Prostate Cancer: A Review of Common Underwriting Problems, Part 1

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Part 1 of a two-part discussion of Prostate Cancer from an underwriting perspective, covers the epidemiology and screening for prostate cancer. Included is a “Primer on Screening Tests” that discusses problems with digital rectal exam (DRE) and prostate specific antigen (PSA) as screening tests. Approaches to enhancing the use of PSA for screening including age and race specific ranging, PSA density, PSA velocity, free PSA, and complexed PSA are discussed. Arguments for and against the use of PSA for prostate cancer are presented. The widespread use of PSA testing in the insurance setting is contrasted with cautious statements concerning general use of PSA in the clinical preventive care setting. In a future issue, Part 2 will cover staging and follow-up of treated prostate cancer.

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Key words: Prostate cancer, prostate specific antigen, digital rectal examination, screening tests, mortality, life insurance.
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Received: January 20, 2004
Accepted: March 23, 2004

It is estimated that 220,900 men will be diagnosed with prostate cancer in 2003, and 28,900 deaths will occur.1 Prostate cancer is the most common cancer in men in the United States except for non-melanoma skin cancer. It is second only to lung cancer as a cause of male mortality due to cancer. As bad as these statistics sound (for an American male the lifetime risk of developing prostate cancer is 16%), the risk of the average American male dying of prostate cancer is only 3%.2 Prostate cancer deaths peaked in 1991 and have decreased an average of 4.5% per year from 1994 through 1998.3

Survival in men with prostate cancer is best correlated with lack of extension of tumor beyond the capsule at the time of diagnosis. The ten-year survival among men with cancer confined to the prostate is 75%, compared to 55% 10-year survival in men with regional extension and 15% 10-year survival in men presenting with distant metastases.4 Eighty percent of men with prostate cancer are now diagnosed with local or regional disease.5

Obviously, the accurate detection and correct management of this cancer is of interest in underwriting male applicants for life insurance and disability.

SCREENING FOR PROSTATE CANCER5

Screening for prostate cancer is often ordered by insurance companies and is com-
monly encountered in reviews of the attending physician’s statement (APS). The problem is what to do with the knowledge gained. There are only two screening tests for prostate cancer: the digital rectal examination (DRE) and measurement of serum prostate-specific antigen (PSA).

Approximately 2% to 3% of men 50 years or older who undergo a single DRE have induration, marked asymmetry, or nodularity of the prostate. Finding these abnormalities on DRE doubles the odds of detecting a clinically important cancer (defined as having a tumor volume $>0.5$ mL) that is confined to the capsule. However, such findings also increase the odds 3 to 9 fold of finding extracapsular extension of tumor (not amenable to curative therapy). Thus, prostate cancers initially detected by DRE are more likely to be non-resectable and non-curable than those found solely by PSA testing.

Any abnormality discovered by DRE is usually further evaluated with measurement of a serum PSA, as even a “normal” PSA (defined by most laboratories as serum PSA $<4.0$ ng/mL) does not exclude malignancy. For example, the positive predictive value of an abnormal DRE in a study of men with normal PSA revealed malignancy in 14% in those with a PSA of 1 to 2.5 ng/mL, and 30% in men with PSA of 2.6 to 4.0 ng/mL. The negative-predictive value of the DRE is lower than the positive-predictive value due to examiner experience, the relative insensitivity of the test, and the low incidence of prostate cancer in a screened population. No controlled studies have shown a reduction in the morbidity or mortality of prostate cancer when detected by DRE at any age.

Interestingly (and certainly contrary to the clinical and underwriting experience of the authors), neither of these two tests is now recommended as part of a well-person routine and complete history and physical examination, according to the U.S. Preventive Services Task Force (USPSTF). DRE done routinely is graded “C” when done as a screen for colorectal cancer, meaning that there is insufficient evidence either for doing or not doing this as part of a routine complete physical exam. DRE done for detection of prostate cancer is graded “D,” meaning that the bulk of medical evidence suggests that doing this may cause more harm than good. Ordering a serum PSA is also graded “D” by the USPSTF, meaning that there is medical evidence including studies grade I (obtained from at least one properly randomized controlled trial), grade II (evidence obtained from controlled trials or analytic studies, or from multiple time series with dramatic results in uncontrolled experiments), and grade III (opinion from respected authorities based on clinical evidence, or reports of expert committees) that attest to the inadvisability of ordering serum PSA as a screening test.

