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Update on Prostate Specific Antigen (PSA)

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Since its discovery in the early 1980s, prostate specific antigen (PSA) has revolutionized the diagnosis, staging, and monitoring of men suffering from prostate cancer. The clinical application of PSA has led to the detection and diagnosis of prostate cancer in men at an earlier age and at an earlier stage in the course of the disease than historically reported. Since its introduction, PSA has been and will be a critical part in the assessment and management of men with prostate cancer.

It is especially important that primary care clinicians be well-versed in the clinical application of PSA, as they are likely to be among the first health professional contacts to initiate prostate cancer screening among their patients and among the variety of clinicians who participate in the long-term care of their patients diagnosed with prostate cancer. They have to be especially astute in deciding when to follow a patient conservatively and when to refer them to a urologist. Furthermore, as the most common cancer in men and the second leading cause of cancer deaths among men in the United States, prostate cancer promises to be a medical ailment that primary care physicians will address on a daily basis.

Although PSA is integral to the management of prostate cancer, it is plagued by inherent flaws and controversies. As a screening tool, PSA is very sensitive but lacks great specificity. As a result, numerous derivatives and serum tests have evolved in an effort to improve specificity while maintaining sensitivity. No definitive recommendations can be made regarding these derivatives, however, they are important to be aware of as they inundate the prostate cancer literature. In addition, several societies do not endorse the routine screening for prostate cancer given the lack of any randomized trials demonstrating improved survival among men that are screened. The controversy is about the use of the PSA test as a screening test and the different treatments offered for prostate cancer.

The purpose of this review article is to elucidate the role of PSA testing in current clinical practice as recommended by the American Urological Association (AUA). The authors outline the milestones in the discovery of PSA and describe its biologic characteristics. They review its normal variations, its derivative tests and their clinical applicability, and results in incidence and mortality in the PSA era. Controversy regarding the use of PSA as a screening test is addressed, along with the recommended guidelines issued by different societies. The authors highlight the merits of PSA and comment on the undisputed utility of PSA as a tumor marker for detecting early recurrence following radical prostatectomy or radiation therapy. Finally, the authors briefly mention future

tumor markers in development and then summarize current clinical practice and the trends that are developing in the management of patients using PSA as a tumor marker.

—The Editor

Introduction

Prostate cancer is the most common cancer occurring in men in the United States and accounts for the second-leading cause of cancer death.[1] The number of new cases per year exceeds 220,000 and is projected to increase to 380,000 by the year 2025.[2] During the past five years, however, the incidence and mortality rates of prostate cancer have been decreasing. Although debate surrounds this issue, this observation may be attributable to earlier detection and treatment of prostate cancer, which has been made possible with the introduction of PSA as a tumor marker.

Prior to the advent of PSA, most prostate cancer was diagnosed clinically by an abnormal digital rectal exam (DRE) or the development of frank distant metastases. Although risk factors such as family history, African-American race, and a high-fat diet identified groups at risk, knowledge of these factors did not correlate with an increased rate of detection. The introduction of PSA detected clinically significant prostate cancer an average of 6.2 years prior to the development of an abnormal DRE.[3] Currently, at least 75% of the prostate cancers detected are associated with an abnormal PSA.[4] PSA has revolutionized the detection of prostate cancer to the point that Stage T1c prostate cancer (nonpalpable on DRE, PSA-detected) has accounted for the most common clinical presentation of prostate cancer during the last 10 years.[5]

Brief History of PSA. In 1938, Gutman and Gutman discovered that serum acid phosphatase was elevated with metastatic adenocarcinoma of the prostate. It lacked specificity for prostatic tissue and as a result, an assay was developed for the fraction of acid phosphatase produced by the prostate (prostatic acid phosphatase [PAP]). PAP, however, still was hampered by decreased sensitivity for clinically localized adenocarcinoma of the prostate as it was only elevated in 20-30% of these patients.[6] This prompted the discovery of PSA, which was made by several groups simultaneously. The first commercial immunoassay for PSA was approved by the U.S. Food and Drug Administration (FDA) in 1986. In 1987, Stamey and colleagues reported the first clinical study showing the effectiveness of PSA as a tumor marker.

