Grupo Português Génito - Urinário

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USA Preventive Services Task Force PSA Screening Recommendations- May 2018

Rationale

Importance

Prostate cancer is one of the most common types of cancer that affects men. In the United States, the lifetime risk of being diagnosed with prostate cancer is approximately 11%, and the lifetime risk of dying of prostate cancer is 2.5%.[1] Many men with prostate cancer never experience symptoms and, without screening, would never know they have the disease. In autopsy studies of men who died of other causes, more than 20% of men aged 50 to 59 years and more than 33% of men aged 70 to 79 years were found to have prostate cancer.[2] In some men, the cancer is more aggressive and leads to death. The median age of death from prostate cancer is 80 years, and more than two-thirds of all men who die of prostate cancer are older than 75 years.[1] African American men have an increased lifetime risk of prostate cancer death compared with those of other races/ethnicities (4.2% for African American men, 2.9% for Hispanic men, 2.3% for white men, and 2.1% for Asian and Pacific Islander men).[1]

Detection

Screening for prostate cancer begins with a test that measures the amount of PSA protein in the blood. An elevated PSA level may be caused by prostate cancer but can also be caused by other conditions, including an enlarged prostate (benign prostatic hyperplasia) and inflammation of the prostate (prostatitis). Some men without prostate cancer may therefore have positive screening results (ie, “false-positive” results). Men with a positive PSA test result may undergo a transrectal ultrasound-guided core-needle biopsy of the prostate to diagnose prostate cancer.

Benefits of Early Detection and Treatment

The goal of screening for prostate cancer is to identify high-risk, localized prostate cancer that can be successfully treated, thereby preventing the morbidity and mortality associated with advanced or metastatic prostate cancer.

Adequate evidence from randomized clinical trials (RCTs) shows that PSA-based screening programs in men aged 55 to 69 years may prevent approximately 1.3 deaths from prostate cancer over approximately 13 years per 1000 men screened.[3, 4] Screening programs may also prevent approximately 3 cases of metastatic prostate cancer per 1000 men screened.[3] Current results from screening trials show no reductions in all-cause mortality from screening. There is inadequate evidence to assess whether the benefits for African American men and men with a family history of prostate cancer aged 55 to 69 years are different than the benefits for the average-risk population. There is also inadequate evidence to assess whether there are benefits to starting screening in these high-risk groups before age 55 years.

Adequate evidence from RCTs is consistent with no benefit of PSA-based screening for prostate cancer on prostate cancer mortality in men 70 years and older.

Harms of Early Detection and Treatment

The harms of screening for prostate cancer include harms from the PSA screening test and subsequent harms from diagnosis and treatment. Potential harms of screening include frequent false-positive results and psychological harms. One major trial in men screened every 2 to 4 years concluded that, over 10 years, more than 15% of men experienced at least 1 false-positive test result.[5] Harms of diagnostic procedures include complications of prostate biopsy, such as pain, hematospermia (blood in semen or ejaculate), and infection. Approximately 1% of prostate biopsies result in complications requiring hospitalization. The false-positive and complication rates from biopsy are higher in older men.[3] Adequate evidence suggests that the harms of screening and diagnostic procedures are at least small.

PSA-based screening for prostate cancer leads to the diagnosis of prostate cancer in some men whose cancer would never have become symptomatic during their lifetime. Treatment of these men results in harms and provides them with no benefit. This is known as overdiagnosis, and follow-up of large randomized trials suggests that 20% to 50% of men diagnosed with prostate cancer through screening may be overdiagnosed.[3] Overdiagnosis rates would be expected to increase with age and to be highest in men 70 years and older because older men have high risk of death from competing causes.

Harms of prostate cancer treatment include erectile dysfunction, urinary incontinence, and bothersome bowel symptoms. About 1 in 5 men who undergo radical prostatectomy develop long-term urinary incontinence requiring use of pads, and 2 in 3 men will experience long-term erectile dysfunction. More than half of men who receive radiation therapy experience long-term sexual erectile dysfunction and up to 1

in 6 men experience long-term bothersome bowel symptoms, including bowel urgency and fecal incontinence.[3] Adequate evidence suggests that the harms of overdiagnosis and treatment are at least moderate.

