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Prostate-specific antigen: How to advise patients as the screening debate continues

ABSTRACT

There is still no consensus on whether prostate-specific antigen (PSA) measurement should be used as a screening test for prostate cancer, but patients have the right to be informed about its risks and possible benefits. PSA testing is more likely to be beneficial in relatively young men and men at higher risk (ie, African Americans and men with a family history of prostate cancer). A possible schedule is to test at age 40, age 45, and every 2 to 3 years from age 50 until about age 75.

KEY POINTS

The usual upper limit of normal for serum PSA (4.0 ng/mL) is neither very sensitive nor specific. Lowering the limit would improve sensitivity but decrease specificity. Thus, many more men would have "abnormal" PSA values, but most of them would not have prostate cancer or would have latent prostate cancer that would never become a problem.

Mortality due to prostate cancer has been declining in the United States, but whether this trend can be attributed to PSA screening is subject to debate.

PSA testing can identify men with high-grade prostate cancer, but at the cost of identifying many men who have indolent disease. Furthermore, a negative PSA test does not rule out high-grade prostate cancer.

PSA screening may result in harm in patients who subsequently undergo prostate biopsy and treatment for prostate cancer if the cancer would never have become clinically apparent in the patient's lifetime.

DOES SCREENING for prostate cancer by measuring prostate-specific (PSA) save lives—or does it harm more patients than it helps by exposing them needlessly to the hazards of prostate biopsy and cancer treatment? Until better data are available, we do not know, and the debate continues.

Several prominent organizations in the United States have developed different policies for PSA screening (TABLE 1). Some recommend it, while others find the evidence insufficient to make a recommendation. Most of them emphasize, however, that patients have the right to be informed about the benefits and risks of screening and to decide whether to undergo screening.

This article reviews several critical issues that surround the debate concerning the value of PSA screening for prostate cancer.

WHAT IS PSA?

Discovered in 1979, PSA is a glycoprotein produced almost exclusively by the prostate epithelium. Several conditions can produce a rise in serum PSA levels, including benign enlargement, inflammation, and prostate cancer. The elevated serum levels may be due to enhanced production of PSA or to architectural distortions in the gland that allow more PSA to enter the blood.

PSA was initially promoted as a marker for assessing responses to treatment for prostate cancer. Shortly thereafter, research

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TABLE 1

PSA screening policies in the United States

American Academy of Family Medicine

Physicians should counsel men between the ages of 50 and 65 regarding the known risks and uncertain benefits of screening so they may make an informed choice, rather than routinely screening men's PSA levels

American Cancer Society

Both the PSA test and the digital rectal examination should be offered annually, beginning at age 50, to men who have a 10-year life expectancy and to younger men who are at high risk

Information about potential risks and benefits of screening should be shared with patients

American College of Physicians

Physicians should describe the potential benefits and known harms of screening, diagnosis, and treatment, listen to the patient's concerns, and then individualize the decision to screen

American Urological Association

Men over 50 should consider testing, as should those at high risk, such as African Americans and men with a family history of prostate cancer

Men at high risk should begin testing at age 45

Centers for Disease Control and Prevention (CDC)

Routine screening is not recommended because there is no consensus on whether screening and treatment of early-stage prostate cancer reduces mortality

The CDC supports a man's right to discuss the pros and cons of screening with his physician

US Preventive Services Task Force

Evidence is insufficient to determine whether the benefits of prostate cancer screening outweigh the harms (eg, frequent false-positive results, unnecessary biopsies, and potential treatment complications)

Prostate cancer is the second-leading cause of cancer death in US men

reports explored its usefulness in detecting preclinical prostate cancer. In 1991, Catalona et al¹ proposed using PSA measurement as a screening test for prostate cancer and suggested 4.0 ng/mL as the upper limit of normal.

■ ISSUES IN PSA SCREENING

Does prostate cancer need a screening test?

Prostate cancer is common and serious, and it usually progresses slowly enough to be detected and treated in its preclinical phase, all of which suggest that a screening test is needed.

Prostate cancer is also the second-leading cause of cancer deaths among men in the United States, after lung cancer. In 2004, an estimated 230,110 US men received the diagnosis and 29,900 died of prostate cancer.² In their lifetimes, approximately 16% of all men will be diagnosed with prostate cancer and 3.4% will die of it.³

Several key studies have shown that the rate of progression depends on the histologic grade of the cancer, which can only be determined by obtaining specimens by biopsy or transurethral resection.