In the 1990s, several studies focused on PSA derivatives that will be described in detail later. In 1992, Carter and colleagues introduced the concept of PSA velocity while Benson and associates introduced the concept of PSA density. In 1993, Oesterling et al and Dalkin et al introduced the concept of age specific reference ranges for PSA values. In the same year, Brawer's group and Catalona's group confirmed the utility of PSA in the detection of prostate cancer. Finally, in a 1997 multi-institutional study, Partin et al demonstrated the clinical application of PSA, clinical stage, and Gleason grade to predict pathological stage. This led to the "Partin" tables which ultimately described the probabilities of nodal and extra-nodal metastases and survival based on presenting PSA level and clinical stage of prostate cancer.

Physiology of PSA. *Biological Function.* PSA is a 33 kD glycoprotein manufactured by the prostatic epithelium and is a serine protease that belongs to the human glandular kallikrein family. Its primary biological function is to liquefy the seminal coagulum or gel formed after ejaculation. By digesting semenogelin-1 and -2 and fibronectin, PSA releases the sperm.[8] Normally, PSA is present predominantly in seminal fluid with low serum levels. Architectural distortions in the prostate gland (e.g., caused by prostate cancer) or increased production of PSA (e.g., found with benign prostatic hyperplasia (BPH) or prostatitis) can cause leakage of PSA into serum by an unknown mechanism that ultimately can result in elevated serum PSA levels. The serum half-life of PSA ranges from 2.2 to 3.2 days.

Normal Variations. In reality, PSA is made by other tissues and has been detected in periurethral glands, perirectal glands, and in the following tumors: colon, ovarian, liver, kidney, adrenal, and parotid. The values, however, are all negligible, and for practical purposes, PSA is considered to be organ-specific but not cancer-specific to the prostate gland. It can be elevated in a number of benign conditions including: recent operative procedure (e.g., prostate biopsy, cystoscopy, or transurethral resection of the prostate), acute urinary retention, acute prostatitis, BPH, subclinical prostatic inflammation, vigorous prostatic massage, placement of urethral catheter, and ejaculation (minor

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[< 1.0 ng/mL] and transient [< 48 hours]).[5,9] Therefore, obtaining a PSA serum level while a patient is an inpatient usually is inaccurate if he recently has undergone urethral catheterization or recovered from urinary retention. A routine DRE, however, does not appreciably affect PSA levels. As a result, a patient presenting for a new patient visit can obtain a DRE and serum PSA level in the same day. Finally, it is important to be aware that concomitant use of 5a-reductase inhibitors can lower serum PSA by 50% in a six-month period. To interpret PSA accurately in this situation, the PSA value must be doubled. Of note, however, the percent of free PSA does not change while on 5a-reductase inhibitors.

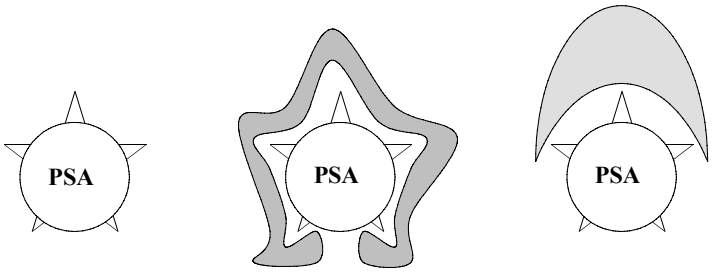
For unknown reasons, African-Americans have the highest incidence and mortality rates of prostate cancer when compared to age-matched controls. Although decreased socioeconomic status and poorer access to health care may account for some of these differences, literature suggests that prostate cancer has a more aggressive course in African-Americans. In equal access health care systems, African-Americans are noted to have tumors that are 2.6 times larger than those in Caucasians. They also present with higher PSA levels, tumor grade, and tumor stage than similarly matched Caucasian controls. These observations form the basis for more aggressive screening protocols in the African-American population.

Circulating Molecular Forms. The PSA molecule has five epitopes that are all unmasked when it exists as free (unbound) PSA. Only those forms of PSA with available epitopes are identified in PSA assays, as these epitopes are what bind to the antibodies employed in these assays. *(See Figure 1.)* The majority of measurable PSA in serum is complexed or bound to protease inhibitors since it normally functions as a serine protease. Between 60% and 95% of PSA is bound to a1-antichymotrypsin (ACT); 0.5-5% is complexed with a1-trypsin inhibitor (a1-antitrypsin, API); and 5-40% exists as free PSA (percentage is higher in men with benign disease).[10] Total measurable serum PSA equals complexed PSA and free PSA. Conversely, PSA in the ejaculate contains free PSA exclusively. Complexed PSA in turn consists of PSA-ACT and PSA-API. Of note, PSA also binds to a2-macroglobulin (AMG) which is not measured by conventional PSA assays because AMG masks all five epitopes of the PSA molecule. Therefore, total PSA measured by conventional assays equals PSA-ACT, PSA-API, and free PSA.

