey minimal excess treatment risks or differences in treatment options. These researchers also note that although Crawford and colleagues initially argue that comorbid conditions lessen the effectiveness of treatment (thus, causing screening to be ineffective in less healthy men), participants in the usual care group with a greater degree of comorbidity actually had a statistically significant lower risk for dying of prostate cancer than healthier men (23, 34). Preliminary results from PIVOT also found that the effect of radical prostatectomy compared with observation did not vary by comorbidity or health status (12).

DISCUSSION

Burden of Disease

An estimated 240 890 U.S. men received a prostate cancer diagnosis in 2011, and an estimated 33 720 men died of the disease (35). The average age of diagnosis was 67 years and the median age of those who died of prostate cancer from 2003 through 2007 was 80 years; 71% of deaths occurred in men older than 75 years (1). Black men have a substantially higher prostate cancer incidence rate than white men (232 vs. 146 cases per 100 000 men) and more than twice the prostate cancer mortality rate (56 vs. 24 deaths per 100 000 men, respectively) (35).

Prostate cancer is a clinically heterogeneous disease. Autopsy studies have shown that approximately one third of men aged 40 to 60 years have histologically evident prostate cancer (36); the proportion increases to as high as three fourths in men older than 85 years (37). Most cases represent microscopic, well-differentiated lesions that are unlikely to be clinically important. Increased frequency of PSA testing, a lower threshold for biopsy, and an increase in the number of core biopsies obtained all increase the detection of lesions that are unlikely to be clinically significant.

Scope of Review

The previous evidence update, done for the USPSTF in 2008, found insufficient evidence that screening for prostate cancer improved health outcomes, including prostate cancer–specific and all-cause mortality, for men younger than 75 years. In men aged 75 years or older, the USPSTF found adequate evidence that the incremental benefits of treatment of screen-detected prostate cancer are small to none and that the harms of screening and treatment outweigh any potential benefits (38). After the publication of initial mortality results from 2 large randomized, controlled trials of prostate cancer screening, the USPSTF determined that a targeted update of the direct evidence on the benefits of PSA-based screening for prostate cancer should be done (39). In addition, the USPSTF requested a separate systematic review of the benefits and harms of treatment of localized prostate cancer (10). Since the release of the USPSTF's draft recommendation statement on prostate cancer screening and its supporting systematic evidence reviews, updated results from the ERSPC and PLCO trials and data on harms related to prostate biopsy from the ProtecT trial have become available; these publications were used to inform this final recommendation statement.

Accuracy of Screening

The conventional PSA cutoff of 4.0 μg/L detects many cases of prostate cancer; however, some cases will be missed. Using a lower cutoff detects more cases of cancer, but at the cost of labeling more men as potentially having cancer. For example, decreasing the PSA cutoff to 2.5 μg/L would more than double the number of U.S. men aged 40 to 69 years with abnormal results (16), most of which

would be false-positive. It also increases the likelihood of detection of indolent tumors with no clinical importance. Conversely, increasing the PSA cutoff to greater than 10.0 μg/L would reduce the number of men aged 50 to 69 years with abnormal results from approximately 1.2 million to roughly 352 000 (16). There is no PSA cutoff at which a man can be guaranteed to be free from prostate cancer (40).

There are inherent problems with the use of needle biopsy results as a reference standard to assess the accuracy of prostate cancer screening tests. Biopsy detection rates vary according to the number of biopsies done during a single procedure; the more biopsies done, the more cancer cases detected. More cancer cases detected with a "saturation" biopsy procedure (≥20 core biopsies) tend to increase the apparent specificity of an elevated PSA level; however, many of the additional cancer cases detected this way are unlikely to be clinically important. Thus, the accuracy of the PSA test for detecting clinically important prostate cancer cases cannot be determined with precision.

Variations of PSA screening, including the use of age-adjusted PSA cutoffs; free PSA; and PSA density, velocity, slope, and doubling time, have been proposed to improve detection of clinically important cases of prostate cancer. However, no evidence has demonstrated that any of these testing strategies improve health outcomes, and some may even generate harms. One study found that using PSA velocity in the absence of other indications could lead to 1 in 7 men having a biopsy with no increase in predictive accuracy (41).