Certainly the recommendations not to do DRE and/or order screening PSA for men ages 50 to 70 fly in the face of what many physicians have been taught about doing a DRE as part of a complete and thorough physical exam. We are divided about the advisability of doing routine screening PSA on males 50 to 70 years of age (Swanson strongly “for” testing, Richie faintly “for” testing—see later remarks on the difference in perspective of insurance medicine vs academic medicine on this point). But, it is noteworthy that knowledge of these recommendations is now part of the requirements for recertification for Internal Medicine licensure by the American Board of Medical Specialties and the American College of Physicians.

**PRIMER ON SCREENING TESTS:**

**PROBLEMS WITH DRE AND PSA AS SCREENING TESTS**

The very nature of a screening test is to seek a disease without current symptoms. Normally, the prevalence is usually low, even among high-risk groups. For a screening test to be good, it should have both high sensitivity, so it does not miss the very few cases of disease that are present, and high specificity, to reduce the number of people with false-positive results who require further workup. Sensitivity and specificity are determined
JOURNAL OF INSURANCE MEDICINE

for screening tests much as they are for diagnostic tests, except that the gold standard for the presence of disease usually is not another test revealing disease but rather a period of follow-up. Thus, considering the sensitivity of serum PSA for the detection of prostate cancer, the sensitivity of this test is determined by the ratio of the number of prostate cancers found during screening to the sum of the number of screen detected prostate cancers plus the number of prostate cancers discovered over the following years in people with negative test results. This assumes that prostate cancers discovered over the following years were present at screening but were missed. Determination of sensitivity and specificity for screening tests in this way is referred to as the detection method.

The detection method for calculating sensitivity works well if the appropriate amount of follow-up time is known, and that the abnormality detected by the screening test would go on to cause trouble if undetected. Both are important, but the second issue proves particularly troublesome in screening for prostate cancer. Histologic prostate cancer is very common in men. It is estimated that 25% of 50-year-old men have histologic foci of prostate cancer and, by the age of 90, virtually all men have prostate cancer. Screening tests can diagnose these cancers, but for most the cancer may remain so small and localized that it will never become clinically apparent or impact morbidity or mortality. Thus, sensitivity and specificity of serum PSA testing by the detection method may look quite good since the numerator includes all cancers found, not just those with malignant potential.

To get around this difficulty, a newer method, the incidence method, calculates sensitivity by using the incidence in persons not undergoing screening and the interval cancer rate in persons who are screened. The rationale for this approach is that the sensitivity of a test should affect interval cancer rates but not disease incidence. For prostate cancer, the incidence method defines sensitivity of the test as 1 minus the ratio of the interval prostate cancer rate in a group of men undergoing periodic screening to the incidence of prostate cancer in a group of men not undergoing screening (the control group). The incidence method of calculating sensitivity gets around the problem of counting “benign” prostate cancers, but it may also underestimate sensitivity because it excludes cancers with long lead time. The true sensitivity of serum PSA screening is probably somewhere between the estimate by these two methods.

Another important concept in assessing screening for prostate cancer is the concept of lead time bias. Because of screening, a disease is found earlier than it would have been after the patient develops symptoms. As a result, people who are diagnosed by screening will survive longer from the time of diagnosis than are people diagnosed with onset of symptoms, even if treatment at screening is no more effective than treatment at clinical presentation. In such cases, screening appears to help people live longer, when in reality they are not given increased “survival time” but more “disease time.”

An analytic method that can avoid lead time bias involves study of a screened and a control group comparing age-specific mortality rates, rather than survival rates from the time of diagnosis. Screening tests for colorectal cancer are accepted as effective because studies have shown that mortality rates of screened persons are lower than those of a comparable group of unscreened persons. Such unequivocal benefit has not yet been proven for serum PSA screening.

Length time bias can also affect studies of screening. This bias occurs because the proportion of slow-growing lesions diagnosed during screening programs is greater than the proportion diagnosed during usual medical care. The effect of including a greater number of slow-growing cancers makes it seem that screening and early treatment is more effective than usual care.

