Prostate Cancer Screening: The Continuing Controversy

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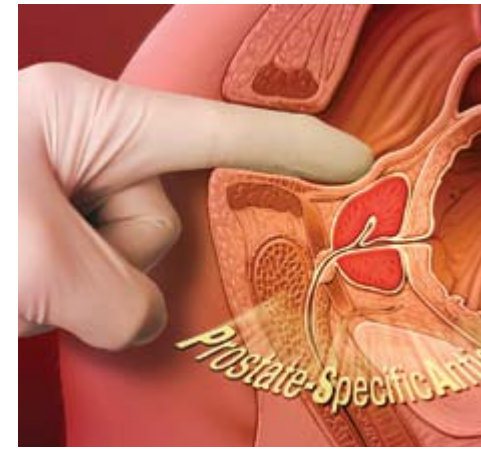
Prostate cancer is the second most common cancer in men, with a lifetime prevalence of 17 percent. Prostate cancer symptoms generally occur in advanced stages, making early detection desirable. Digital rectal examination and prostate-specific antigen testing are the most commonly used screening tools. The goal of screening is to detect clinically significant prostate cancers at a stage when intervention reduces morbidity and mortality; however, the merits and methods of screening continue to be debated. Prostate-specific antigen levels may be less than 4 ng per mL in 15 to 38 percent of men with cancer, indicating a high false-negative rate. The positive predictive value of the prostate-specific antigen test is approximately 30 percent; therefore, less than one in three men with an abnormal finding will have cancer on biopsy. These limitations of the prostate-specific antigen test have led to variations designed to improve its accuracy (e.g., age- and race-specific cutoffs, free prostate-specific antigen tests); however, none of these modifications have been widely adopted because of unclear benefits. Although treatments have improved in the past two decades, therapy for prostate cancer is not benign and may lead to urinary incontinence, sexual dysfunction, or bowel dysfunction. New evidence affecting screening recommendations continues to accumulate, and two large randomized controlled trials of screening will be completed in the next few years. Current guidelines recommend an individualized, targeted, patient-centered discussion to facilitate a shared decision about screening plans. (*Am Fam Physician.* 2008;78(12):1377-1384.



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▶ **Patient information:** A handout on this topic is available at http://familydoctor.org/361.xml.

▶ **See related editorial on page 1338.**

About 218,890 new prostate cancer diagnoses were expected in the United States during 2007, with 27,050 men dying of the disease.[1] Men have a 17 percent lifetime risk of prostate cancer, but only a 3 percent risk of dying from the disease. Black men have the highest incidence of prostate cancer in the world. The age-adjusted death rate from prostate cancer is 64.4 per 100,000 for black men compared with 26.6 per 100,000 for white men. Asian and Hispanic men are at lower risk than white men.[2]

In addition to race, other risk factors for prostate cancer are age and family history. The disease rarely occurs before 45 years of age, but the incidence rises exponentially thereafter; nearly 70 percent of cases are diagnosed in men 65 years and older.[2] The rate of prostate cancer is about 2.5-fold greater in men who have a first-degree relative with the disease.[3] The risk of prostate cancer appears to be even greater if the affected relative is a brother rather than a father, if the affected relative is younger than 55 years, or if two or more first-degree relatives are affected.[3,4] Investigation into nutrition-related risk is ongoing.[5]

Treatment

When prostate cancer is diagnosed, there are a number of treatments available depending on disease stage, patient age, patient preference, and other factors. Unfortunately, prostate cancer treatments have not been compared in randomized controlled trials (RCTs). Only one large, high-quality RCT has compared radical prostatectomy with watchful waiting. This Scandinavian trial found that radical prostatectomy was superior to watchful waiting in lowering prostate cancer–specific mortality (10-year absolute

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations	*Evidence rating*	*References*
Patients should be counseled about the risks and potential benefits of prostate cancer screening.	C	30, 31
Prostate cancer screening should be limited to patients who have a life expectancy of at least 10 years.	C	30, 31
Patients with an abnormal prostate-specific antigen or digital rectal examination test result should be referred for possible prostate biopsy if consistent with the patient's goals for health care.	C	30
Patients with localized, high-grade (Gleason score of greater than 6) prostate cancer should be considered for radical prostatectomy.	B	6

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

risk reduction = 5.3 percent, number needed to treat = 19).[6] Furthermore, the reduction in prostate cancer deaths also constituted much of the reduction in all-cause mortality. However, it is important to note that most of these cancers were not detected with screening, and only 12 percent were diagnosed by prostate-specific antigen (PSA) testing. Other treatment options are available (e.g., radiation, brachytherapy, hormone therapy), but radical prostatectomy is the most common treatment for localized prostate cancer and possesses the strongest evidence for decreasing mortality rates.