Effectiveness of Early Detection and Treatment

Two poor-quality (high risk of bias) randomized, controlled trials initiated in the 1980s in Sweden each demonstrated a nonstatistically significant trend toward increased prostate cancer mortality in groups invited to screening (21, 22). A third poor-quality (high risk of bias) trial from Canada showed similar results when an intention-to-screen analysis was used (20). The screening protocols for these trials varied; all included 1 or more PSA tests with cutoffs ranging from 3.0 to 10.0 μg/L; in addition, digital rectal examination and transrectal ultrasonography were variably used.

The more recently published PLCO and ERSPC trials were the principal trials considered by the USPSTF. The fair-quality prostate component of the PLCO trial randomly assigned 76 685 men aged 55 to 74 years to annual PSA screening for 6 years (and concomitant digital rectal examination for 4 years) or to usual care. It used a PSA cutoff of 4.0 μg/L. Diagnostic follow-up for positive screening test results and treatment choices were made by the participant and his personal physician; 90% of men with prostate cancer diagnoses received active treatment (surgery, radiation, hormonal therapy, or some combination). After 7 years (complete follow-up), a nonstatistically significant trend toward increased prostate cancer mortality

was seen in the screened group (RR, 1.14 [CI, 0.75 to 1.70]) compared with men in the control group (19). Similar findings were seen after 13 years (RR, 1.09 [CI, 0.87 to 1.36]) (23). The primary criticism of this study relates to the high contamination rate; approximately 50% of men in the control group received at least 1 PSA test during the study, although the investigators increased both the number of screening intervals and the duration of follow-up to attempt to compensate for the contamination effects. In addition, approximately 40% of participants had received a PSA test in the 3 years before enrollment, although subgroup analyses stratified by history of PSA testing before study entry did not reveal differential effects on prostate cancer mortality rates (19). Contamination may attenuate differences in the 2 groups but would not explain both an increased prostate cancer incidence and mortality rate in men assigned to screening.

The fair-quality ERSPC trial randomly assigned 182 160 men aged 50 to 74 years from 7 European countries to PSA testing every 2 to 7 years or to usual care. Prostate-specific antigen cutoffs ranged from 2.5 to 4.0 μg/L, depending on study center (1 center used a cutoff of 10.0 μg/L for several years). Subsequent diagnostic procedures and treatment also varied by center. Sixty-six percent of men who received a prostate cancer diagnosis chose immediate treatment (surgery, radiation therapy, hormonal therapy, or some combination). Among all men who were randomly assigned, there was a borderline reduction in prostate cancer mortality in the screened group after a median follow-up of 9 years (RR, 0.85 [CI, 0.73 to 1.00]) (4). Similar results were reported after 11 years of follow-up and were statistically significant (RR, 0.83 [CI, 0.72 to 0.94]) (15). After a median follow-up of 9 years in a prespecified subgroup analysis limited to men aged 55 to 69 years, a statistically significant reduction in prostate cancer deaths was seen in the screened group (RR, 0.80 [CI, 0.65 to 0.98]) (4). After 11 years of follow-up, a similar reduction was seen (RR, 0.79 [CI, 0.45 to 0.85]); the authors estimated that 1055 men needed to be invited to screening and 37 cases of prostate cancer needed to be detected to avoid 1 death from prostate cancer (15). Of the 7 individual centers included in the mortality analysis, 2 (Sweden and the Netherlands) demonstrated statistically significant reductions in prostate cancer deaths with PSA screening. The magnitude of effect was considerably greater in these 2 centers than in other countries (**Figure 2**). Primary criticisms of this study relate to inconsistencies in age requirements, screening intervals, PSA thresholds, and enrollment procedures used among the study centers, as well as the exclusion of data from 2 study centers in the analysis. There is also concern that differential treatments between the study and control groups may have had an effect on outcomes. Of note, men in the screened group were more likely than men in the control group to have been treated in a university setting, and control participants with high-risk prostate cancer were more likely than screened partic-

ipants to receive radiotherapy, expectant management, or hormonal therapy instead of radical prostatectomy (42). Furthermore, ascertainment of cause of death in men with a diagnosis of prostate cancer included men whose prostate cancer was detected at autopsy. How this cause-of-death adjudication process may affect estimates is unknown, but previous research has demonstrated difficulties in accurately ascertaining cause of death and that small errors could have an important effect on results (43, 44).

After publication of the initial ERSPC mortality results, a single center from within that trial (in Göteborg, Sweden) reported data separately. Outcomes for 60% of this center's participants were reported as part of the full ERSPC publication, and the subsequent country-specific results within the ERSPC trial reflect the separately reported results from Sweden (which included some men not included in the overall ERSPC trial) (45).