Adequate evidence shows that the harms of screening in men older than 70 years are at least moderate and greater than in younger men because of increased risk of false-positive results, harms from diagnostic biopsy, and harms from treatment.

USPSTF Assessment

PSA-based screening for prostate cancer has both potential benefits and harms. The USPSTF does not recommend screening for prostate cancer unless men express a preference for screening after being informed of and understanding the benefits and risks. The decision about whether to be screened for prostate cancer requires that each man incorporate his own values about the potential benefits and harms. The potential harms of screening, diagnostic procedures, and treatment occur soon after screening takes place. Although the potential benefits may occur any time after screening, they generally occur years after treatment, because progression from asymptomatic, screen-detected cancer to symptomatic, metastasized cancer or death (if it occurs at all) may take years or decades to occur.

The USPSTF concludes with moderate certainty that the net benefit of PSA-based screening for prostate cancer in men aged 55 to 69 years is small for some men. How each man weighs specific benefits and harms will determine whether the overall net benefit is small.

The USPSTF concludes with moderate certainty that the potential benefits of PSA-based screening for prostate cancer in men 70 years and older do not outweigh the expected harms.

Discussion

Burden of Disease

For men in the United States, the lifetime risk of being diagnosed with prostate cancer is approximately 11%, and the lifetime risk of dying of prostate cancer is 2.5%.[1] In 2013, the most recent year for which data are available, approximately 172,000 men in the United States were diagnosed with prostate cancer and almost 28,000 died of prostate cancer.[22] From 2003 to 2012, the prostate cancer mortality rate among US men decreased significantly by 3.4% per year (3.3% and 3.9% per year in white and black men, respectively).[23] Most cases of prostate cancer found in autopsy studies are microscopic, well-differentiated lesions that did not affect men's health during their lifetime. Data from screening trials suggest that many cases of low-risk cancer detected by screening would never have caused symptoms or affected men's health had they never been identified through screening.

Scope of Review

To update its 2012 recommendation, the USPSTF commissioned a systematic review of the evidence regarding the benefits and harms of PSA-based screening for prostate cancer and subsequent treatment of screen-detected prostate cancer.[3, 4] The USPSTF also commissioned a review of multiple contextual questions, including a review of existing decision analysis models and what they suggest about the potential for mitigating the harms of screening and treatment and the overdiagnosis rate of PSA-based screening.[14, 24] The commissioned reviews also examined the effectiveness and harms of PSA-based screening in patient subpopulations at higher risk of prostate cancer, including older men, African American men, and men with a family history of prostate cancer.

Effectiveness of Early Detection

Potential Benefits of Screening

To understand the potential benefits of PSA-based screening for prostate cancer, the USPSTF examined the results of the ERSPC, PLCO, and CAP trials and site-specific reports from 4 ERSPC trial sites. To understand the effectiveness of treatment of screen-detected, early-stage prostate cancer, the USPSTF also examined the results of 3 randomized trials and 9 cohort studies.[3]

The ERSPC trial randomly assigned a core group of more than 160,000 men aged 55 to 69 years from 7 European countries to PSA-based screening vs usual care.[8] Four ERSPC sites reported on the cumulative incidence of metastatic prostate cancer. After a median follow-up of 12 years, the risk of developing metastatic prostate cancer was 30% lower among men randomized to screening compared with usual care (RR, 0.70 [95% CI, 0.60-0.82]; *P* = 0.001). The absolute reduction in long-term risk of metastatic prostate cancer associated with screening was 3.1 cases per 1000 men.[11] After a median follow-up of 13 years, the prostate cancer mortality rate among men aged 55 to 69 years was 4.3 deaths per 10,000 person-years in the screening group and 5.4 deaths per 10,000 person-years in the usual care group (RR, 0.79 [95% CI, 0.69-0.91]; *P* = 0.001).[8] The ERSPC trial did not find a reduction in all-cause mortality.[8]