Length time bias as it relates to screening tests for prostate cancer occurs as follows. Screening works best when a medical condition develops slowly. Most prostate cancers
demonstrate a wide range of growth rates
(Gleason grades 2–6 vs grades 7–10). Screening tests are likely to find mostly slow-growing tumors (Gleason grades 2–6) because they are present for a longer period of time before they cause symptoms. Fast-growing tumors (Gleason grades 7–10) are more likely to cause symptoms that lead to diagnosis in the interval between screening examinations. Screening, therefore, tends to find tumors with inherently better prognoses. As a result, the mortality rates of prostate cancers found on screening are invariably better than those not found on screening, but it is not necessarily because of the screening itself.

Randomized controlled trials (RCTs) are difficult to conduct, take a long time, and are expensive. There are only two randomized controlled trials regarding the benefits of screening for prostate cancer. Neither provide overwhelming support for screening, and both have been criticized (see later discussion). Therefore, investigators commonly use other kinds of studies—cohort studies or case-controlled studies—to investigate effectiveness of screening. Case studies, in which participants in a screening program are followed over time, are a common but suboptimal method of evaluating the effectiveness of screening programs, as they are most subject to lead and length time bias. Unfortunately, most of our working information on screening for prostate cancer is derived from such studies.

**BIOLOGY OF SERUM PSA**

Prostate specific antigen (PSA) is a glycoprotein that is expressed by both normal and neoplastic prostatic tissues. Under normal conditions, PSA is secreted by cells that line the prostate glands (acini) as a prohormone (proPSA). A polypeptide in normal acini removes the propeptide, creating active PSA. This molecule normally undergoes proteolysis to generate inactive PSA, which enters the bloodstream and circulates in an unbound state called free PSA. 

Interestingly, the amount of PSA expressed by neoplastic prostate tissue vs normal prostate tissue, on a per-cell bases, is less in neoplastic tissue. Increased PSA levels are seen in prostate neoplasms because of the increased number of cells present in the neoplastic vs normal prostate. Or, another reason is because the prostate cancer has disrupted the basement membrane, basal cells, and normal lumen architecture, thus allowing more PSA (proPSA, active PSA, and “free PSA”) to gain access to the circulation.

Much of the PSA release in prostate cancer occurs before the active PSA is degraded by proteolytic cleavage into inactive PSA. So while increasing levels of PSA in sera correlate with increasing likelihood of prostate cancer, there is also a correspondingly reduced level of free PSA occurring in prostate cancer, such that the percentage of free or unbound PSA is lower in the serum of men with prostate cancer. 

**PSA AS A SCREENING TEST**

Although data suggest that the increased incidence of prostate cancer predates the introduction of PSA screening, much of the continuing increase in incidence of prostate cancer is attributed to increased detection due to the widespread use of screening with serum PSA. Unfortunately, PSA serum testing alone is not a very good screening test. Although a serum PSA value below 4.0 ng/mL is generally considered “normal,” an estimated 20% to 35% of men with existing prostate cancer will have a serum PSA level below this “normal” cut-off.

Cancers detected when the serum PSA is less than 4.0 ng/mL have a higher likelihood of being organ-confined than cancers detected when the PSA level is greater than 4.0 ng/mL. Seven-year progression-free survival for prostate cancer has been related to the pre-operative PSA levels:

- 93% with levels less than 2.5 ng/mL
- 80% with levels of 2.5 to 4.0 ng/mL
- 76% with levels of 4.1 to 10.0 ng/mL
- 40% with levels greater than 10.0 ng/mL
As helpful as knowing this data may seem, from the perspective of assessing life insurance risk, knowledge of pre-treatment PSA seems less helpful than knowledge of grade and stage of prostate cancer.

Sensitivity and specificity of serum PSA for detection of prostate cancer varies widely. This variation arises because it is difficult to recognize false-negative results. Prostate biopsies are generally not performed if the PSA is normal. The positive-predictive value (PPV) is felt by some to be a better way to assess the performance of serum PSA as a screening tool for prostate cancer, although this measure is also subject to wide variation.\(^2\) A serum PSA of 4 to 10 ng/mL has a positive-predictive value of 21%, and PSA values greater than 10 ng/mL have PPV of 42% to 64%, depending on the degree of elevation of the PSA.\(^3\)

**AGE-SPECIFIC RANGING FOR PSA MEASUREMENTS**

In one study of 471 men, the serum PSA concentration increased by 0.04 ng/mL per year (3.2% increase) for a healthy 60 year old.\(^2\) To adjust for this normal change, the following ranges were suggested (as an alternative to using the standard 0 to 4.0 ng/mL):

- 40 to 49 years old = 0 to 2.5 ng/mL
- 50 to 59 years old = 0 to 3.5 ng/mL
- 60 to 69 years old = 0 to 4.5 ng/mL
- 70 to 79 years old = 0 to 6.5 ng/mL

A study that used these age-specific ranges vs an arbitrary serum PSA cutoff of 4.0 ng/mL in men over age 50 confirmed that age-specific ranges increased the positive-predictive value of PSA testing, but at a cost of reducing the number of cancers found during screening (5.3% vs 4.1%). The authors determined that using the standard serum-PSA cutoff of 4.0 ng/mL would have saved 182 more life years compared to using the age-specific ranges.