Few randomized, controlled trials have compared treatments for localized prostate cancer with watchful waiting. A randomized, controlled trial of 695 men with localized prostate cancer (Scandinavian Prostate Cancer Group Study 4) reported an absolute reduction in the risk for distant metastases (11.7% [CI, 4.8% to 18.6%]) in patients assigned to radical prostatectomy versus watchful waiting after 15 years of follow-up. An absolute reduction in prostate cancer mortality (6.1% [CI, 0.2% to 12.0%]) and a trend toward a reduction in all-cause mortality (6.6% [CI, −1.3% to 14.5%]) were also seen over this period. Subgroup analysis suggests that the benefits of prostatectomy were limited to men aged 65 years or younger. The applicability of these findings to cancer detected by PSA-based screening is limited, because only 5% of participants were diagnosed with prostate cancer through some form of screening, 88% had palpable tumors, and more than 40% presented with symptoms (13, 17). An earlier, poor-quality study found no mortality reduction from radical prostatectomy versus watchful waiting after 23 years of follow-up (46). Another randomized trial of 214 men with localized prostate cancer detected before initiation of PSA screening that compared EBRT versus watchful waiting presented preliminary mortality results after completion of the evidence review. At 20 years, the observed survival did not differ between men randomly assigned to watchful waiting and EBRT (31% vs. 35%; $P = 0.26$). Prostate cancer mortality at 15 years was high in each group but did not differ between groups (23% vs. 19%; $P = 0.51$). External beam radiotherapy did reduce distant progression and recurrence-free survival (25).

Preliminary results from PIVOT have also become available since the evidence review was completed. PIVOT, conducted in the United States, included men with prostate cancer detected after the initiation of widespread PSA testing and, thus, included a much higher percentage of men with screen-detected prostate cancer. The trial randomly assigned 731 men aged 75 years or younger (mean age, 67 years) with a PSA level less than 50 μg/L (mean, 10

μg/L) and clinically localized prostate cancer to radical prostatectomy versus watchful waiting. One third of participants were black. On the basis of PSA level, Gleason score, and tumor stage, approximately 43% had low-risk tumors, 36% had intermediate-risk tumors, and 21% had high-risk tumors. After a median follow-up of 10 years, prostate cancer–specific or all-cause mortality did not statistically significantly differ between men treated with surgery versus observation (absolute risk reduction, 2.7% [CI, −1.3% to 6.2%] and 2.9% [CI, −4.1% to 10.3%], respectively). Subgroup analysis found that the effect of radical prostatectomy compared with observation for both overall and prostate cancer–specific mortality did not vary by patient characteristics (including age, race, health status, Charlson comorbidity index score, or Gleason score), but there was variation by PSA level and possibly tumor risk category. In men in the radical prostatectomy group with a PSA level greater than 10 μg/L at diagnosis, there was an absolute risk reduction of 7.2% (CI, 0.0% to 14.8%) and 13.2% (CI, 0.9% to 24.9%) for prostate cancer–specific and all-cause mortality, respectively, compared with men in the watchful waiting group. However, prostate cancer–specific or all-cause mortality was not reduced among men in the radical prostatectomy group with PSA levels of 10 μg/L or less or those with low-risk tumors, and potential (nonstatistically significant) increased mortality was suggested when compared with the watchful waiting group (12).

Harms of Screening and Treatment

False-positive PSA test results are common and vary depending on the PSA cutoff and frequency of screening. After 4 PSA tests, men in the screening group of the PLCO trial had a 12.9% cumulative risk for at least 1 false-positive result (defined as a PSA level greater than 4.0 μg/L and no prostate cancer diagnosis after 3 years) and a 5.5% risk for at least 1 biopsy due to a false-positive result (47). Men with false-positive PSA test results are more likely than control participants to worry specifically about prostate cancer, have a higher perceived risk for prostate cancer, and report problems with sexual function for up to 1 year after testing (48). In 1 study of men with false-positive PSA test results, 26% reported that they had experienced moderate to severe pain during biopsy; men with false-positive results were also more likely to have repeated PSA testing and additional biopsies during the 12 months after the initial negative biopsy (49). False-negative results also occur, and there is no PSA level that effectively rules out prostate cancer. This has, in part, led to recommendations for doing prostate biopsy at lower PSA thresholds than previously used in randomized screening trials (for example, <2.5 μg/L).