The results of the overall ERSPC trial provide some of the most important evidence about the potential benefits of PSA-based screening for prostate cancer. The trial was rated as fair quality by the USPSTF review because of several important methodologic issues, including observed differences in how men in the screening and control groups were treated for prostate cancer. Among men diagnosed with nonmetastatic prostate cancer, a greater proportion of men in the screening group underwent radical prostatectomy (41.3%) than in the usual care group (32.8%).[25] Although one might expect treatment differences by screening group if screening produces a shift toward more localized clinical stages, treatment differences across ERSPC study groups persisted even with stratification by clinical stage and tumor grade. The cause for these differences is not known.

In the prostate component of the PLCO trial, more than 76,000 men aged 55 to 74 years were randomized to either annual PSA-based screening for 6 years or usual care. Abnormal screening results (PSA level >4.0 ng/mL or abnormal digital rectal examination findings) were forwarded to patients and their primary care clinician, who coordinated further diagnostic evaluation.[17] The majority of men were non-Hispanic white (86.2% and 83.8% of the screening and control groups, respectively). Approximately one-third of men in both groups had either a PSA test or digital rectal examination within the 3 years prior to enrollment. An estimated 78% of men in the control group had a PSA test during the screening phase of the trial.[25] On average, men in the intervention group received 5 PSA tests during the screening phase of the trial and men in the usual care group received 3 PSA tests.[26] This high PSA testing rate in the control group limits the study's ability to identify a potential screening benefit. Despite the common use of PSA testing in the control group, after 13 years more cases of prostate cancer were diagnosed in the screening group than in the control group (108.4 vs 97.1 cases per 10,000 person-years, respectively) (RR, 1.12 [95% CI, 1.07-1.17]). At a median follow-up of 14.8 years in the PLCO trial, the prostate cancer mortality rate was not significantly different between the intervention and control group (4.8 vs 4.6 deaths per 10,000 person-years, respectively) (RR, 1.04 [95% CI, 0.87-1.24]).[7] This result does not rule out the possibility of a reduction in prostate cancer mortality from screening for prostate cancer.

The CAP trial was a cluster randomized trial in the United Kingdom among 415,357 men aged 50 to 69 years invited for a single PSA-based screening for prostate cancer.[12] Men with a PSA level of 3.0 ng/mL or greater were referred for biopsy. Men with localized prostate cancer were offered enrollment into the Prostate Testing for Cancer and Treatment (ProtecT) trial, in which the primary outcome was prostate cancer mortality. At intervention sites, 34% of men received a valid PSA screening test; the percentage of men at control sites who received a PSA test for screening purposes was estimated to be about 10% to 15% over 10 years. After a median follow-up of 10 years, there was no significant difference in prostate cancer mortality between the group of men invited to screening and control group (RR, 0.99 [95% CI, 0.94-1.03]; *P* = 0.49).

Neither the ERSPC, PLCO, or CAP trials, nor any of the ERSPC site-specific analyses, found an overall all-cause mortality benefit from screening for prostate cancer.

There are limited data on the benefit of screening in younger men. The PLCO trial did not recruit men younger than 55 years. The ERSPC trial reported a slightly higher and nonsignificant risk reduction (RR, 0.84 [95% CI, 0.28-2.49]) for prostate cancer mortality in men aged 50 to 55 years compared with men in the core group aged 55 to 69 years (RR, 0.79 [95% CI, 0.69-0.91]).

There are few data that screening is effective in men older than 70 years. The PLCO and ERSPC trials enrolled men 74 years and younger; men older than 70 years were not in the core age group (55-69 years) in the ERSPC trial. The CAP trial did not enroll men older than 69 years. In the ERSPC trial, the prostate cancer mortality rate ratio in the screening vs control group among men 70 years and older at randomization was 1.17 (95% CI, 0.82-1.66); however, a statistical test found no significant heterogeneity

across age groups. In the PLCO trial, the analogous rate ratio at a median follow-up of 13 years among men aged 65 to 74 years at randomization was 1.02 (95% CI, 0.77-1.37); the test for heterogeneity was not significant (*P* = 0.81).

