

## Clinical Practice

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

## PROSTATE-SPECIFIC-ANTIGEN TESTING FOR EARLY DIAGNOSIS OF PROSTATE CANCER

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**A 65-year-old man with no risk factors for prostate cancer except his age has a normal digital rectal examination. Should a prostate-specific-antigen (PSA) test be ordered?**

### THE CLINICAL PROBLEM

The introduction of PSA testing in 1987 resulted in an enormous increase in the reported incidence of prostate cancer in the United States. After peaking in 1992, the incidence fell, presumably owing to the identification of preexisting cases among men who had been tested. The rate of death from prostate cancer has risen and fallen over the same period for reasons that are unclear (Fig. 1).<sup>1</sup> Advocates of screening attribute the decline to early detection. However, in England and Wales, there are similar trends in the rates of death from prostate cancer even though the intensity of screening is much lower and the incidence of prostate cancer has increased minimally.<sup>2</sup>

PSA screening is controversial primarily because of the absence of randomized trials documenting that early detection and aggressive treatment of prostate cancer can reduce mortality. Although widespread screening in the United States has led to a shift toward the identification of earlier-stage disease and better short-term outcomes after diagnosis, only randomized trials can prove that these apparent benefits are not simply attributable to lead-time bias and length bias. Lead-time bias refers to the bias that arises by adding the time gained as a result of earlier diagnosis to the survival time, and length bias refers to the bias that arises because of the preferential diagnosis of more indolent cases of cancer through the use of screening.

In the absence of randomized trials, the unusual epidemiology and natural history of prostate cancer

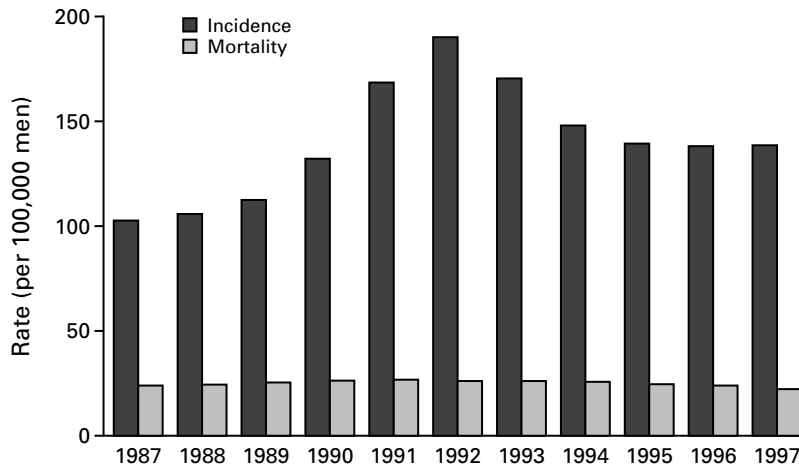
further fuel the controversy. With the advent of PSA screening, the lifetime risk of a diagnosis of prostate cancer is now about 16 percent, whereas the lifetime risk of death from prostate cancer is about 3.4 percent.<sup>1</sup> Obviously, most prostate cancers that are diagnosed in the United States are not destined to be fatal. This relatively high ratio of the cumulative incidence to the cumulative mortality was evident even before PSA testing became widespread, at a time when treatment was less aggressive. It is attributable to the relatively slow doubling time of early prostate cancer, commonly three years or more,<sup>3</sup> and to the fact that this diagnosis is frequently made in older men, who are likely to die of other causes.

Nevertheless, an estimated 31,900 men died of prostate cancer in the United States last year.<sup>4</sup> The rationale for early detection is not only to reduce mortality, but also to prevent morbidity from local symptoms such as bleeding and urinary tract obstruction and the development of painful metastases. For men concerned about prostate cancer, the finding that they have normal results on PSA testing may provide reassurance, although the possibility of a false negative result must be recognized. These potential benefits must be weighed against the potential drawbacks of PSA testing, primarily the side effects of aggressive treatment in the event of an abnormal test result and a subsequent diagnosis of cancer, the anxiety associated with a false positive result, and the burden of dealing with cancers that otherwise might never have become evident.