Another analysis involved 6600 men 50 years of age or older who underwent prostate biopsy for either a serum PSA >4.0 ng/mL or an abnormal digital rectal exam (DRE). Decreasing the PSA cutoff from 4.0 to 3.5 ng/mL in the 50–59 age range with a normal DRE resulted in a 45% increase in the number of biopsies and a projected 15% increase in cancer detection. Increasing the PSA cutoff from 4.0 to 4.5 ng/mL in men 60–69 years of age resulted in 15% fewer biopsies, but 8% of organ-confined tumors would have been missed. And finally, increasing the PSA cutoff to 6.5 ng/mL in men over age 70 resulted in 44% fewer biopsies but at the expense of missing 47% of organ-confined (ie, potentially curable) cancers.\(^2\)

Finally, in a study of 1046 men who underwent PSA screening, 9 of 15 cancers (60%) were missed using age-specific cutoffs, but detected using the standard cutoff (serum PSA 4.0 ng/mL), had characteristics of life-threatening tumors (ie, Gleason scores ≥7, and evidence of extracapsular spread).\(^2\)

Thus, the use of age-specific PSA ranges for cancer screening remains controversial. From an insurance perspective, the results of testing men in the 6\(^{th}\) and 7\(^{th}\) decades seems especially relevant. Applications from these men are often for sizable insurance amounts, where a single adverse claim would wipe out any savings from not ordering PSA testing upon application. This financial perspective is obviously different from the clinical medicine perspective. The insurance medicine concern is with the financial justifications for testing, rather than weighing the pros and cons of testing for false positives. Thus, our discussion of the problems with DRE and PSA screening are meant to educate readers in our profession of the controversy that exists, and not to necessarily argue for or against companies ordering PSA testing on applicants.

**RACE-SPECIFIC NORMAL RANGES**

Several studies in populations with and without known prostate cancer have confirmed that black men have higher PSA levels than white men.\(^2\) Later studies have suggested that the use of race-specific cutoff
ranges for black males has not been beneficial.\textsuperscript{31,32} One of these studies noted that disease stage and grade were worse in black men for any PSA range, and the use of race-specific cutoff values for blacks actually resulted in a worse outcome after radical prostatectomy than in white men.\textsuperscript{33}

**PSA DENSITY**

Modifications to PSA measurements have been proposed, especially for serum PSA 4.1 to 10 ng/mL. The most confusion distinguishing elevated PSA levels due to benign prostatic hypertrophy (BPH) and asymptomatic prostatitis from prostate cancer occurs in this range. To more directly compensate for BPH and prostate size, transrectal ultrasound (TRUS) has been used to measure prostate volume. Serum PSA is then normalized by prostate volume to give a prostate density. Higher PSA density values (>0.15) are more suggestive of prostate cancer than BPH.

An early study using PSA density evaluated 61 men with prostatic disease (41 with cancer, 20 with BPH).\textsuperscript{34} The mean PSA density in those with prostate cancer was 0.581, and in those with BPH it was 0.044. No patient with BPH had a PSA density greater than 0.117, and only one had a density of 0.1 or greater. Of the 34 patients with PSA density of 0.1 or greater, 33 had prostate cancer.