Potential Benefits of Treatment

The USPSTF examined 3 good-quality randomized trials of treatment of localized prostate cancer and 9 observational cohort studies to understand the potential benefit of active treatment (radical prostatectomy or radiation therapy) compared with conservative treatment (active surveillance or watchful waiting) on overall mortality, prostate cancer mortality, and progression to metastatic prostate cancer.[3]

The UK ProtecT trial randomized more than 1600 men aged 50 to 69 years with screen-detected, localized prostate cancer to radical prostatectomy, radiation therapy, or active surveillance and followed them up for 10 years. Approximately 77% of men had low-grade prostate cancer (Gleason score of 6) with a favorable prognosis. Thus, some men randomized to active surveillance had an intermediate-grade tumor (or other tumor characteristics) such that they may not have been considered a candidate for active surveillance in some settings. The trial did not find a significant improvement in all-cause or prostate cancer mortality in any of the treatment groups. The unexpectedly high survival rate across the trial groups (99%) made any potential differences harder to detect. Longer-term follow-up studies may provide important additional information. The trial reported a significant reduction in progression to metastatic cancer when comparing both radical prostatectomy (61% reduction [95% CI, 27%-79%]) and radiation therapy (52% reduction [95% CI, 13%-73%]) with active surveillance. In the active surveillance group, 6.0% of men developed metastatic cancer, compared with 2.7% and 2.3% in the radiation therapy and radical prostatectomy groups, respectively. During the 10-year follow-up period, 54.8% of men randomized to active surveillance crossed over to active treatment.[15]

The other 2 randomized trials of radical prostatectomy took place prior to widespread PSA-based screening and thus recruited many men with tumors detected from clinical symptoms. Approximately 50% of men in the US-based Prostate Cancer Intervention vs Observation Trial (PIVOT) and almost 90% of men in the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial had palpable tumors. The SPCG-4 trial compared radical prostatectomy with watchful waiting (a passive protocol dissimilar to active surveillance) and found a significant reduction over 13 years in all-cause and prostate cancer mortality.[27] The PIVOT trial did not find significant reductions overall in all-cause or prostate cancer mortality.[28] Recent results from extended follow-up of the PIVOT trial to a median of 12.7 years reported similar results; radical prostatectomy did not significantly reduce prostate cancer mortality (HR, 0.63 [95% CI, 0.39-1.02]) or all-cause mortality (HR, 0.94 [95% CI, 0.81-1.09]) compared with conservative management.[29]

Several cohort studies examining radical prostatectomy or radiation therapy found significant reductions in prostate cancer mortality when comparing active treatment with watchful waiting or other conservative approaches.[3] The cohort study results, however, should be interpreted with caution because of the potential for bias in

treatment assignment. In these clinical settings, men who are healthier may have been more likely to receive active treatment.

Two studies reported on the difference in benefit by age. The PIVOT trial reported no significant differences by age (younger or older than 65 years) in the association between radical prostatectomy and all-cause mortality. In the SPCG-4 trial, the risk of all-cause mortality after radical prostatectomy vs watchful waiting was not significantly reduced among men 65 years and older (but was significantly reduced in men younger than 65 years).

