Draft Recommendation Statement

I would like to comment on the draft Recommendation Statement.

What is in a Recommendation Statement?

Return to the Public Comment Home Page

Return to the USPSTF Page

Note: This draft Recommendation Statement is not the final recommendation of the U.S. Preventive Services Task Force. This draft is distributed solely for the purpose of pre-release review. It has not been disseminated otherwise by AHRQ. It does not represent and should not be interpreted to represent an AHRQ determination or policy.

This draft Recommendation Statement is based on an evidence review that was published on October 7, 2011 (available at http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm).

The 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 decisionmaking 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.

This draft Recommendation Statement is available for comment from October 11, 2011 until November 8, 2011 at 5:00 PM ET. You may wish to read the entire Recommendation Statement before you comment.

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

Summary of Recommendation and Evidence

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

This recommendation applies to men in the U.S. population that do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history. The Task Force did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms that are highly suspicious for prostate cancer. This recommendation also does not consider the use of the PSA test for surveillance after diagnosis and/or treatment of prostate cancer.

Rationale

Importance

Prostate cancer is the most commonly diagnosed nonskin cancer in men in the United States, with a lifetime risk of diagnosis currently estimated at 15.9%. Most cases of prostate cancer have a good prognosis, but some are aggressive; the lifetime risk of dying from 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. The majority 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. The evidence is convincing that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer. The evidence is also convincing that the majority of men who have asymptomatic cancer detected by PSA screening have a tumor that meets histological criteria for prostate cancer, but the tumor either will not progress or is so indolent and slow-growing that it will not affect the man's lifespan or cause adverse health effects, as he will die of another cause first. The terms “overdiagnosis” or “pseudodisease” are used to describe both of

these situations. It is difficult to determine the precise magnitude of overdiagnosis associated with any screening and treatment program. 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 underwent biopsy irrespective of PSA level detected cancer in nearly 25% of men (2). The rate of overdiagnosis will also depend upon the age at which diagnosis is made. Cancer diagnosis in older men with shorter life expectancies is much more likely to be overdiagnosis.

Benefits of Detection and Early Intervention

The primary goal of prostate cancer screening is to reduce deaths due to prostate cancer, and a reduction in either prostate cancer death or overall mortality was the primary outcome addressed in all prostate cancer screening studies assessed by the Task Force. The evidence is convincing that for men aged 70 years and older, screening has no mortality benefit. For men aged 50 to 69 years, the evidence is convincing that the reduction in prostate cancer mortality 10 years after screening is small to none. Screen-detected cancer can fall into one of three categories: cancer that results in death in spite of early diagnosis and treatment, cancer for which early diagnosis and treatment improves survival, and cancer for which the outcome would be good in the absence of screening due to indolent tumors. Ninety-five percent of men with PSA-detected cancer who are followed for 12 years do not die from that cancer, even in the absence of definitive treatment (3). The possibility is very small that death from prostate cancer is less likely in men whose prostate cancer is detected by PSA screening rather than waiting for clinical detection, and the time to any potential benefit is long. No prostate cancer screening study, individually or combined with other screening studies, or study of treatment of screen-detected cancer, has demonstrated a reduction in all-cause mortality.

Harms of Detection and Early Intervention

Harms related to screening. Convincing evidence demonstrates that the PSA test often produces false-positive results (approximately 80% of positive PSA tests are false positives when a cut-off point of 2.5–4.0 ng/mL is used) (4). The evidence is adequate that false-positive PSA tests are associated with negative psychological effects, including a persistent worry about prostate cancer. Men that have a false-positive test are more likely to have additional testing, including biopsies, in the following year than those who have a negative test (5). Over a 10-year period, approximately 15%–20% of men will have an abnormal result that triggers a biopsy, depending upon the PSA threshold and testing interval used (4). The evidence is convincing that prostate biopsy causes fever, infection, bleeding, and transient urinary difficulty in some men (about 68 events per 10,000 biopsies), as well as pain (6, 7).

The evidence is also convincing that PSA-based screening leads to substantial overdiagnosis of prostate tumors. As noted above, overdiagnosis occurs when, despite a tumor's pathological characteristics, it does not progress to cause illness or death in a man's lifetime. Overdiagnosis is of particular concern in prostate cancer because a high percentage of men are treated at the time of diagnosis, and a man with an indolent lesion may experience any of the associated harms of a therapy but cannot benefit, by the very nature of the condition, from that intervention.