Watchful waiting (active surveillance) is a viable option for certain patients, specifically men who are older or have localized, low-grade cancers (usually defined as a Gleason score of less than 7). Additionally, radical prostatectomy, radiation, and androgen deprivation therapy all carry risks *(Table 1[7])*, such as sexual dysfunction, urinary incontinence, and bowel dysfunction. Nonetheless, patient-reported quality of life and psychological well-being are similar between prostatectomy and watchful waiting.[8] Patients with localized, high-grade (Gleason score of greater than 6) prostate cancer should be considered for radical prostatectomy.[6]

The clinical presentation of prostate cancer varies greatly. Low-grade tumors confined to the prostate gland are usually asymptomatic

Table 1. Estimated Rates of Adverse Events Associated with Prostate Cancer Treatments

Adverse event	*Radical prostatectomy (%)*	*External beam radiation (%)*	*Brachytherapy (%)*	*Androgen deprivation therapy (%)*
Bowel dysfunction	9 to 15	6 to 35	4 to 20	—
Mortality	< 1	< 1	< 1	—
Sexual dysfunction	50 to 80	30 to 60	20 to 60	70 to 92
Urinary incontinence	10 to 50	2 to 16	6 to 16	—

NOTE: *Data are not available where no percentage is given.*

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and may only be discovered with screening. However, many low-grade, localized cancers are unlikely to lead to significant disease. In contrast, aggressive metastatic cancers may cause bone pain. Because symptoms of early prostate cancer may be mild or nonexistent, adverse effects of treatment may outweigh the benefits. When prostate cancer leads to metastases, treatment may not be effective.[9]

Digital Rectal Examination

Digital rectal examination (DRE) is the only method in which a physician can physically examine the prostate gland, although only part of the gland can be palpated and tumors can be missed easily. A DRE is considered abnormal if the prostate is enlarged, asymmetric, nodular, or tender. A firm nodule, generalized nodularity, and asymmetry are more concerning; whereas, symmetric enlargement is common in aging men. The test interpretation is ultimately based on the physician's impression, but DRE has poor inter-rater reliability.[10] Additionally, up to 25 percent of prostate cancers detected with biopsy after abnormal DRE findings are found in a different area than the palpable abnormality; in other words, the prostate cancer was not directly related to the DRE findings.[11]

The effectiveness of DRE for prostate cancer screening is not well established. No studies are available to compare DRE with the standard prostate biopsy. However, meta-analyses have estimated the sensitivity and specificity of DRE in primary care and secondary care populations. Sensitivity of DRE is fairly poor (estimated at 53 to 59 percent), although specificity is better (estimated at 83 to 94 percent); the positive predictive value (PPV) is estimated at 18 to 28 percent.[12,13] Therefore, despite the attendant morbidity and cost, 72 to 82 percent of patients who undergo biopsy based on DRE findings will not have prostate cancer.

PSA Test

PSA, a glycoprotein expressed by normal and neoplastic prostate tissue, was originally developed to measure the extent of prostate cancer at diagnosis and to monitor for recurrence. Widespread use of the PSA test for prostate cancer screening began in the late 1980s. At that time, the incidence of prostate cancer rose dramatically, peaking in 1992, although it had been slowly increasing during the 1970s and early 1980s as well.[14] The incidence has since fallen and has now stabilized.[14] The evolution to mass screening with PSA is one explanation often cited for both of these epidemiologic observations.[15]

Furthermore, prostate cancer mortality increased in the early 1990s, but has declined since then.[14] Advocates of PSA screening point to the mortality trend as evidence that PSA is reducing prostate cancer–specific mortality. However, there are arguments against this claim. Competing theories include attribution bias (i.e., cause of death was misattributed to prostate cancer because of its high incidence) and improved therapies for prostate cancer.[16]

Digital rectal examination has poor inter-rater reliability.