Potential Harms of Screening and Treatment

Potential Harms of Screening and Diagnosis

In addition to the ERSPC and PLCO trials, the USPSTF examined the results of a good-quality cohort study embedded within the ProtecT trial (Prostate Biopsy Effects [ProbE]), a fair-quality cohort study conducted in the US Department of Veterans Affairs (VA) health system, as well as a report on complications of prostate biopsy from the ERSPC Rotterdam site to understand the potential harms of screening and diagnosis.[3]

In the large RCTs, one-fourth to one-third of men offered PSA-based screening had at least 1 positive screening test result. In the PLCO trial, 13% of men had undergone at least 1 biopsy. In the ERSPC trial, nearly 28 biopsies were performed for every 100 men randomized to screening.[3] In the ProbE trial, 7.3% of men reported moderate or greater pain, 5.5% reported moderate to severe fever, and 26.6% reported troublesome hematospermia within the 35 days after biopsy.[28] Complications from transrectal prostate biopsy resulted in 1.3% of men in the UK cohort, 1.6% of men in the VA cohort, and 0.5% of men in the Rotterdam cohort requiring hospitalization.[30-32] In these studies, two-thirds to three-fourths of biopsies demonstrated that the PSA screening test was a false positive.[3]

Overdiagnosis, the identification of asymptomatic cancer that would never cause symptoms or contribute to death, is one of the most important harms of PSA-based screening programs. Although there is no way to conclusively determine the overdiagnosis rate, the USPSTF used data from trials and reviewed decision analysis models to estimate the overdiagnosis rate. Trial data suggest that 21% of cases of screen-detected cancer in the PLCO trial and 50% in the ERSPC trial were overdiagnosed.[3] Using a different type of methodology (ie, not estimates based directly on single trials),[3] decision analysis models produced by the Cancer Intervention and Surveillance Modeling Network estimated that between 1988 and 2000 in the United States, the overdiagnosis rate among cases of screen-detected prostate cancer was 22% to 42%.[24] Overdiagnosis increases with age; 1 study estimates that the overdiagnosis rate is more than 15-fold higher in men older than 85 years than in men aged 50 to 54 years.[24]

Men older than 70 years in the ERSPC trial had a higher rate of false-positive results than younger men (younger than 55 years) (20.6% vs 3.5% in the first screening round, respectively). In the VA cohort study, fewer older men were sent for biopsy for a PSA level greater than 4.0 ng/mL (50.5% of men aged 65-69 years vs 25.4% of men aged 75-79 years). Data from the PLCO trial suggest that older men may be more likely than younger men to experience biopsy complications (28.2 vs 17.7 complications per 1000 biopsies, respectively; OR, 1.4 [95% CI, 0.9-2.4]; *P* = 0.06).

The USPSTF reviewed studies evaluating psychological harms of screening and diagnosis. In 2 observational studies, men who had abnormal PSA screening results but benign biopsy results had significantly increased worry about prostate cancer at 6- to 8-week and at 1-year follow-up compared with men with normal PSA screening results.[33] After 1 year, one-third of men with a benign biopsy finding after an abnormal screening result thought about prostate cancer “a lot” or “some,” compared with 18% of men who had a normal PSA level (*P* = 0.005). In a prospective cohort study embedded in the UK ProtecT trial (n = 7344), there was no increase in anxiety or depression and similar scores on the Mental Health Component of the 12-Item Short Form Health Survey compared with baseline among men who had abnormal PSA screening results.[34] In a cross-sectional US study (n = 210), men with benign biopsy findings after abnormal PSA screening results did not have significantly greater anxiety than men who had normal results.[35]

Potential Harms of Treatment

Men who undergo active surveillance may undergo repeated biopsies and be exposed to potential repeated harms from biopsies (as discussed above). In addition, a significant proportion of men will go on to have active treatment with surgery or radiation therapy, with resultant harms (as discussed below).

The USPSTF identified 3 good-quality and 1 fair-quality randomized trials and 7 large fair-quality observational studies that examined the potential harms of active treatment of prostate cancer.[3] A meta-analysis of the harms of radical prostatectomy concluded that 1 man will experience substantial urinary incontinence (requiring daily use of pads or worse) for every 7.9 men who undergo radical prostatectomy rather than conservative management (95% CI, 5.4-12.2), and 1 man will experience long-term erectile dysfunction for every 2.7 men who undergo radical prostatectomy rather than conservative management (95% CI, 2.2-3.6).[3] In addition, more than 20% of men in the PIVOT trial had a perioperative complication and 5.3% of men in a large US cohort study required reintervention for a surgical complication.[3] A meta-analysis of the harms of radiation therapy found that 1 man will experience long-term erectile dysfunction for every 7 men treated with radiation therapy rather than conservative management (95% CI, 5.1-10.7).[3] Although results are conflicting across cohort studies regarding the association of urinary incontinence and radiation therapy, rates of fecal incontinence and bowel urgency were as high as 31.8% after radiation therapy in 1 cohort study,[36] and these bowel complications were more common compared with conservative management in 2 trials and 3 cohort studies.[3]