The USPSTF considered the magnitude of these screening-associated harms 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 undergo early treatment with surgery, radiation, or androgen deprivation therapy. Adequate evidence also shows that up to 5 in 1,000 men will die within 1 month of prostate cancer surgery and between 10 and 70 men will have serious complications but survive. Radiotherapy and surgery result in 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 (6, 8).

Some clinicians have utilized androgen deprivation therapy for early-stage prostate cancer, particularly in older men, despite the fact that this is not an U.S. Food and Drug Administration (FDA)-approved indication and it has not been shown to improve clinical outcomes in localized prostate cancer. Adequate evidence shows that androgen deprivation therapy for localized prostate cancer is associated with erectile dysfunction (in about 400 out of 1,000 men treated), as well as gynecomastia and hot flashes. In addition, in patients given androgen deprivation therapy for advanced prostate cancer, some evidence suggests an increased risk of other serious harms, such as myocardial infarction and coronary heart disease, diabetes, and fractures, although these harms have not been well studied in men treated for localized prostate cancer (6, 8).

PSA-based screening for prostate cancer results in the diagnosis and treatment of many more cancer cases than would occur without screening; thus, screening results in many more men who are subject to treatment-related adverse events. A sizable proportion of the additional cancer cases that are detected with screening represent overdiagnosis. Overdiagnosed men cannot reap benefit from the intervention, but are subject to all of the related risks of surgery, radiation, or hormone therapy. As such, overtreatment represents a critical consequence of PSA-based screening as currently utilized, most notably in the context of a high propensity for physicians and patients to elect to treat most cases of screen-detected cancer. Even for those men whose screen-detected cancer would otherwise have been later identified symptomatically, a high proportion experience the same outcome, and are thus subjected to the harms of treatment for a much longer period of time (3, 9). The evidence is convincing that PSA-based screening for prostate cancer results in considerable overtreatment.

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

USPSTF Assessment

The common perception that PSA-based early detection of prostate cancer prolongs lives is not supported by the scientific evidence. The findings of the two largest trials highlight the uncertainty that remains about the precise effect that screening may have, and demonstrate that if any benefit does exist, it is very small after 10 years. The European trial found a statistically insignificant 0.06% absolute reduction in prostate cancer deaths for men aged 50 to 74 years, while the U.S. trial found a statistically insignificant 0.03% absolute increase in prostate cancer

deaths (6, 7). A meta-analysis of all published trials found no statistically significant reduction in prostate cancer deaths (10). At the same time, overdiagnosis and overtreatment of prostatic tumors that will not progress to cause illness or death are frequent consequences of PSA-based screening. Although about 90% of men are currently treated for PSA-detected prostate cancer in the United States—usually with surgery or radiotherapy—the vast majority of men who are treated do not have prostate cancer death prevented or lives extended from that treatment, but are subjected to significant harms.

The USPSTF concludes that there is moderate certainty that the harms of PSA-based screening for prostate cancer outweigh the benefits.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to men in the general U.S. population. Older age is the strongest risk factor for development of prostate cancer. However, a more favorable balance of benefits and harms for PSA-based screening does not accompany this increase in risk. Across age ranges, African American men and men with a family history of prostate cancer have an increased risk for developing and dying from prostate cancer compared with other men. However, the observed risk differences for race/ethnicity or family history are each relatively small when compared with the risk differences seen with increasing age (1), and there are no data that suggest that the net benefit of PSA-based screening is altered by race or family history.

The USPSTF did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms that are highly suspicious for prostate cancer. This recommendation also does not include the use of the PSA test for surveillance after diagnosis and/or treatment of prostate cancer.

Screening Tests

PSA-based screening in men aged 50 to 74 years has been evaluated in five unique randomized, controlled trials of single or interval PSA testing with various PSA cut-off points and screening intervals, along with other screening modalities such as digital rectal examination or transrectal ultrasonography (4, 11-14). None of these trials has shown a statistically significant prostate cancer mortality benefit in all enrolled men; most demonstrated a trend toward harm in the screened arm. Two meta-analyses also have not demonstrated a benefit of PSA screening on prostate cancer-specific or overall mortality (10, 15).

The U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) found a nonstatistically significant increase in prostate cancer mortality in the screened group after a median followup of 11.5 years, with results consistently favoring the nonscreened population, even after 11 years of followup (11).