### The PSA Test

PSA is a glycoprotein produced almost exclusively by the epithelial component of the prostate gland. Men with prostatic diseases, including adenocarcinoma of the prostate, may have high serum PSA levels because of enhanced production of PSA as well as architectural distortions in the gland that allow PSA greater access to the circulation. A biopsy of the prostate, transurethral prostatectomy, acute urinary retention, and acute prostatitis can raise PSA levels. A digital rectal examination appears to have no clinically important effect, but ejaculation may cause a minor (less than 1.0 ng per milliliter), transient (gone within 48 hours) increase in PSA levels.<sup>5,6</sup> Many false positive elevations in PSA (false positive in the sense that they do not indicate the presence of prostate cancer) are attributable to benign prostatic hyperplasia, and others may be due to subclinical prostatic inflammation.<sup>7</sup> PSA test kits are made by a number of manufacturers, and there is debate about whether variations from kit to kit are clinically important. A change

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**Figure 1.** Incidence of and Mortality from Prostate Cancer in the United States, 1987 through 1997. Data are from Ries et al.<sup>1</sup>

from the use of one test kit to another, however, should be considered in the differential diagnosis of a change in a patient's PSA level.

The sensitivity and specificity of the PSA test and the threshold at which a result should prompt a biopsy are unclear. The results of prostatic biopsies are often considered a gold standard, but biopsies are generally performed only when the results of a PSA test or digital rectal examination arouse concern, which leads to a workup bias with respect to defining the sensitivity and specificity of the PSA test, and to an overestimation of the sensitivity of the test in particular. Moreover, the majority of small prostate cancers present in many older men are not clinically important and should not be included in the spectrum of disease used to determine the sensitivity of the PSA test. To overcome these problems, Gann and colleagues assessed the relation between PSA levels in base-line serum samples and the subsequent clinical diagnosis of prostate cancer among the male subjects in the Physicians' Health Study.<sup>8</sup> They found that a cutoff value of 4.0 ng of PSA per milliliter at base line had a sensitivity of 46 percent with respect to the identification of cases of prostate cancer that would occur within the next 10 years. The specificity in this population (with a mean age of 63 years) was 91 percent, but specificity will vary according to age and the underlying probability of benign prostatic hyperplasia. Among older men with benign prostatic hyperplasia, the specificity of the PSA test with a cutoff value of 4.0 ng per milliliter may be as low as 54 percent.<sup>9</sup>

Interestingly, in one screening study, although the probability of an elevated PSA level (defined as more than 4.0 ng per milliliter) increased from about 5 percent among men in their 50s to 25 percent among

men in their 70s, the probability of prostate cancer, given an elevated PSA level, remained about 30 percent, since the age-related increase in the prevalence of prostate cancer was inversely proportional to the decline in the specificity of the test.<sup>10</sup> In this study, the PSA test detected 45 percent more cases of cancer than digital rectal examination alone, whereas digital rectal examination detected 18 percent more cases of cancer than the PSA test alone; that is, each test detects cancers missed by the other.

Traditionally, a PSA value of 4.0 ng per milliliter has been used as the upper limit of the normal level (Table 1). In two studies, however, biopsies were performed in men with PSA values of 2.5 to 4.0 ng per milliliter and normal results on digital rectal examinations, and 12 to 23 percent of the men were found to have prostate cancer.<sup>11,16</sup> Many of these cancers might never have become evident. These results have led some experts to recommend lowering the threshold for biopsy,<sup>17</sup> whereas others argue that serial testing using the traditional threshold will identify cancers destined to progress at a point when they are still curable, while reducing the overdetection of cancers that are not destined to cause problems.<sup>18</sup> Regardless of the threshold used, the test should be repeated in a patient with mildly abnormal levels, perhaps with a recommendation of sexual abstinence for 48 hours before the test, to ensure that the results are consistent.

The standard evaluation for men with suspicious findings on PSA tests or digital rectal examination is a transrectal ultrasound-guided biopsy. Men with suspicious findings on digital rectal examination and a PSA level of 4.0 ng per milliliter or less have a probability of cancer of at least 10 percent,<sup>19</sup> and biopsy is usually recommended. Biopsy specimens are ob-

**TABLE 1.** ESTIMATED PROBABILITY OF PROSTATE CANCER IN MEN WITH NORMAL FINDINGS ON DIGITAL RECTAL EXAMINATION, ACCORDING TO THE PROSTATE-SPECIFIC ANTIGEN LEVEL.\*

PROSTATE-SPECIFIC ANTIGEN LEVEL	PROBABILITY OF PROSTATE CANCER
ng/ml	%
0–2.4	Uncertain
2.5–4.0	12–23†
4.1–10.0	25
>10.0	>50