PSA Serum Test

Current Limitations. Prior to the PSA-era, prostate cancer was diagnosed with a DRE with or without a serum PAP level. The addition of PSA to a DRE increased the overall positive predictive value (PPV) of detecting prostate cancer. The PPV of a DRE alone and a serum PSA test alone is 31.4% and 42.1%, respectively. Combined, however, the PPV improves to 60.6%.[5] These results are corroborated by Catalona et al in an early study that demonstrates that the combination of PSA and DRE is superior to DRE alone in the detection of prostate cancer.[11] Overall, the PSA test has a sensitivity of 68-80% and a specificity of 60-70% for detecting prostate cancer when a serum PSA level

Figure 1. Epitopes Identified in PSA Assays



Free PSA (all 5 epitopes unmasked)

PSA-AMG complex (all 5 epitopes masked as PSA bound to a2-macroglobulin)

PSA-ACT complex (3 epitopes masked as PSA bound to a1-antichymotrypsin)

Adapted from: Brawer MK. How to use prostate-specific antigen in the early detection or screening for prostatic carcinoma. *CA Cancer J Clin* 1995;45:158.

greater than 4 ng/mL is used as the threshold for proceeding with a prostate biopsy.[12] In fact, the average man older than 50 years has a 20-30% likelihood of having prostate cancer if his serum PSA is greater than 4 ng/mL.

As a screening test, PSA lacks ideal sensitivity and specificity. In terms of prioritization, false-negative results (i.e., decreased sensitivity) are less important than false-positive (i.e., decreased specificity) results. A false-negative result implies a small focus of carcinoma or a low-grade neoplasm that will ultimately be detected given periodic screening with serial DREs, PSA serum tests, and prostate biopsies. False-positive rates, however, are more problematic. They result in tremendous expense due to repeated use of antibiotics (with prostate biopsies), transrectal ultrasound-guided prostate biopsies, pathology costs, laboratory costs of the PSA test, and the emotional cost of "PSAdynia" (patient anxiety over PSA levels).[13] The problem in specificity results from the significant overlap of PSA levels between the populations with and without cancer. Unfortunately, benign disease can present with high PSA serum levels. Between 4% and 19% of patients with benign glands have a serum PSA level greater than 10 ng/mL, and the test naturally has reduced specificity in older men with BPH. As a result, only 20-25% of men biopsied ultimately will have carcinoma.

Attempts at improving the use of PSA as a screening test have focused on 1) increasing specificity and 2) increasing sensitivity. A number of alternate, derivative PSA serum tests have been developed to lower the false-positive rate and to decrease the number of false negative prostate biopsy results. These PSA refinements are explored in the next section. As for increasing sensitivity, several investigators have suggested lowering the PSA level used as a threshold or cutoff for prostate biopsy, an aspect addressed later as well.

PSA Derivatives. *Free PSA.* The concept of free PSA was introduced in the 1990s by Stenmen et al and Lilja et al. At that time, several investigators had made the observation that free

Table 1. Age-Specific PSA Reference Ranges

	AGE 40-49 YRS	50-59 YRS	60-69 YRS	70-79 YRS
African American	0-2.0 ng/mL	0-4.0 ng/mL	0-4.5 ng/mL	0-5.5 ng/mL
Specificity	93%	88%	81%	78%
Caucasian	0-2.5 ng/mL	0-3.5 ng/mL	0-4.5 ng/mL	0-5.5 ng/mL
Specificity	95%	95%	95%	95%
Asian	0-2.0 ng/mL	0-3.0 ng/mL	0-4.0 ng/mL	0-5.0 ng/mL
Specificity	95%	95%	95%	95%

PSA makes up a greater proportion of total serum PSA in men without prostate cancer. In other words, prostate cancer is associated with a lower percentage of circulating free PSA and, hence, a lower free-to-total PSA ratio. Although there is no satisfactory explanation for this observation, some researchers postulate that the free PSA produced by benign or BPH tissue may exist in another isoform than that produced by prostate cancer, and as a result, does not bind to ACT but may bind to AMG, which is undetectable in conventional PSA assays. As a result, PSA is complexed less than in men with prostate cancer.