As with DRE, PSA testing has not been thoroughly evaluated as a screening test in primary care populations, although some data exist for estimating sensitivity and specificity. When considering these numbers, it is important to note that most studies used a cutoff of greater than 4 ng per mL (4 mcg per L) for abnormal PSA, and prostate biopsy was not performed in men with normal PSA levels. Thus, the results are subject to verification bias.

The Prostate Cancer Prevention Trial, the only large study that routinely performed biopsy in asymptomatic men with PSA levels less than 4 ng per mL, found that 15.2 percent of patients had prostate cancer; 14.9 percent of these cancers were high grade.[17] Another study calculated sensitivity and specificity for a PSA cutoff of 4.1 ng per mL (4.1 mcg per L) in the entire study population and determined them to be 20.5 and 93.8 percent, respectively.[18] The study produced a fairly linear receiver operating characteristic curve, indicating that there is no PSA cutoff value with a high sensitivity and high specificity for detecting prostate cancer but rather a continuum of risk across all PSA values.

One meta-analysis estimated that the

PSA test has a sensitivity of 72.1 percent and a specificity of 93.2 percent for prostate cancer.[13] However, retrospective studies, which looked back at PSA values after men were diagnosed with prostate cancer, demonstrate that up to 38 percent of prostate cancers occur in men with PSA values less than 4 ng per mL.[13]

Effectiveness of Screening

A screening test should be cost-effective, be easy to administer, and have a relatively high sensitivity and specificity. To a large degree, PSA testing and DRE fulfill these criteria. They are inexpensive and easy to administer. When these tests are combined, the PPV ranges from about 30 percent to more than 50 percent,[19] but combining the tests also increases the false-positive rate.[20] The relatively high PPV may have more to do with the high prevalence of prostate cancer than the ability of these tests to detect disease.

PSA values can be elevated for reasons other than prostate cancer *(Table 2[21,22])*. Although false negatives occur, the true rate is unknown because of the lack of biopsies in men with normal screening test results. A common cause of low PSA values is the use of 5-alpha reductase inhibitors (finasteride [Proscar], dutasteride [Avodart]). These agents can reduce the PSA value by 50 percent, and this should be considered when starting therapy.[21]

For a screening test to be effective, it must detect disease in asymptomatic patients so that treatment can alter the disease course, and the benefits of the screening test must outweigh the risks. PSA seems to meet the former criteria. Ample evidence demonstrates that PSA can detect prostate cancers that otherwise would not have been detected.[23] Most asymptomatic cancers detected with PSA are not high grade.[7] When the incidence of prostate cancer skyrocketed in the 1990s, presumably because of the increased use of PSA testing, 86 percent of prostate cancers were localized to the prostate gland.[2] It is not known whether these cancers would have become clinically significant because the natural history of prostate cancer varies. This raises the concern of overdiagnosis or overtreatment. Regardless, asymptomatic, early prostate cancers can be detected with PSA.

Table 2. Causes of Elevated PSA Values Other than Prostate Cancer

Acute urinary retention
Benign prostatic hyperplasia
DRE (minimal, should not deter PSA after DRE)
Ejaculation
Perineal trauma
Prostate biopsy
Prostate surgery
Prostatitis

DRE = digital rectal examination; PSA = prostate-specific antigen.

Information from references 21 and 22.

Information on whether treating prostate cancer detected with screening alters the course of the disease is scarce and based mostly on expert opinion. There are two questions: (1) does an intervention exist that will alter the outcome of prostate cancer? and (2) will screening with PSA and DRE allow that intervention to occur in time to alter the outcome?

To improve the accuracy of PSA screening, modifications to the test have been suggested *(Table 3)*.[17,24-29] Several of these methods may reduce unnecessary prostate biopsies, but all of them require further study. Although some laboratories use age- or race-specific reference ranges for PSA, the traditional cutoff of greater than 4 ng per mL is the most widely used and recommended cutoff for screening.[20] One meta-analysis has demonstrated that using reflex measurements of PSA isoforms (complexed PSA or free PSA) may be effective.[25] However, these modifications miss cancers in some men and lead to overdiagnoses in others without clearly identifying men who would most benefit from treatment.