Considering the findings of the two largest trials, the effect of PSA-based screening on death from prostate cancer after 10 years may range from a 0.03% absolute risk increase to a 0.06% absolute risk reduction (6, 7). Screening tests or programs that do not incorporate PSA testing, including digital rectal examination alone, have not been evaluated adequately in controlled studies.

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 (17). There is no consensus regarding 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 before the test was introduced (18).

In the Scandinavian Prostate Cancer Group (SPCG)-4 trial, surgical management of localized, clinically-detected prostate cancer was associated with about a 6% absolute reduction in prostate cancer and all-cause mortality at 12–15 years' followup; benefit appeared to be limited to men younger than age 65 years (9). Preliminary findings from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) show that after 12 years, intention to treat with radical prostatectomy resulted in nonstatistically significant differences in disease-specific and all-cause mortality compared with observation that were less than 3% in absolute terms, in men with localized prostate cancer detected in the early PSA era (3).

Up to 0.5% of men will die within 30 days of undergoing radical prostatectomy, and 3%–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 impotence, urinary incontinence, or both after 1 to 10 years. Radiation therapy is also associated with increases in erectile, bowel, and bladder dysfunction (6, 8).

Other Considerations

Implementation

While 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 and some physicians will continue to offer screening. An individual man may choose to be screened because he places a higher value on the possibility of benefit, however small, than the known harms that accompany screening and treatment of screen-detected cancer, particularly the harms of overdiagnosis and overtreatment. This decision should be an informed decision, preferably made in consultation with a regular care provider. No man should be screened without his understanding and consent; community-based and employer-

based screening that does not allow an informed choice should be discontinued.

Research Needs and Gaps

Because the balance of benefits and harms of prostate cancer screening is heavily influenced by overdiagnosis and overtreatment, research is necessary to identify ways to reduce the occurrence of these events, including evaluating the effect of altering PSA thresholds for an abnormal test or biopsy on false-positive rates and the detection of indolent disease. Similarly, new screening modalities must improve discriminatory accuracy between indolent disease and disease that is likely to clinically progress, thus reducing the number of men who require biopsy and subsequent treatment for disease that has a favorable prognosis without intervention. Research is also needed to compare the long-term benefits and harms of immediate treatment versus observation with delayed intervention in men with screen-detected prostate cancer. Two randomized, controlled trials—the PIVOT trial (19) and the U.K. Prostate Testing for Cancer and Treatment study (20)—are studying this issue. Preliminary results from the PIVOT trial potentially support raising the PSA threshold for recommending a biopsy and making treatment decisions in men subsequently diagnosed with prostate cancer.

Accurately ascertaining cause of death in older individuals 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 impact 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 5-alpha-reductase inhibitors (finasteride, dutasteride) have shown that these drugs reduce the risk of being diagnosed with 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 and dutasteride for the 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 importantly, it noted that in both trials there was an absolute increase in the incidence of high-grade prostate cancer in men randomized to finasteride or dutasteride compared with controls (21). Additional research would be useful to better understand the association of these drugs with the development of high-grade prostatic lesions, to determine the impact of 5-alpha-reductase inhibitors (or other potential preventive agents) on prostate cancer mortality and identify the population of men that might benefit most from prostate cancer prevention.

Discussion

Burden of Disease

An estimated 217,730 U.S. men received a prostate cancer diagnosis in 2010, and an estimated 32,050 men died from the disease (22). The average age of diagnosis was 67 years and the median age of death from prostate cancer from 2003 through 2007 was 80 years; 71% of deaths occurred in men older than age 75 years (1). African American men have a substantially higher prostate cancer incidence rate than white men (231.9 vs.146.3 cases per 100,000 men), and more than twice the prostate cancer mortality rate (56.3 vs. 23.6 deaths per 100,000 men, respectively) (22).

Prostate cancer is a clinically heterogeneous disease. Autopsy studies have shown that approximately one third of men aged 40–60 years have histologically evident prostate cancer (23); the proportion increases to as high as three fourths in men older than age 85 years (24). Most of these cases represent microscopic, well-differentiated lesions that are unlikely to be of clinical importance. The detection of lesions that are unlikely to be of clinical significance increases with frequency of PSA testing, lower thresholds to indicate an abnormal result, and the number of core biopsies obtained per diagnostic workup.