\*Data are from Catalona et al.,<sup>11,12</sup> Lodding et al.,<sup>13</sup> Djavan et al.,<sup>14</sup> Babaian,<sup>15</sup> and Babaian et al.<sup>16</sup>

†This range is derived from three studies<sup>11,13,16</sup> that reported probabilities of 12, 22, and 23 percent; the lowest estimate is from a population-based study.<sup>13</sup>

tained of any areas identified as possibly abnormal by the digital rectal examination or lesions identified as hypoechoic on transrectal ultrasonography. Because these methods are insensitive, biopsy specimens are systematically obtained from areas that were deemed normal on ultrasonography and digital rectal examination. The traditional strategy has been to obtain a set of six biopsy specimens in a sextant pattern, but recent studies suggest that this approach results in a residual probability of cancer of at least 10 percent.<sup>20</sup> As a result, the optimal number and pattern of biopsy specimens and the number of times biopsies should be repeated are now hotly debated.<sup>21,22</sup> For patients, the fact that a biopsy cannot completely rule out prostate cancer may lead to a chronic state of anxiety, or “PSAdynia.”<sup>23</sup>

In the United States, the main factors that increase the likelihood of receiving a diagnosis of prostate cancer (other than having a PSA test) are older age, black race (which increases the risk by a factor of approximately 1.5), and a family history of prostate cancer (a history of having an affected first-degree relative at least doubles the risk). The presence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia does not appear to increase the risk of prostate cancer.<sup>19</sup> The high prior probability of prostate cancer, even among older white men without a family history of prostate cancer, argues against the use of different screening strategies depending on risk factors. The exception might be to offer a PSA test at an earlier age — for example, at the age of 40 or 45 years rather than 50 years — to black men and men who have a first-degree relative with prostate cancer (particularly if the relative was affected at a fairly young

age). Many urologists question the benefit of screening men who have a life expectancy of less than 10 years or who are 75 years of age or older and who are in average health for their age. Interestingly, primary care physicians in the United States generally do not subscribe to this idea.<sup>24</sup>

#### Tests That May Improve the Performance of the PSA Test

The specificity of the PSA test is suboptimal, and as a result, about 75 percent of men who undergo a prostate biopsy because they have PSA levels of 4.0 to 10.0 ng per milliliter do not have cancer. A critical challenge is discriminating benign prostatic hyperplasia from prostate cancer. Many approaches have been proposed to make this task easier.<sup>25</sup> Adjusting the PSA level to account for the volume or density of the prostate (or specifically the transition zone), measured ultrasonographically, is limited by the inaccuracy of such measurements and is logistically difficult. The use of age-specific reference ranges in which the threshold for biopsy is lower for younger men (with a proposed cutoff value of 2.5 ng of PSA per milliliter for men 40 to 49 years of age and 3.5 ng per milliliter for men 50 to 59 years of age) and higher for older men (with a proposed cutoff value of 4.5 ng of PSA per milliliter for men 60 to 69 years of age and 6.5 ng per milliliter for men 70 to 79 years of age) has been criticized by some because of the low sensitivity of this approach with respect to older men. A rate of change in the PSA level (referred to as “PSA velocity”) of more than 0.75 ng per milliliter per year is more suggestive of prostate cancer than of benign prostatic hyperplasia, but in order to determine this rate, one should measure PSA levels three times at least a year apart to obtain reasonable precision.

PSA circulates both free and in complexes with macromolecules. Measurement of free PSA or PSA complexes can stratify the risk of prostate cancer for men with total PSA values ranging from 4.0 (or 2.5) to 10 ng per milliliter, because for unclear reasons, prostate cancer is associated with a lower percentage of circulating free PSA than is benign prostatic hyperplasia. In a widely cited study, the probability of prostate cancer at biopsy among men with a PSA value of 4.0 to 10.0 ng per milliliter and normal findings on digital rectal examination ranged from 56 percent for men with a ratio of free PSA to total PSA of up to 10 percent, to 8 percent for men with a ratio of more than 25 percent.<sup>12</sup> The authors suggested that men with ratios of more than 25 percent do not require a biopsy. However, only 20 percent of the men in this study had such a ratio, and these men still had a probability of cancer of 8 percent, a value high enough for many physicians and patients to decide to proceed with the biopsy. Moreover, there appears to be greater variability in the results of kits that measure free PSA than in the results of kits that measure total PSA.<sup>26</sup>

### Screening Interval

Many men have annual PSA tests. However, given the slow rate of growth of early prostate cancers, longer intervals between tests might be more appropriate. Recent decision analyses have supported the use of screening every two years.<sup>27,28</sup> They have also suggested the possible benefits of starting testing at an earlier age, 40 or 45 years, and of stopping testing at the age of 75 or even 65 years in men with persistently low levels of PSA (0.5 to 1.0 ng per milliliter).