Johansson et al,⁴ in a series of four articles published between 1989 and 2004, documented the outcomes of 648 Swedish men with clinically localized prostate cancer that was not treated. No screening for prostate cancer took place during the period when this cohort was recruited.

The 5-year and 10-year rates of progression to metastatic disease and of prostate cancer death were relatively low, a finding that challenged the practice of aggressive initial treatment for all patients with early-stage prostate cancer. However, rates may begin to rise 15 years after diagnosis.

Chodak et al⁵ in 1994 analyzed the results of conservative management of clinically localized prostate cancer in 828 patients in six nonrandomized studies published during the decade preceding their report.

Patients with poorly differentiated cancer had a significantly lower cancer-specific survival rate (34%) compared with men who had well-differentiated or moderately differentiated cancer (87%). In addition, men with poorly differentiated tumors were much more likely to develop metastases than were men with well-differentiated tumors.



FIGURE 1

**Not available for online publication.
See print version of the
*Cleveland Clinic Journal of Medicine***

**The grade
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Albertsen et al⁶ in 1998 reported the long-term outcomes of 767 men with clinically localized prostate cancer diagnosed between 1971 and 1984 who were managed

expectantly (FIGURE 1).⁶ Few men (4%–7%) whose Gleason scores were 2 to 4 died of prostate cancer within 15 years of diagnosis. (Gleason scores range from 2 to 10; in this

system two representative areas of a biopsy sample are graded on a scale of 1 [well differentiated] to 5 [poorly differentiated], and the two grades are added to give the Gleason score.)

The higher the Gleason score, the worse the prognosis; the mortality rate at 15 years was:

- 6% to 11% for men with a score of 5
- 18% to 30% with a score of 6
- 42% to 70% with a score of 7
- 60% to 87% for men with scores of 8 to 10, regardless of their age at diagnosis.

Very few men of any age with scores of 7 to 10 survived more than 15 years.

These studies reveal that men with high-grade disease (Gleason score ≥ 7) face a high risk of death from prostate cancer if they do not undergo treatment. These are the men who could potentially benefit from PSA testing. On the other hand, these studies also reveal that many men, especially older men with low-grade disease (Gleason score ≤ 6) have a relatively low risk of disease progression. These men are unlikely to benefit from PSA testing and would be exposed to the harms associated with screening and treatment.

There is no PSA level below which prostate cancer does not occur

Can PSA screening identify men destined to die of prostate cancer?

PSA testing can identify men with high-grade prostate cancer, but at the cost of identifying many men who have indolent disease. Furthermore, a negative PSA test does not rule out high-grade prostate cancer.

Gann et al⁷ assessed the relationship between baseline serum PSA levels and the subsequent development of clinically significant prostate cancer in a case-control analysis of men participating in the Physicians' Health Study. A cut point of 4.0 ng/mL had a sensitivity of 46% for predicting the diagnosis of clinically important prostate cancer within the next 10 years; the specificity was 91%.

Thompson et al,⁸ in a large chemoprevention study comparing finasteride with placebo, found no minimum PSA level below which prostate cancer did not occur. In the placebo group, the prevalence of prostate cancer was 6.6% among men whose PSA level was consistently below 0.5 ng/mL and as high as 26.9% among men whose PSA was between 3.1 and 4.0 ng/mL.

Can PSA testing be improved?

Lowering the upper limit of normal would increase the sensitivity of PSA testing but decrease its specificity. Many more men would have "abnormal" PSA values, but most of them would not have prostate cancer or would have latent prostate cancer that would never become a problem.

Is there a role for measuring free PSA? Various forms of PSA can be detected in the circulation: it exists both free (unbound) and in complexes with macromolecules. For reasons that are uncertain, men with prostate cancer have a lower percentage of circulating free PSA than men with benign prostatic hypertrophy. Unfortunately, free PSA is also a relatively poor discriminator of men with clinically significant prostate cancer.

Age-specific reference ranges for PSA are often used, but on an informal basis. Younger men (< 60 years old) should have PSA levels lower than 3.0 ng/mL, while older men (> 70 years) often have PSA between 4.0 and 6.0 ng/mL.

Serial testing. Several other issues confound the ability of PSA testing to identify high-grade prostate cancers. PSA values may fluctuate for physiologic reasons, including a recent ejaculation. In view of this fluctuation, Eastham et al⁹ encourage patients who have minimally elevated PSA values to have their PSA rechecked before considering prostate ultrasound and biopsy. If PSA levels are rechecked in 1 year, as many as 21% of men with initial PSA values higher than 4.0 ng/mL subsequently have normal values on follow-up.