Scope of Review

The previous evidence update, performed 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 age 75 years. In men aged 75 years or older, the USPSTF found adequate evidence that the incremental benefits of treatment for screen-detected prostate cancer are small to none, and that the harms of screening and treatment outweigh any potential benefits (25). After the publication of initial mortality results from two 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 performed (7). Additionally, the USPSTF requested a separate systematic review of the benefits and harms of treatment for localized prostate cancer (8).

Accuracy of Screening

The conventional PSA cut-off point of 4.0 ng/mL detects many cases of prostate cancer; however, some cases will be missed. Using a lower cut-off point detects more cases of cancer, but at the cost of labeling more men as potentially having cancer. For example, lowering the PSA cut-off point to 2.5 ng/mL would more than double the number of U.S. men aged 40 to 69 years with abnormal results (26), and the majority of these would be false-positive results. It also increases the likelihood of detection of indolent tumors with no clinical importance. Conversely, raising the PSA cut-off point to >10.0 ng/mL would reduce the number of men aged 50 to 69 years with abnormal results from approximately 1.2 million to around 352,000 individuals (26). There is no PSA cut-off point at which a man can be guaranteed to be free from prostate cancer (27).

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 performed during a single procedure; the more biopsies performed, 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 cut-off points, free PSA, and PSA density, velocity, slope, and doubling time, have been proposed to improve detection of clinically important prostate cancer cases. However, no evidence has demonstrated that any of these testing strategies improve health outcomes, and some may even generate harms. One study found that utilizing PSA velocity in the absence of other indications could lead to 1 in 7 men undergoing a biopsy with no increase in predictive accuracy (28).

Effectiveness of Early Detection and Treatment

Two poor-quality 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 (13, 14). A third poor-quality trial from Canada showed similar results when an intention-to-screen analysis was used (12). The screening protocols for these trials varied; all included one or more PSA tests with cut-off points ranging from 3.0 to 10.0 ng/mL, in addition to digital rectal examination and/or transrectal ultrasonography.

The prostate component of the PLCO trial randomized 76,693 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 utilized a PSA cut-off point of 4.0 ng/mL. Diagnostic followup for positive screening tests and treatment choices were made by the participant and his personal physician; 90% of men with a prostate cancer diagnosis received active treatment (surgery, radiation, and/or hormonal therapy). After 7 years (complete followup), a nonstatistically significant trend toward increased prostate cancer mortality was seen in the screened arm (rate ratio [RR], 1.14 [95% CI, 0.75–1.70]) compared with men in the control arm. Similar findings were observed after 10 years. The primary criticism of this study relates to the high contamination rate; approximately 50% of men in the control arm received at least one PSA test during the study, although the investigators specifically increased both the number of screening intervals and the duration of followup to attempt to compensate for the contamination effects. About 40% of participants had received a PSA test in the 3 years prior to enrollment, though subgroup analyses stratified by history of PSA testing prior to study entry did not reveal differential effects on prostate cancer mortality rates (11).

The ERSPC trial randomized 182,000 men aged 50 to 74 years from seven European countries to PSA testing every 2 to 7 years or to usual care. PSA cut-off points ranged from 2.5 to 4.0 ng/mL, depending on study center (one center utilized a cut-off point of 10.0 ng/mL for several years). Sixty-six percent of men who received a prostate cancer diagnosis chose immediate treatment—surgery, radiation therapy, hormonal therapy, or some combination. After a median followup of 9 years, there was no statistically significant difference in prostate cancer mortality for all enrolled men (RR, 0.85 [95% CI, 0.73 to 1.00]). In a prespecified subgroup analysis limited to men aged 55 to 69 years, a statistically significant reduction in prostate cancer deaths was seen (RR, 0.80 [95% CI, 0.65–0.98]). Subgroup analyses demonstrated a nonsignificant trend toward increased prostate cancer mortality in screened men aged 50 to 54 and 70 to 74 years. The observed difference in prostate cancer mortality for the subgroup of men aged 55 to 69 years first emerged at approximately 9 years (the median length of followup for the trial); thus, the effect size may change (increase or disappear) with further followup. The authors estimated that 1,410 men would need to be screened and 48 additional men would need to be treated to prevent one prostate cancer death (4). Primary criticisms of this study relate to inconsistencies in age requirements, screening intervals, PSA thresholds, and enrollment procedures utilized among the study centers, as well as the exclusion of data from two study centers in the analysis. There is also concern that differential treatments between the study and control groups may have had an impact on outcomes. Of note, men in the screened group were more likely to have been treated in a university setting than men in the control group, and a control subject with high-risk prostate cancer was more likely than a screened subject to receive radiotherapy, expectant management, or hormonal therapy instead of radical prostatectomy (29).