The major difficulty in calculating PSA density is accurately measuring prostate volume with TRUS. Within patient variation of up to 15% in PSA density with repeated measurements has been reported.\textsuperscript{35} One multicenter study that compared PSA density vs PSA for the early detection of prostate cancer found that almost one half of the cancers would have been missed using 0.15 as a cutoff for biopsy.\textsuperscript{36}

Thus, although PSA density can reliably differentiate between large groups of patients with BPH and prostate cancer, the ability to extrapolate these data to the individual patient is apparently limited. In addition, the requirement for TRUS substantially increases cost and is somewhat impractical for widespread screening purposes.\textsuperscript{35}

**PSA VELOCITY**

Another approach has been to assess the rate of PSA change over time—the PSA velocity. The intuitive reasoning behind PSA velocity is that elevated PSA levels due to prostate cancer will continue to rise over time, as compared to elevations due to BPH or asymptomatic prostatitis. In one study, a PSA velocity cutoff of 0.75 ng/mL per year distinguished patients with prostate cancer from those with either BPH or no prostate disease with a specificity of 90% and 100%, respectively.\textsuperscript{37}

The clinical usefulness (not so much for underwriting) is limited, because within patient variability in measurements of serum PSA, at least 3 consecutive measurements at one-year intervals are recommended.\textsuperscript{38} It is unlikely that many men or their urologists would postpone further evaluation and/or biopsy to meet this criteria. Furthermore, men with cancer often have a PSA velocity of less than 0.75 ng/mL per year, especially those with lower PSA levels.\textsuperscript{39} Those represent the early and curable cases that screening is intended to detect.

**SERUM FREE AND BOUND PSA**

Prostate cancer is associated with a lower concentration of free PSA in the serum as compared to benign conditions, an observation made earlier in this paper. The percentage of free to total PSA (f/t PSA) is another attempt to improve the sensitivity of cancer detection when total PSA is in the normal range (<4 ng/mL), and to increase the specificity of cancer detection when total PSA is in that troublesome "gray zone" of 4.1 to 10 ng/mL. In the latter group in particular, the lower the f/t PSA the greater the likelihood that an elevated PSA represents cancer and not BPH.

As an example, in men with total PSA in the range 4.1 to 10 ng/mL with a cutoff of
f/t PSA <10%, the probability of cancer is 56%, compared to a probability of cancer of only 8% in men with f/t PSA >25%. As is so often the case with testing, the optimal cutoff value for f/t PSA to differentiate prostate cancer from BPH is dependent on the desire for sensitivity vs specificity. The higher the cutoff value, the greater the sensitivity (ie, fewer cancers missed), but the lower the specificity (greater number of false positives).

One study that used a cutoff of 15% f/t PSA to determine which patients required prostate biopsy would have left two thirds of prostate cancers undetected. Raising the cutoff level to 25% f/t PSA in a study of 770 men ages 50 to 75 years with a palpably benign prostate gland and a serum PSA of 4 to 10 ng/mL found that 95% of cancers were detected, while avoiding 20% of unnecessary biopsies. The authors further noted that the cancers that were associated with higher percentage f/t PSA tended to occur in older patients and were less aggressive tumors. A report from the Physician's Health Study concluded that lowering the cutoff from 25% to 20% may decrease the number of false positives by almost one half, while successfully diagnosing the majority of clinically relevant prostate cancers. Among men with total PSA 3 to 10 ng/mL, performing a biopsy only in those with f/t PSA of 20% or less, detected 10% more cancers (all of which would not occur until the 9th year of follow-up), with 12.5% fewer false positives than the conventional strategy of biopsy for all men with total PSA greater than 4 ng/mL.

In a remarkable study of 965 consecutive volunteers in a prostate cancer screening program who had a “normal PSA” (PSA between 2.6 and 4.0 ng/mL), a negative DRE, and percentage of f/t PSA measured as part of the observational data and nevertheless underwent TRUS and biopsy, cancer was detected in 25%. Using a 25% f/t PSA cutoff would have detected 85% of all cancers and avoided 19% of negative biopsies; in contrast, a 30% cutoff detected 93% of the cancers, but avoided only 9% of the negative biopsies.

As suggested, lower percentage of f/t PSA may also be associated with more aggressive prostate cancers. This was illustrated in a study that examined banked frozen serum from 20 men with prostate cancer. Ten years before the diagnosis of cancer, the total PSA was not different between those who ultimately developed aggressive vs nonaggressive tumors. An aggressive tumor was defined as clinical stage T3 disease, nodal or bone metastases, pathologically positive margins, or Gleason score ≥7. However, there was a statistically significant difference in the percentage of f/t PSA between the two groups. All 8 men with aggressive prostate cancer had a f/t PSA ≤14%, compared to only 2 of 6 (33%) with nonaggressive cancer.