Screening Follow-up

The controversies and inherent limitations of prostate cancer screening methods make interpretation of the results difficult

for physicians and perplexing for patients. The physician should know how to proceed after an abnormal screening result, and the patient should understand follow-up procedures before undergoing a screening test. For the primary care physician, the next step after an abnormal PSA or DRE result is urology referral for ultrasonography-guided prostate biopsy, if consistent with the patient's goals for health care.[30]

Follow-up decisions become more difficult with a slightly elevated PSA value because the elevation may not be caused by cancer—up to 70 percent of men with PSA values greater than 4 ng per mL do not have cancer.[13] In general, men with PSA values greater than 10 ng per mL (10 mcg per L) should be referred immediately. Because benign disease can cause PSA elevations, there is controversy regarding how to follow-up with patients who

Table 3. PSA Modifications to Improve Screening Accuracy

Modification	*Description*	*Advantages*	*Disadvantages*
Age-specific PSA cutoffs[24]	Lower cutoffs for younger men (2.5 ng per mL [2.5 mcg per L] for 40- to 50-year-olds) and higher cutoffs for older men	Improves sensitivity in younger men and specificity in older men	Unnecessary biopsies increased in younger men, and cancers may be missed in older men; clinical utility is uncertain; not currently recommended
Complexed PSA[25]	PSA bound to serum alpha$_1$-antichymotrypsin, with the usual reference range of less than 3 ng per mL (3 mcg per mL)	May improve specificity of elevated total PSA levels, reducing unnecessary biopsies	Benefit is uncertain
Free PSA[26]	PSA unbound to serum protease inhibitors; ratio of free-to-total PSA is reduced in men with cancer	Unnecessary prostate biopsies can be reduced if biopsies are performed only in men with a PSA between 4 and 10 ng per mL [4 and 10 mcg per L] and a free-to-total PSA of less than 25 percent	8 percent of men with a normal free-to-total PSA have cancer; only the extremes of free-to-total PSA help to inform biopsy decisions
Increased PSA intervals[27]	Extending the screening interval—often recommended annually; in men with PSA levels less than 3 ng mL, progression of PSA to greater than 3 ng per mL after four years is 4.8 percent	Reduces unnecessary blood draws and possibly unnecessary biopsies	May be unacceptable to patients who desire regular screening; may miss some cancers
Lower PSA cutoff[17]	Uses a lower cutoff level, such as 2.5 ng per mL	Increased sensitivity	Decreased specificity, leading to more unnecessary biopsies
PSA density[24]	PSA adjusted for prostate volume (cancers produce more PSA than normal prostate tissue)	PSA density may improve specificity of elevated total PSA levels, reducing unnecessary biopsies	Must perform transrectal ultrasonography or MRI to assess prostate volume
PSA velocity[28]	Rate of change in PSA values over time	Higher velocity may predict cancer and portend a poorer prognosis	Does not independently predict cancer after adjusting for PSA level
Race-specific PSA cutoffs[29]	Lower cutoffs for young black men and higher cutoffs for older black men	Improves sensitivity in younger black men and improves specificity in older black men	Cancers may be missed in older black men; clinical utility is uncertain; not currently recommended

NOTE: *None of these modifications are recommended to replace the traditional total PSA cutoff of 4 ng per mL.*

MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Information from references 17, and 24 through 29.

have initial PSA levels of 4 to 10 ng per mL. Some recommendations suggest immediate referral for biopsy because there appears to be a linear association between PSA value and risk of prostate cancer.[17] However, if prostatitis is suspected, antibiotic treatment before repeating the PSA test may be appropriate. Men should be reminded to avoid ejaculation for a few days before having the repeat PSA test. PSA values persistently greater than 4 ng per mL warrant urology consultation.