After the publication of the ERSPC results, a single center from within that trial (Göteborg, Sweden) reported data separately. At this center, 20,000 men aged 50 to 64 years were randomized to an invitation to screening with PSA every 2 years or to usual care; median followup was 14 years. A PSA cut-off point of 3.0 ng/mL was initially used but was lowered to 2.5 ng/mL. Fifty-eight percent of participants diagnosed with prostate cancer in the screened arm chose immediate treatment. The rate ratio for prostate cancer mortality in the screened arm was 0.56 (95% CI, 0.39–0.82); the absolute risk reduction was 0.34% (16). Outcomes for 60% of this center's participants had previously been reported as part of the full ERSPC publication, and comparative mortality rates are not available for any other individual study center, making it somewhat challenging to interpret these findings in context. An analysis in the overall ERSPC publication demonstrated that, of all participating countries, Sweden demonstrated the most favorable effect on the combined prostate cancer mortality reduction estimate, and that the overall study results for the "core" population were no longer statistically significant when findings from Sweden were excluded (4). None of the other centers published individual results.

Two meta-analyses found no statistically significant differences in prostate cancer mortality (RR, 0.88 [95% CI, 0.71–1.09] and 0.95 [95% CI, 0.85–1.07]) or overall mortality (RR, 0.99 [95% CI, 0.98–1.01] and 1.00 [95% CI, 0.98–1.02]) in men undergoing PSA-based screening compared with controls (10, 15).

There have been few randomized, controlled trials comparing prostate cancer treatments with watchful waiting. A randomized, controlled trial of 695 men with localized prostate cancer (SPCG-4) reported an 11.7% (95% CI, 4.8–18.6) absolute reduction in the risk of distant metastases in patients assigned to radical prostatectomy versus watchful waiting after 15 years' followup. An absolute reduction in prostate cancer mortality (6.1% [95% CI, 0.2–12]) and a trend toward a reduction in all-cause mortality (6.6% [95% CI, −1.3 to 14.5]) were also observed over this time period. Subgroup analysis suggests that the benefits of prostatectomy may have been restricted to younger (<65 years) men, but were seen in men with PSA values less than 10 and Gleason histological scores of 6 or less. Additionally, radical prostatectomy reduced the use of hormonal therapy by 23.8%. The applicability of these findings to cancer detected via PSA-based screening is limited, as only 5% of participants were diagnosed with prostate cancer via some form of screening, 88% had palpable tumors, and more than 40% of participants presented with symptoms (9, 30).

Preliminary results from the PIVOT trial have become available. The PIVOT trial was composed of men with prostate cancer detected after the initiation of widespread PSA testing and took place within the United States. The trial randomized 731 men aged 75 years or younger (mean age, 67 years) with a PSA value less than 50 ng/mL (mean PSA value, 10 ng/mL) and clinically localized prostate cancer to radical prostatectomy versus watchful waiting. One third of participants were African American. Based upon PSA value, 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 followup of 10 years, there were no statistically significant differences in prostate cancer-specific or all-cause mortality between men treated with surgery versus observation (absolute risk reduction, 2.7% [95% CI, −1.3 to 6.2] and 2.9% [95% 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 mortality did not vary by patient characteristics (including age, race, health status and comorbidities, or Gleason histologic score), but there was variation by PSA level and possibly tumor risk category. In men in the radical prostatectomy group with a PSA value greater than 10 ng/mL at diagnosis, there was an absolute risk reduction of 7.2% (95% CI, 0.0–14.8) and 13.2% (95% CI, 0.9–24.9) for prostate cancer-specific and all-cause mortality, respectively, compared with men in the watchful waiting group. However, men in the radical prostatectomy group with PSA values of 10 ng/mL or less, or those with low-risk tumors, did not experience a reduction in prostate cancer-specific or all-cause mortality, and there was a potential suggestion (nonstatistically significant) of increased harm when compared with the watchful waiting arm (3).