After a median follow-up of 6 years in the ProtecT trial, there was no significant difference among men randomized to radical prostatectomy, radiation therapy, or active surveillance in reported anxiety, depression, health status, and cancer-related quality of life.[36] The older SPCG-4 trial had similar results after a median follow-up of 12 years when comparing men who received radical prostatectomy vs watchful waiting.[37] There was no evidence of an adverse effect of radical prostatectomy on generic quality-of-life measures compared with conservative management in cohort studies.

In several studies, men older than 70 years had a significantly increased risk of medical complications and perioperative mortality after radical prostatectomy compared with younger men.[3]

Estimate of Magnitude of Net Benefit

Conclusions from decision analysis models, which are consistent with the findings of randomized trials and cohort studies, suggest that more aggressive screening strategies, particularly those that use a lower PSA threshold for biopsy than generally used in the United States, provide the greatest potential reduction in death from prostate cancer. However, these strategies are also associated with more false positives, more biopsies, and higher rates of overdiagnosis.[24]

Options for reducing the overdiagnosis rate include lowering the age at which to stop screening, extending the interval between screenings, and using higher PSA thresholds for biopsy. However, no strategy completely eliminates overdiagnosis. PSA-based screening for prostate cancer every 2 or 4 years instead of annually appears to provide a good trade-off between a reduction in overdiagnosis and a small reduction in mortality benefit.[24]

Decision analysis models confirm the USPSTF's conclusion that the overall benefit of PSA-based screening for prostate cancer is sensitive to the values of individual men. The magnitude of net benefit of PSA-based screening depends on how each man weighs the potential benefits and harms of screening, diagnosis, and treatment. The value a man places on potential benefits and harms may also change over time. It may therefore be useful for clinicians to regularly revisit the decision to screen (or not screen) with their patients (Table).

Although active surveillance may reduce exposure to the potential harms of active treatment, it may not be viewed favorably by some men who value definitive action, are concerned about repeat biopsies, or want to avoid a potential increase in metastatic cancer.

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Table. Estimated Effects After 13 Years of Inviting Men Aged 55 to 69 Years in the United States to PSA-Based Screening for Prostate Cancer[a]

	Number of Men Affected
Men invited to screening	1000
Men who received at least 1 positive PSA test result	240
Men who have undergone 1 or more transrectal prostate biopsies	220[b]
Men hospitalized for a biopsy complication	2
Men diagnosed with prostate cancer	100
Men who initially received active treatment with radical prostatectomy or radiation therapy	65
Men who initially received active surveillance	30
Men who initially received active surveillance who went on to receive active treatment with radical prostatectomy or radiation therapy	15
Men with sexual dysfunction who received initial or deferred treatment	50
Men with urinary incontinence who received initial or deferred treatment	15
Men who avoided metastatic prostate cancer	3
Men who died of causes other than prostate cancer	200
Men who died of prostate cancer despite screening, diagnosis, and treatment	5
Men who avoided dying of prostate cancer	1.3

[a] Estimates based on benefits observed in the ERSPC trial for men aged 55 to 69 years and on treatment harms derived from pooled absolute rates in the treatment groups in the 3 treatment trials (ProtecT, PIVOT, SPCG-4).
[b] Result based on biopsy rate in the ERSPC trial. Current practice in the United States will likely result in fewer biopsies. The potential effect of fewer biopsies on other outcomes, including reductions in prostate cancer diagnosis and mortality, are not clear