**COMPLEXED PSA**

Another strategy to improve the specificity of PSA at an early and potentially curable stage has been to study the proportion of serum PSA complexed with alpha-1-antichymotrypsin (ACT). Studies have shown that cPSA outperforms both total and f/t PSA, with higher specificity and similar sensitivity. Complexed PSA has been approved for the monitoring of men with prostatic carcinoma but not yet for screening. A multicenter screening trial is currently underway.

**EFFICACY OF PROSTATE CANCER SCREENING**

Although it would seem intuitive that earlier diagnosis of any cancer would reduce mortality, this has not been the case with screening for neuroblastoma in infants or for the screening for lung cancer. Prostate cancer that has spread beyond the capsule is not curable with surgery, radiation, hormones, or chemotherapy. The only way to decrease the mortality of this disease is by detecting it at an earlier stage.
Only two randomized controlled trials (RCT) have examined the outcome of screening on prostate cancer-related mortality. The first was the Quebec Screening Study, which randomly assigned men to screening vs no screening and compared mortality over time. Men were screened with both DRE and PSA testing. TRUS was performed if the PSA was greater than 3.0 ng/mL. There were 137 deaths due to prostate cancer in the 38,056 unscreened males compared to only 5 deaths among the 8137 screened males (50 vs 15 per 100,000 man years). Unfortunately, this study has been criticized because of methodological flaws, primarily on the basis that screening was not performed on 77% of the men originally randomized to screening. Thus, the intent-to-treat analysis in the entire group that was randomized to screening suggests a 6% mortality reduction, a lower magnitude of survival benefit.58

The second study was a population-based trial from Finland wherein 8000 men aged 55 to 67 were randomly assigned to annual screening with PSA alone. These were compared with 12,000 men in the target population that were not screened, who were considered the control arm. Screened men who had a PSA >4.0 ng/mL were referred for diagnostic evaluation. At 3 years, 2.6% of those screened were found to have prostate cancer with 0.4% Gleason grade ≥7.59

Additional large, randomized, controlled trials are ongoing and will hopefully clarify the role of screening for prostate cancer. These include the US Prostate, Lung, Colon, and Ovary Screening Trial, and the European Randomized Study of Screening of Prostate Cancer. Another study that has been helpful in supporting on-going PSA and DRE screening is the Physician's Health Study. The study reported that men with PSA levels between 2.0 and 3.0 ng/mL compared to men with PSA levels <1.0 ng/mL had a relative risk of 5.5 for the development of prostate cancer. Also, had serum PSA testing been acted upon prospectively rather than studied retrospectively, 80% of the prostate cancers diagnosed within the first 5 years of the study would have been identified at the initial screening. The discovery of an elevated PSA level would have advanced the detection of aggressive cancers by an average of 5.4 years. This study did not, however, address the important question of whether serum PSA levels would have identified aggressive cancers at a curable stage.60

In a study of 10,000 men over age 50 who were discovered to have cancer of the prostate by either single PSA testing, serial PSA testing, or by digital rectal examination (DRE), the percentages of cancers not confined (and therefore assumed to be incurable) were 37% by single PSA testing, 29% by serial PSA testing, and 57% by just DRE.61

There is considerable indirect evidence of a positive role for prostate screening since PSA was introduced in the late 1980s. The proportion of prostate cancers that are localized at the time of detection has risen. There has been a corresponding increased use of radical prostatectomy and radiation therapy with curative intent. There has been a reduction in hormone therapy for palliation and “watchful waiting” since the advent of PSA screening.62,63 Between 1994 and 1998, mortality rates for prostate cancer in the United States declined by 4.5% per year.64

In Tyrol, Austria, PSA testing was made available to all males ages 45 to 75. Thirty-two percent of the 65,123 potential candidates took advantage of the screening offer. The rate of organ-confined tumors increased from 29% in 1993 to 66% in 1997, and mortality from prostate cancer declined 42% between 1994–1998 after having remained constant between 1970–1993.65

ARGUMENTS AGAINST PSA SCREENING

Mortality from prostate cancer in Great Britain has decreased at a rate similar to that seen in the United States. Great Britain does not screen men for prostate cancer.66 Interesting statistics have also come from a retrospective review of two population-based cohorts of male Medicare beneficiaries ages 65
and 70 from Seattle-Puget Sound and Connecticut. Despite significantly greater PSA testing rate (5.39-fold higher) and prostate biopsy rate (2.2-fold higher) in Seattle vs Connecticut, there was no significant difference in prostate cancer-specific mortality in these two areas with 11 years of follow-up.67