Harms of Screening and Treatment

False-positive PSA test results are common and vary depending on the PSA cut-off point and frequency of screening. After four PSA tests, men in the screening arm of PLCO had a 12.9% cumulative risk of receiving at least one false-positive result (defined as PSA >4.0 ng/mL and no prostate cancer diagnosis after 3 years) and a 5.5% risk of having at least one biopsy due to a false-positive result (31). Men with false-positive PSA test results are more likely to worry specifically about prostate cancer, have a higher perceived risk for prostate cancer, and report problems with sexual function compared with control participants for up to 1 year after testing (32). In one study of men with false-positive PSA test results, 26% reported that they had experienced moderate to severe pain during the biopsy; men with false-positive results were also more likely to undergo repeated PSA testing and additional biopsies during the 12 months following the initial negative biopsy (33).

Harms of prostate biopsy reported by the Rotterdam center of the ERSPC trial include persistent hematospermia (50.4%), hematuria (22.6%), fever (3.5%), urinary retention (0.4%), and hospitalization for signs of prostatitis or urosepsis (0.5%) (34). Pain and discomfort are also associated with prostate biopsy. The documented range varies widely, from around one quarter to more than 90% of men, depending on the definition of "pain/discomfort" utilized, use of analgesia, number of core biopsies taken (as taking more samples appears to be associated with greater pain), and age of the patient (as younger men have reported higher levels and frequencies of pain than older individuals) (35).

The low specificity of the PSA test coupled with its inability to distinguish indolent from aggressive tumors means that a substantial number of men are

being overdiagnosed with prostate cancer. Estimates derived from the ERSPC trial suggest overdiagnosis rates of 48% to 67% of prostate cancer cases detected by the PSA test (36, 37). 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 men diagnosed with clinically localized prostate cancer through PSA testing undergo early treatment—primarily radical prostatectomy and radiation therapy.

Radical prostatectomy is associated with a 20% increased absolute risk of urinary incontinence and a 30% increased absolute risk of impotence compared with watchful waiting (i.e., increased 20% over a median rate of 6% and 30% over a median rate of 45%, respectively) after 1 to 10 years. Perioperative deaths or cardiovascular events occur in about 0.5% and 0.6%–3% of patients (6, 8). Comparative data on outcomes using different surgical techniques are limited; one population-based observational cohort study using U.S. Surveillance, Epidemiology, and End Results (SEER) and Medicare linked data found that minimally invasive/robotic radical prostatectomy for prostate cancer was associated with higher risks for genitourinary complications, incontinence, and erectile dysfunction than open radical prostatectomy (38).

Radiation therapy is associated with a 17% absolute increase in risk of impotence (i.e., increased 17% over a median rate of 50%) and an increased risk of bowel dysfunction compared with watchful waiting after 1 to 10 years; the effect is most pronounced in the first few months after treatment (6, 8).

Localized prostate cancer is not an FDA-approved indication for androgen deprivation therapy, and clinical outcomes for older men receiving this treatment for localized disease are worse than for those who are conservatively managed (39). Androgen deprivation therapy is associated with an increased risk of impotence compared with watchful waiting (absolute risk difference, 43%), as well as systemic effects such as hot flashes and gynecomastia (6, 8). 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.

Estimate of Magnitude of Net Benefit

No trial has shown a decrease in overall mortality with the use of PSA-based screening through 11 years of followup. Most randomized trials have 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 morbidities associated with overdiagnosis and overtreatment. In a prespecified subgroup of men aged 55 to 69 years in the ERSPC trial, a small (0.07%) absolute reduction in prostate cancer deaths was observed after a median followup of 9 years. No statistically significant effect was seen when all enrolled men (ages 50 to 74 years) were included in the analysis. The time until any potential cancer-specific mortality benefit 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 (40); as such, even among men diagnosed with prostate cancer via PSA screening, very few will have prostate cancer death prevented or their lives extended as a result of screening.

The harms of PSA-based screening for prostate cancer include a high rate of false-positive results and accompanying negative psychological effects, complications associated with diagnostic biopsy, and, most importantly, a risk for overdiagnosis coupled with overtreatment. Depending on the modality employed, treatments for prostate cancer carry the risk of death, cardiovascular events, urinary incontinence, impotence, and bowel dysfunction.

The mortality benefits of PSA-based prostate cancer screening through 10 years are small to none, while the harms are moderate to substantial. Therefore, the USPSTF concludes with moderate certainty that PSA-based screening for prostate cancer, as currently utilized and studied in randomized, controlled trials, has no net benefit.