More biopsy samples. During the past decade, biopsy protocols have changed and now usually call for 10 to 12 cores. (In the past, 6 samples were taken.) Increasing the number of samples taken will lead to more cases of prostate cancer being detected, but it will also increase the probability of detecting insignificant disease.

Does early detection lower prostate cancer mortality rates?

PSA screening is valuable if it can detect prostate cancer early enough in its course to allow intervention, but this does not necessarily imply that PSA testing must find all



prostate cancers in a localized phase: it must simply detect disease early enough to implement a treatment that will alter the outcome.

Indirect evidence suggests that PSA screening may lower prostate cancer mortality rates. The mechanism, however, is unclear.

Prostate cancer mortality rates have been falling since the advent of PSA testing: a 16% decline in the United States in the past decade.² A similar but less dramatic trend has been observed in England and Wales, where many fewer men undergo PSA testing.¹⁰ What can be the cause of these findings?

One hypothesis suggests that PSA testing has encouraged clinicians to use androgen withdrawal therapy much earlier in the course of disease, thereby delaying the progression of prostate cancer sufficiently to increase survival. Evidence to support this theory comes from clinical trials in patients with advanced localized disease.^{11,12}

Another hypothesis attributes the decline in mortality to early intervention with either surgery or radiation. Unfortunately, evidence to support this hypothesis is much more tenuous and consists of only one large randomized trial. During the 1980s Holmberg et al¹³ randomized 695 patients to undergo either radical prostatectomy or expectant management. After 8 years, the mortality rate due specifically to prostate cancer was 14% in the expectant management group and 7% in the radical prostatectomy group. To date, no difference has been noted in overall survival between the two treatment groups.

This population of patients was not identified by PSA testing. Therefore, researchers would need to adjust for “lead-time bias” and disease prevalence to generalize these findings to contemporary practice in the United States. (Lead-time bias refers to patients appearing to survive longer if their disease is discovered by screening, but only because the disease is discovered earlier.) Any significant differences in cause-specific survival between aggressively and conservatively managed patients are unlikely to appear within 10 years of diagnosis. Therefore, the declines in prostate cancer mortality have occurred too soon after the introduction of PSA screening to be

explained by early detection and subsequent treatment by surgery and radiation.

Advocates of PSA testing often cite its ability to identify men with localized prostate cancer as proof that screening is effective. Recent trends in prostate cancer incidence rates have shown a dramatic shift towards early-stage disease.² Although a stage shift is a necessary indicator of the success of a screening program, by itself it is not sufficient. Similar stage shifts were seen following the introduction of screening programs for lung cancer and neuroblastoma. Unfortunately, early intervention in these diseases did not yield a corresponding decline in mortality rates.

Survival rates are improving. Improvements in 5-year and 10-year survival rates after the diagnosis of prostate cancer are also often cited as proof that PSA testing is effective. But these improvements could reflect lead-time bias. In 2000, Welch and Black¹⁴ published an elegant paper exploring the impact of lead time on cancer mortality rates. They noted that the prevalence of any cancer and the consequences of any treatments depend on the level of screening. During the period 1950 to 1996, the 5-year survival rate for prostate cancer increased by 50%, while prostate cancer mortality rates increased by 10%.

It is difficult to adjust for lead-time bias. Simply adding or subtracting several years to survival estimates assumes that cases detected by PSA testing progress at the same rate as those that eventually present clinically.

This assumption may or may not be true and can result in “length-time bias”—the tendency of a screening test to over-represent less-aggressive disease. The rate of disease progression is usually inversely proportional to the length of the preclinical phase in which testing can identify disease. Slow-growing tumors are preferentially identified when screening tests are applied repeatedly. During the past decade, many men have undergone multiple PSA tests. As a consequence, contemporary cancers are much more likely to be relatively slow-growing compared with cancers detected during the early 1990s.

If the detection threshold for PSA screening is lowered, length-time bias increases in magnitude and the spectrum of detected dis-

**Changes
in PSA may
be important
even at levels
< 4.0 ng/dL**

ease is widened to include cases that are unlikely to progress during a patient's lifetime.

Does screening do more harm than good?

The benefits of any screening test must be balanced against the potential harms that result from testing or treatment. In the case of PSA testing, the risks of performing the assay itself are trivial; it is the downstream consequences of abnormal results that deserve closer scrutiny.

Because of the relatively low specificity of PSA testing, a large number of men will be advised to undergo transrectal ultrasonography and prostate biopsy. Many of them will have negative biopsy results and will be told that they have no evidence of disease. Prostate biopsy is uncomfortable, but it has become much more tolerable with the application of local anesthetic. The primary risks of the procedure are infection and bleeding, which fortunately occur in only 1% to 4% of cases.