The arguments against screening for prostate cancer have focused mainly upon the issue of over-diagnosing clinically insignificant prostate cancers (usually considered those <0.5 cm in size). Opponents of screening68 cite the following:

- Screening has not yet been proven to decrease the morbidity or mortality associated with prostate cancer
- A positive screening test may lead to large numbers of men having side effects from therapy for prostate cancer, with little or no benefit in cancer morbidity or mortality.
- Treatment for early stage prostate cancer may not have an impact on overall and cause-specific survival, especially in men with low-grade cancers or serious competing comorbidities.
- The optimal screening test or combination of tests is not known.

Although the goal of screening from prostate cancer is to detect early-stage and curable disease, the treatment for early stage prostate cancer may have serious adverse effects. Radical prostatectomy may be associated with impotence (less with a nerve-sparing procedure). Perioperative death occurs in 0.5% to 1.0% of patients undergoing radical prostatectomy. Although complete incontinence is uncommon, a significant number of men will experience some degree of stress urinary incontinence, with up to 5% having severe problems. The overall incidence of adverse effects is lower with radiotherapy, but a substantial number of men have bowel, sexual dysfunction and urinary incontinence.69–71

A cost-effectiveness model using one-time DRE and serum PSA screening found that screening added about 2 additional weeks of life expectancy for men between the ages of 50 and 69 years was of no benefit, and likely to be of some harm.72 A Monte Carlo simulation was used in one study to define optimal frequency of PSA screening. Compared with a commonly recommended strategy of annual PSA testing beginning at age 50, a strategy that included single PSA measurements at age 40 and 45 (to detect men with early disease) followed by biennial testing beginning at age 50 had similar effects on mortality while decreasing the number of PSA tests and prostate biopsies performed.73 Others have suggested that this strategy should be limited to those men with a PSA level <2.0 ng/mL.74

WHO DOES AND DOES NOT ENDORSE PSA SCREENING?

As previously noted, the US Preventive Services Task Force and many European cancer societies have not endorsed routine serum PSA screening for the early detection of prostate cancer.75–77 Updated guidelines from the American Cancer Society (ACS) in 2001, the American College of Physicians (ACP), and the American Urological Association (AUA) endorse screening using serum PSA but “only after all the potential benefits and known harms of screening, diagnosis, and treatment” are thoroughly discussed with men.78–80 A study done to assess the results of providing such informed consent revealed that, in general, men who are given detailed information about prostate cancer screening are more likely to refuse PSA testing than men who are not counseled in detail.81

DEFINITE INDICATIONS FOR PSA TESTING

If an abnormal DRE is found during a routine physical examination, further evaluation that includes measurement of serum PSA is definitely indicated. A frequent concern is the issue of whether DRE affects a subsequently measured serum PSA. This concern was answered in a study of 2750 healthy men over the age of 40 undergoing DRE who were divided into 4 groups based on their initial pre-
DRE serum PSA. The two groups with the lowest initial serum PSA values (0.1 to 4 ng/mL, and 4.1 to 10 ng/mL) had statistically insignificant changes in their serum PSA after DRE. PSA increases in the group with an initial serum PSA 10.1 to 20 ng/mL showed a trend toward statistical significance, and those with a pre-DRE PSA >20 did have statistically significant increases after DRE. The PSA increase in the two latter groups with the highest serum values were not clinically relevant since they did not change ultimate management.82

Mechanical manipulation of the prostate by cystoscopy, prostate biopsy, or transurethral resection of the prostate (TURP) will raise serum PSA levels, necessitating up to a 1-month delay in testing.83 Vigorous bicycle riding also may cause substantial elevations in serum PSA.84 And sexual activity may minimally elevate (usually in the 0.4 to 0.5 ng/mL range) PSA readings that persist for up to 72 hours post ejaculation.85

If the serum PSA concentration is measured as a result of an abnormal DRE, the test should be repeated in 2 to 4 weeks, with many physicians recommending antibiotic therapy in that interval. The most common cause of an elevated PSA is benign prostatic hypertrophy and/or prostatitis (often without signs or symptoms), and initially elevated levels may fall back into normal range after repeated testing.

Part 2 of this article will appear in a future issue and cover clinical staging, tissue staging, and follow-up of treated prostate cancer.

REFERENCES