Table 4. Expert Recommendations for Prostate Cancer Screening

Organization	*Recommendation*
AAFP[31]	Evidence is insufficient to recommend for or against PSA or DRE screening
ACS[32]	Offer DRE and PSA screening annually to all men 50 years and older with a life expectancy of at least 10 years; men at high risk (e.g., black men, men with one or more first-degree relatives with prostate cancer before 65 years of age) should be screened starting at 45 years of age
AUA[30]	Offer DRE and PSA screening annually to all men 50 years and older with a life expectancy of at least 10 years
USPSTF[20]	Evidence is insufficient to recommend for or against routine PSA or DRE screening; screening is unlikely to benefit men older than 75 years of age

AAFP = American Academy of Family Physicians; ACS = American Cancer Society; AUA = American Urological Association; DRE = digital rectal examination; PSA = prostate-specific antigen; USPSTF = U.S. Preventive Services Task Force.

Information from references 20, and 30 through 32.

Table 5. Discussion Points for Prostate Cancer Screening

Prostate cancer is an important and common disease and becomes more common with age
Although prostate cancer is the second most common cause of cancer-related death in men, most men with prostate cancer do not die of the disease
No one knows if regular prostate cancer screening reduces the risk of dying from the disease
False-positive test results occur: about 70 percent of men with an abnormal result do not have cancer
False-negative test results occur: about 20 percent of men with a normal result have cancer
Prostate-specific antigen values can be elevated for reasons other than cancer (Table 2)
If a test result is abnormal, a biopsy of the prostate gland is the next step
If a prostate biopsy shows cancer, treatment options will be offered
Treatment for prostate cancer depends on the extent of disease and may include surgery, radiation, hormone therapy, and chemotherapy
Treatment for prostate cancer is associated with sexual dysfunction, urinary incontinence, bowel dysfunction, and other adverse effects; the rates of these complications (Table 1) depend on the treatment used and are higher with increasing age and the presence of other diseases

Information from references 7 and 34.

EXPERT RECOMMENDATIONS

There is a lack of data regarding important patient outcomes after prostate cancer screening. Various organizations have published recommendations *(Table 4)*.[20,30-32] Although none of these organizations recommend against screening, they vary in the strength of their endorsements. However, the recommendations universally incorporate patient education and shared decision making.

SHARED DECISION MAKING

Numerous published recommendations, reviews, and resources on prostate cancer screening exist to educate physicians and patients. Unlike many routine preventive services, the discussion about prostate cancer screening involves more nuances that may be difficult to explain in an efficient, patient-centered manner during a routine health maintenance visit. In practice, informed decision making about PSA testing rarely occurs.[33] Barriers to achieving true shared decision making include lack of time during the office visit, physician forgetfulness, and lack of patient knowledge or health literacy.[34,35]

Because time is a major factor limiting the discussion about screening, brief but accurate information to assist the patient in making a decision is necessary *(Table 5*[7,34]*)*. Patients should be counseled about the risks and potential benefits of screening.[30,32] Physicians should emphasize shared decision making, help answer the patient's questions, and guide him toward accurate and accessible information. Despite the discussions, the ultimate decision regarding screening is often influenced by patient characteristics, including anxiety about cancer, expectations about testing, and family history of cancer.[36]

There are several resources to assist physicians and patients with shared decision making. Evidence reviews are available

for physicians,[7,37] and the American Academy of Family Physicians and the National Cancer Institute provide patient Web sites: http://familydoctor.org/361.xml, http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/patient_ed/prostatescreening_patient.Par.0001.File.tmp/prostate_patient_tool.pdf, and http://www.cancer.gov/cancertopics/factsheet/Detection/PSA.

UPCOMING STUDIES

Two large-scale RCTs are underway to help answer questions about the effect of prostate cancer screening on mortality. The European Randomized Study of Screening for Prostate Cancer has enrolled about 200,000 men from eight countries[38]; and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial has enrolled about 155,000 men and women from across the United States.[39] Most of the participants were enrolled in the 1990s. Both trials have published preliminary results, none of which is conclusive with regard to morbidity and mortality. Ultimately, the data from the two trials will be pooled, and final results are not expected for at least a few more years. The results of the trials may be affected by improved treatment in prostate cancer during the enrollment phase, changes in active surveillance, opportunistic screening in the control group, and other factors; therefore, conclusions may be disputed.[40]

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