Harms of prostate biopsy reported by the Rotterdam center of the ERSPC trial include persistent hematospermia (50.4%), hematuria (22.6%), fever (3.5%), urine retention (0.4%), and hospitalization for signs of prostatitis

or urosepsis (0.5%) (50). The ProtecT study, an ongoing randomized, controlled trial evaluating the effectiveness and acceptability of treatments for men with PSA-detected, localized prostate cancer, found that 32% of men experienced pain; fever; blood in the urine, semen, or stool; infection; transient urinary difficulties; or other issues requiring clinician follow-up after prostate biopsy that they considered a "moderate or major problem." At 7 days after biopsy, 20% of men reported that they would consider a future biopsy a "moderate or major problem" and 1.4% of men were hospitalized for complications (6). Similar findings were reported at 30 days after biopsy in a U.S. study of older, predominately white male Medicare beneficiaries (51).

The high likelihood of false-positive results from the PSA test, coupled with its inability to distinguish indolent from aggressive tumors, means that a substantial number of men undergo biopsy and are overdiagnosed with and overtreated for prostate cancer. The number of men who have biopsies is directly related to the number of men having PSA testing, the threshold PSA level used to trigger a biopsy, and the interval between PSA tests. Estimates derived from the ERSPC and PLCO trials suggest overdiagnosis rates of 17% to 50% of prostate cancer cases detected by the PSA test (3, 52, 53). Overdiagnosis is of particular concern because, although these men cannot benefit from any associated treatment, they are still subject to the harms of a given therapy. Evidence indicates that nearly 90% of U.S. men diagnosed with clinically localized prostate cancer through PSA testing have early treatment (primarily radical prostatectomy and radiation therapy) (7, 8).

Radical prostatectomy is associated with a 20% increased absolute risk for urinary incontinence and a 30% increased absolute risk for erectile dysfunction compared with watchful waiting (that is, increased 20% above a median rate of 6% and 30% above a median rate of 45%, respectively) after 1 to 10 years (9, 10). Perioperative deaths or cardiovascular events occur in approximately 0.5% or 0.6% to 3% of patients, respectively (9, 10). Comparative data on outcomes using different surgical techniques are limited; 1 population-based observational cohort study using the SEER database and Medicare-linked data found that minimally invasive or robotic radical prostatectomy for prostate cancer was associated with higher risks for genitourinary complications, incontinence, and erectile dysfunction than open radical prostatectomy (54).

Radiation therapy is associated with a 17% absolute increase in risk for erectile dysfunction (that is, increased 17% above a median rate of 50%) and an increased risk for bowel dysfunction (for example, fecal urgency or incontinence) compared with watchful waiting after 1 to 10 years; the effect on bowel function is most pronounced in the first few months after treatment (9, 10).

Localized prostate cancer is not an FDA-approved indication for androgen deprivation therapy, and clinical outcomes for older men receiving this treatment for local-

ized disease are worse than for those who are conservatively managed (55). Androgen deprivation therapy is associated with an increased risk for impotence compared with watchful waiting (absolute risk difference, 43%), as well as systemic effects, such as hot flashes and gynecomastia (9, 10). In advanced prostate cancer, androgen deprivation therapy may generate other serious harms, including diabetes, myocardial infarction, or coronary heart disease; however, these effects have not been well-studied in men treated for localized prostate cancer. A recent meta-analysis of 8 randomized, controlled trials in men with nonmetastatic high-risk prostate cancer found that androgen deprivation therapy was not associated with increased cardiac mortality (56).

Estimate of Magnitude of Net Benefit

All but 1 randomized trial has failed to demonstrate a reduction in prostate cancer deaths with the use of the PSA test, and several—including the PLCO trial—have suggested an increased risk in screened men, potentially due to harms associated with overdiagnosis and overtreatment. In a prespecified subgroup of men aged 55 to 69 years in the ERSPC trial, a small (0.09%) absolute reduction in prostate cancer deaths was seen after a median follow-up of 11 years. The time until any potential cancer-specific mortality benefit (should it exist) for PSA-based screening emerges is long (at least 9 to 10 years), and most men with prostate cancer die of causes other than prostate cancer (57). No prostate cancer screening study or randomized trial of treatment of screen-detected cancer has demonstrated a reduction in all-cause mortality through 14 years of follow-up.