The more important issues concern the potential morbidity associated with treatment. For men who have been diagnosed with prostate cancer by PSA testing but who are not destined to die from their disease, any morbidity associated with treatment results in a loss of quality of life.

Many reports have documented the potential morbidity associated with surgery and radiation. During the past decade we have worked with five other Surveillance Epidemiology and End Results (SEER) sites to develop the Prostate Cancer Outcomes Study.¹⁵ This large, prospective population-based study has followed men from the date of their diagnosis in 1994–1995 to the present. Of the 1,291 men who underwent radical prostatectomy, 8.4% were incontinent and 59.9% were impotent 18 or more months after surgery. Men who underwent a nerve-sparing prostatectomy had an impotence rate of 56%.

Men undergoing radiation therapy did not fare much better. Of the 497 patients who received external-beam radiation, 28.9% reported a decline in sexual function and 5.4% reported a decline in bowel function 24 months after treatment was completed. Of the men who were potent before treatment, 43%

became impotent within 2 years.

Although prostate cancer treatment can result in considerable morbidity, the most important question about testing for PSA is whether it improves the overall health and well-being of patients. The US Preventive Services Task Force recently re-evaluated PSA screening and again concluded that the evidence was insufficient to determine whether the benefits outweigh the harms (eg, frequent false-positive results, unnecessary biopsies, and potential treatment complications).¹⁶ For this reason, clinical trials in Europe and the United States continue and are expected to yield results by 2009.

Proponents of PSA screening believe that the benefits have already been demonstrated, especially when one considers the dramatic stage shift in prostate cancer towards localized disease and the falling prostate cancer mortality rates. For them, withholding PSA screening while men die of prostate cancer is unethical. Critics of PSA screening worry that it identifies too many cases of subclinical disease that would never threaten patients' lives. Until better data become available, the true balance of benefits and risks remains a matter of opinion.

■ HOW TO ADVISE THE PATIENT

The following generalizations should help patients who are considering prostate cancer screening.

If screening is effective, it will be most effective in men who are younger and who are at high risk of developing prostate cancer. This includes men in their 50s and 60s, African American men, and men who have a family history of prostate cancer. Men who have a life expectancy less than 10 years are unlikely to benefit from screening.

Patients who choose to be screened face an additional decision, ie, when to undergo repeat testing. Most men have annual tests, but this is often unnecessary. Given the slow rate of growth of most prostate cancers, long intervals between tests may be more appropriate. Recent decision analyses¹⁷ have suggested it may be beneficial to screen at age 40, age 45, and then every 2 to 3 years after age 50. Data from the European Randomized

**18 months
after nerve-
sparing
prostatectomy,
56% of men
were still
impotent**



Trial of Screening suggest that relatively few significant prostate cancers are detected in follow-up testing, even when conducted at an interval as long as 4 years after the initial screening.¹⁸ For men with PSA values lower than 1.0 ng/mL, the risk of a rising PSA during the next several years is extremely low. PSA screening should probably stop around age 75, or earlier in men with persistently low levels.

Changes in PSA values on repeat testing should be monitored carefully. Gann et al⁷ observed that simply classifying results as normal or abnormal ignores important information contained in levels below the usual cut point. Thompson et al⁸ demonstrated that the risk of harboring a high-grade prostate cancer increases incrementally with PSA levels between 0 and 4.0 ng/mL. Therefore, it seems reasonable to track the rate of rise in PSA values.

Several studies have also documented that PSA values rise with age. Men in their 50s usually have PSA values below 2.0 ng/mL, while men in their 70s often have PSA values between 4.0 and 6.0 ng/mL. A gradual increase in PSA (< 0.75 ng/mL/year) is of much less concern than rapidly rising values.

For men with a minimally elevated PSA, a low percent of free PSA should raise concerns about clinically significant prostate cancer.

Before ordering a serum PSA screening test, physicians should discuss the following topics with their patients:

- The likelihood that prostate cancer will be diagnosed
- The possibilities of false-positive and false-negative results
- The anxiety associated with a positive test
- The uncertainty regarding whether screening reduces the risk of death from prostate cancer.

Patients who are unfamiliar with PSA testing have a right to know about the availability of the test and what various health care organizations recommend about it. Physicians who do not have enough time to discuss the potential risks and benefits of PSA testing should direct their patients to instructional videos and Internet sites.¹⁹



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Before ordering a PSA test, discuss the implications with the patient