### STRATEGIES AND EVIDENCE

No appropriately designed and analyzed randomized trials have yet proved that the early detection of prostate cancer has a clear net benefit or harm. Large randomized trials of PSA-based screening programs are under way in the United States (the Prostate, Lung, Colon, and Ovary Screening Trial is expected to be completed in 2009) and Europe (the European Randomized Study of Screening for Prostate Cancer is expected to be completed between 2004 and 2009). One small trial showed similar rates of death from prostate cancer among men randomly assigned to undergo optional PSA screening and those assigned to a control group; however, only 23 percent of the men assigned to screening actually underwent it.<sup>29</sup> The men who did undergo screening had substantially lower rates of death from prostate cancer than the men in the control group, but these results were not based on a strictly randomized comparison. Whether the findings of this trial should be interpreted as positive or negative has been debated.<sup>30</sup>

### AREAS OF UNCERTAINTY

In the absence of firm evidence from controlled trials, it is difficult to advocate a particular strategy of testing. In addition, there is controversy about the optimal treatment for cases of prostate cancer identified by screening programs. Although both urologists and radiation oncologists advocate active treatment for most subgroups of patients, they often recommend the treatment their own specialty delivers.<sup>31</sup> The two groups of specialists agree, however, that standard treatments, including radical prostatectomy, external-beam radiation therapy, and brachytherapy, are associated with clinically significant side effects such as sexual dysfunction and incontinence. If these treatments had fewer side effects, there would be less debate about the value of early detection of prostate cancer.

### GUIDELINES

The 1996 guidelines of the U.S. Preventive Services Task Force do not recommend the use of digital rectal examination, measurement of serum tumor markers (e.g., PSA), or transrectal ultrasonography for routine screening for prostate cancer.<sup>32</sup> In contrast, the American Cancer Society recommends that health

care providers offer the PSA test and digital rectal examination yearly to men 50 years of age or older who have a life expectancy of at least 10 years. Earlier testing, starting at the age of 45 years, is recommended for men at high risk, specifically those with a family history of the disease and those who are black. PSA testing is also recommended for men who ask their clinicians to make the decision about screening on their behalf.<sup>33</sup> The clinical guidelines of the American College of Physicians–American Society of Internal Medicine suggest that decisions about screening should be individualized and reached after a discussion with the patient of the potential benefits and established harms of screening, diagnosis, and treatment.<sup>34</sup> The recommendations of the American Academy of Family Physicians are similar. The American Urological Association also recommends discussing the risks and potential benefits with the patient but, like the American Cancer Society, supports the policy of offering annual PSA testing to asymptomatic men 50 years of age or older who have an estimated life expectancy of at least 10 years and to younger men with established risk factors.<sup>35</sup> The last four organizations all emphasize the importance of informed decision-making about PSA testing on the part of the patient.

### CONCLUSIONS AND RECOMMENDATIONS

The PSA test detects prostate cancer at an early stage in many cases. At present, data are not yet available from large, well-designed, randomized trials to determine whether early detection is beneficial or harmful or has no effects. As a result, the optimal strategy for early detection with PSA testing remains unknown. Decision analyses suggest that given certain assumptions about its effectiveness, PSA screening could be cost effective, at least for younger men.<sup>29</sup> On the basis of available data, men who are approximately 50 to 75 years of age (depending on the presence of risk factors at the lower age limit and the general state of health at the upper age limit) should be made aware of the availability of the PSA test and its potential harms and benefits, so that they can make an informed choice about screening. A discussion about testing should include the following points: the likelihood that prostate cancer will be diagnosed, the possibilities of false positive and false negative results, the anxiety associated with a positive test, and the uncertainty regarding whether screening reduces the risk of death from prostate cancer. In a recent study, these points were among those that men and their wives thought all men should know before undergoing a PSA test.<sup>36</sup> Randomized trials have indicated that routinely providing such information reduces the proportion of men who decide to be tested,<sup>37</sup> although substantial proportions of men still elect to do so. Clinicians should not be dismayed by either choice.

Supported in part by a grant from the Agency for Healthcare Research and Quality (HS 08397).

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