How Does Evidence Fit With Biological Understanding?

PSA-based screening and subsequent treatment, as currently practiced in the United States, presupposes that the majority of asymptomatic prostate cancer cases will ultimately become clinically important and lead to poor health outcomes. However, long-term, population-based cohort studies of conservatively managed men with localized prostate cancer do not support this hypothesis. A review of the Connecticut Tumor Registry—initiated before the PSA 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 withdrawal therapy. After 15 years of followup, the overall risk of dying from prostate cancer was 18 deaths per 1,000 person-years. For men with well-differentiated prostate cancer, it was 6 deaths per 1,000 person-years; far more of these men had died from causes other than prostate cancer (75% vs. 7%) (41). An analysis of the SEER database after the widespread introduction of PSA-based screening examined the risk of death in men with localized prostate cancer who did not undergo initial attempted curative therapy. The 10-year prostate cancer mortality rate for well- or moderately-differentiated tumors among men aged 66–69 years at diagnosis was 0%–7%, depending on tumor stage, versus 0%–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 (42).

Update of Previous USPSTF Recommendation

This recommendation replaces the 2008 recommendation (25). Whereas the USPSTF previously recommended against PSA-based screening for prostate cancer in men aged 75 years and older and concluded that the evidence was insufficient to make a recommendation in 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 should be offered to men aged 40 years or older (43). The American Cancer Society emphasizes informed decisionmaking for prostate cancer: men at average risk should receive information beginning at age 50 years, while African American men or men with a family history of prostate cancer should receive information at age 45 years (44). The American College of Physicians (45) and the American College of Preventive Medicine (46) recommend that clinicians discuss the potential benefits and harms of PSA screening with men aged 50 years and older, consider their patients' preferences, and individualize screening decisions.

Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force* at the time this recommendation was drafted 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, New York); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); 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); George J. Isham, MD, MS (HealthPartners, Minneapolis, Minnesota); Rosanne M. Leipzig, MD, PhD (Mount Sinai School of Medicine, New York, New York); Joy Melnikow, MD, MPH (University of California Davis, Sacramento,

California); Bernadette Melnyk, PhD, RN (Ohio State University College of Nursing, Columbus, Ohio); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Carolina Reyes, MD, MPH (Virginia Hospital Center, Arlington, Virginia); J. Sanford Schwartz, MD, MBA (University of Pennsylvania Medical School and the Wharton School, Philadelphia, Pennsylvania); and Timothy J. Wilt, MD, MPH (University of Minnesota Department of Medicine and Minneapolis Veteran Affairs Medical Center, Minneapolis, Minnesota). Ned Calonge, MD, MPH, a previous Task Force member, also made significant contributions to this recommendation.

* For a list of current Task Force members, go to http://www.uspreventiveservicestaskforce.org/about.htm.

Table 1: What the 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	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	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 "Clinical Considerations" section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Table 2: 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 factors such as: ● the number, size, or quality of individual studies; ● inconsistency of findings across individual studies; ● limited generalizability of findings to routine primary care practice; ● or 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 not generalizable to routine primary care practice; or ● a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

The U.S. Preventive Services Task Force 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 based on the nature of the overall evidence available to assess the net benefit of a preventive service.

References

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, et al. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011. Accessed at http://seer.cancer.gov/csr/1975_2008/index.html on 6 October 2011.
2. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215-24.
3. Wilt TJ. The VA/NCI/AHRQ Cooperative Studies Program #407: Prostate cancer Intervention Versus Observation Trial (PIVOT): main results from a