The harms of PSA-based screening for prostate cancer include a high rate of false-positive results and accompanying negative psychological effects, high rate of complications associated with diagnostic biopsy, and—most important—a risk for overdiagnosis coupled with overtreatment. Depending on the method used, treatments for prostate cancer carry the risk for death, cardiovascular events, urinary incontinence, erectile dysfunction, and bowel dysfunction. Many of these harms are common and persistent. Given the propensity for physicians and patients to treat screen-detected cancer, limiting estimates of the harms of PSA testing to the harms of the blood test alone, without considering other diagnostic and treatment harms, does not reflect current clinical practice in the United States.

The mortality benefits of PSA-based prostate cancer screening through 11 years are, at best, small and potentially none, and the harms are moderate to substantial. Therefore, the USPSTF concludes with moderate certainty that the benefits of PSA-based screening for prostate cancer, as currently used and studied in randomized, controlled trials, do not outweigh the harms.

How Does Evidence Fit With Biological Understanding?

Prostate-specific antigen–based screening and subsequent treatment, as currently practiced in the United

States, presupposes that most asymptomatic prostate cancer cases will ultimately become clinically important and lead to poor health outcomes and that early treatment effectively reduces prostate cancer–specific and overall mortality. However, long-term, population-based cohort studies and randomized treatment trials of conservatively managed men with localized prostate cancer do not support this hypothesis. A review of the Connecticut Tumor Registry, which was initiated before the PSA screening era, examined the long-term probability of prostate cancer death among men (median age at diagnosis, 69 years) whose tumors were mostly incidentally identified at the time of transurethral resection or open surgery for benign prostatic hyperplasia. Men received observation alone or early or delayed androgen deprivation therapy. After 15 years of follow-up, the prostate cancer mortality rate was 18 deaths per 1000 person-years. For men with well-differentiated prostate cancer, it was 6 deaths per 1000 person-years; far more of these men had died of causes other than prostate cancer (75% vs. 7%) (58). An analysis of the SEER database after the widespread introduction of PSA-based screening examined the risk for death in men with localized prostate cancer who did not have initial attempted curative therapy. The 10-year prostate cancer mortality rate for well- or moderately differentiated tumors among men aged 66 to 69 years at diagnosis was 0% to 7%, depending on tumor stage, versus 0% to 22% for other causes. The relative proportion of deaths attributable to other causes compared with prostate cancer increased substantially with age at prostate cancer diagnosis (59). In the only randomized, controlled trial comparing early intervention versus watchful waiting that included men primarily detected by PSA testing, prostate cancer mortality at 12 years or more was infrequent (7%) and did not differ between men randomly assigned to surgery versus observation (12).

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

This recommendation replaces the 2008 recommendation (38). Whereas the USPSTF previously recommended against PSA-based screening for prostate cancer in men aged 75 years or older and concluded that the evidence was insufficient to make a recommendation for younger men, the USPSTF now recommends against PSA-based screening for prostate cancer in all age groups.

RECOMMENDATIONS OF OTHERS

The American Urological Association recommends that PSA screening, in conjunction with a digital rectal examination, should be offered to asymptomatic men aged 40 years or older who wish to be screened, if estimated life expectancy is greater than 10 years (60). It is currently updating this guideline (61). The American Cancer Society emphasizes informed decision making for prostate cancer screening: Men at average risk should receive information beginning at age 50 years, and black men or men with a family history of prostate cancer should receive information at age 45 years (62). The American College of Preventive Medicine recommends that clinicians discuss the potential benefits and harms of PSA screening with men aged 50 years or older, consider their patients' preferences, and individualize screening decisions (63). The American Academy of Family Physicians is in the process of updating its guideline, and the American College of Physicians is currently developing a guidance statement on this topic.

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APPENDIX 1: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (Baylor College of Medicine, Houston, Texas); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Joy Melnikow, MD, MPH (University of California, Davis, Sacramento, California); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Stanford University, Stanford, California); Carolina Reyes, MD, MPH (Virginia Hospital Center, Arlington, Virginia); and Timothy J. Wilt, MD, MPH (University of Minnesota and Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota). For-

mer USPSTF members who contributed to the development of this recommendation include Ned Calonge, MD, MPH, and Rosanne Leipzig, MD, PhD.

† For a list of current Task Force members, visit www.uspreventiveservicestaskforce.org/members.htm.

APPENDIX 2: ASSUMPTIONS AND REFERENCES INFORMING TABLE 3

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 (23) and ERSPC (15) trials. False-positive rates for PSA tests are derived from the PLCO trial and the Finnish center of the ERSPC trial (47, 64). 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 (23). 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 USPSTF (10).

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