randomized trial comparing radical prostatectomy to watchful waiting in men with clinically localized prostate cancer. Paper presented at: 107th Annual Meeting of the American Urological Association; May 2011; Washington, DC.
4. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-8.
5. Lin K, Lipsitz R, Miller T, Janakiraman S; U.S. Preventive Services Task Force. Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008;149:192-9.
6. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011 Oct 7. [Epub ahead of print]
7. Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 90. AHRQ Publication No. 12-05160-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
8. Chou R, Dana T, Bougatsos C, Fu R, Blazina I, et al. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 91. AHRQ Publication No. 12-05161-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
9. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364:1708-17.
10. Ilic D, O'Connor D, Green S, Wilt TJ. Screening for prostate cancer: an updated Cochrane systematic review. *BJU Int*. 2011;107:882-91.
11. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360:1310-9.
12. Labrie F, Candas B, Cusan L, Gomez JL, Bélanger A, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate*. 2004;59:311-8.
13. Sandblom G, Varenhorst E, Rosell J, Löfman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. *BMJ*. 2011;342:d1539.
14. Kjellman A, Akre O, Norming U, Törnblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. *J Uro*l. 2009;181:1615-21.
15. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2010;341:c4543.
16. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. 2010;11:725-32.
17. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med*. 2008;148:435-48.
18. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. *J Natl Cancer Inst*. 2009;101:1325-9.
19. Wilt TJ, Brawer MK, Barry MJ, Jones KM, Kwon Y, et al. The Prostate cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemp Clin Trials*. 2009;30:81-7.
20. Moore AL, Dimitropoulou P, Lane A, Powell PH, Greenberg DC, et al. Population-based prostate-specific antigen testing in the UK leads to a stage migration of prostate cancer. *BJU Int*. 2009;104:1592-8.
21. Theoret MR, Ning YM, Zhang JJ, Justice R, Keegan P, Pazdur R. The risks and benefits of 5a-reductase inhibitors for prostate-cancer prevention. *N Engl J Med*. 2011;365:97-9.
22. American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010. Accessed at http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010 on 6 October 2011.
23. Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol. 1993;150:379-85.
24. Grönberg H. Prostate cancer epidemiology. *Lancet*. 2003;361:859-64.
25. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149:185-91.
26. Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. *J Natl Cancer Inst*. 2005;97:1132-7.
27. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA*. 2005;294:66-70.
28. Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *J Natl Cancer Inst*. 2011;103:462-9.
29. Wolters T, Roobol MJ, Steyerberg EW, van den Bergh RC, Bangma CH, et al. The effect of study arm on prostate cancer treatment in the large screening trial ERSPC. *Int J Cancer*. 2010;126:2387-93.
30. Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian Prostate Cancer Group-4 randomized trial. *J Natl Cancer Inst*. 2008;100:1144-54.
31. Croswell JM, Kramer BS, Kreimer AR, Prorok PC, Xu JL, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. *Ann Fam Med*. 2009;7:212-22.
32. McNaughton-Collins M, Fowler FJ Jr, Caubet JF, Bates DW, Lee JM, et al. Psychological effects of a suspicious prostate cancer screening test followed by a benign biopsy result. *Am J Med*. 2004;117:719-25.
33. Fowler FJ Jr, Barry MJ, Walker-Corkery B, Caubet JF, Bates DW, et al. The impact of a suspicious prostate biopsy on patients' psychological, socio-behavioral, and medical care outcomes. *J Gen Intern Med*. 2006;21:715-21.
34. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schröder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology*. 2002;60:826-30.
35. De Sio M, D'Armiento M, Di Lorenzo G, Damiano R, Perdonà S, et al. The need to reduce patient discomfort during transrectal ultrasonography-guided prostate biopsy: what do we know? *BJU Int*. 2005;96:977-83.
36. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102:605-13.
37. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst*. 2003;95:868-78.
38. Hu JC, Gu X, Lipsitz SR, Barry MJ, D'Amico AV, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. 2009;302:1557-64.
39. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA*. 2008;300:173-81.
40. Lu-Yao G, Stukel TA, Yao SL. Changing patterns in competing causes of death in men with prostate cancer: a population based study. *J Urol*. 2004;171:2285-90.
41. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005;293:2095-101.
42. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, et al. Outcomes of localized prostate cancer following conservative management. *JAMA*. 2009;302:1202-9.
43. Carroll P, Albertsen PC, Greene K, Babaian RJ, Carter HB, et al. Prostate-Specific Antigen Best Practice Statement: 2009 Update. Linthicum, MD: American Urological Assocation; 2009. Accessed at http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf on 6 October 2011.

44. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010;60:70-98.
45. American College of Physicians. Screening for prostate cancer. *Ann Intern Med*. 1997;126:480-4.
46. Lim LS, Sherin K; ACPM Prevention Practice Committee. Screening for prostate cancer in U.S. men: ACPM Position Statement on Preventive Practice. *Am J Prev Med*. 2008;34:164-70.

Current as of October 2011

Internet Citation:

U.S. Preventive Services Task Force. Screening for Prostate Cancer: Draft Recommendation Statement. http://www.uspreventiveservicestaskforce.org/draftrec3.htm

---