Catalona et al studied the clinical applicability of free PSA by performing a prostate biopsy in patients with a normal DRE and a serum PSA in the range of 4-10 ng/mL only when their free/total PSA ratio was less than 25%.[14] Using this free PSA cutoff, the PSA test specificity was enhanced 20% over total PSA while maintaining 95% sensitivity (i.e., detected 95% of the prostate cancers and avoided unnecessary prostate biopsies by 20%). Unfortunately, the widespread clinical application of free PSA is limited by three factors: 1) great variability[13] and lack of reproducibility because free PSA is less stable than complexed PSA and different manufacturers' assays lead to different results; 2) increased costs because two different PSA determinations must be done (free and total); and 3) variability regarding ideal free/total PSA cutoff (15-25%). The data, however, support the clinical use of free PSA in determining when to perform a prostate biopsy in three different scenarios[15]: 1) benign DRE and serum PSA 4-10 ng/mL; 2) benign DRE, serum PSA 4-10 ng/mL, and previous negative biopsy; and 3) benign DRE, serum PSA 2.5-4, and high risk of prostate cancer (positive family history of prostate cancer, African-American race, age 45-59). These scenarios increase the sensitivity of detecting cancer when serum PSA is less than 4.0 ng/mL and increase the specificity when total PSA is elevated (between 4 and 10 ng/mL).

PSA Velocity. PSA velocity was described by Carter et al in 1992 as part of the Baltimore Longitudinal Aging Study. The group noted that when using a rate of change in total serum PSA (i.e., PSA velocity) of greater than 0.75 ng/mL per year to determine when to perform a prostate biopsy, the sensitivity of cancer detection was 72% while the specificity was 95%. Their study, however, was flawed by several factors, including the retrospective nature of the study, small number of cancer patients, long interval between consecutive PSAs in patients (at least seven years), and predominance of men younger than the age of 70 with a normal PSA at the time of entry into the study.[16] Nevertheless, their findings were confirmed in a subsequent study in which patients had a shorter interval between consecutive PSAs.

Several drawbacks exist to PSA velocity. First, PSA serum test variability, including daily variation and variation among different assays, make PSA velocity unreliable in the short run. Second, accurate calculation of PSA velocity requires at least three PSA measurements spanning a two-year period. Finally, the sensitivity is too low to avoid a prostate biopsy in a healthy man with an elevated PSA who would otherwise be an excellent candidate for therapy if prostate cancer was diagnosed. In summary, PSA velocity with a cutoff of 0.75 ng/mL per year may be useful in guiding the decisions to biopsy in men with a normal serum total PSA and to re-biopsy in men who initially have a negative biopsy.

PSA Density. PSA density was originally suggested by Benson and colleagues in 1992 and represents an effort to normalize total serum PSA for a given prostate volume. Assuming equal volumes of prostate tissue, cancer causes a greater elevation in total serum PSA per unit of volume than BPH does. Mathematically, PSA density equals the total serum PSA concentration divided by the volume of the prostate with less than 0.15 being normal. This PSA derivative suffers from tremendous variability not only in PSA measurements but also in ultrasound measurements of prostate gland volume. In addition, estimated volume in BPH does not necessarily correlate with serum total PSA given variations in epithelial-to-stromal ratios between individuals since only the epithelial component produces PSA. This test compromises sensitivity for greater specificity. Overall, PSA density is not a reliable test to use to guide biopsy decisions.

Age-Specific PSA. The concept of age-specific PSA was originally proposed by Oesterling and associates and Dalkin et al and is based on the fact that total serum PSA normally increases with age. Total serum PSA increases by 3.2% (0.04 ng/mL) per year.[17] Based on large series, age-specific reference ranges (ASRRs) were constructed.[17-20] *(See Table 1.)*

ASRRs are an attempt to increase sensitivity in younger men by detecting more organ-confined prostate cancer and to improve PSA specificity in older men by reducing a number of unnecessary prostate biopsies. Partin et al detected 74 additional cancers (81% of which were pathologically favorable) in men age 60 years and younger using ASRRs.[21] Using age-specific PSA, prostate cancer detection increased 18% in younger men and decreased 22% in older men. Reissigl and colleagues demonstrated an 8% increase in the number of positive biopsies and organ-confined cancers detected in men younger than 59 years of age when using age-specific PSA compared to a standard PSA cutoff of greater than 4.0 ng/mL.[22]

ASRRs are controversial because they are not sensitive in men older than 60 years of age, as sensitivity decreases by 9% while specificity and PPV increase by 11% and 5%, respectively.[23] Furthermore, 95% of the cancers undetected by age-specific PSA that would have been detected by using a standard cutoff of 4 ng/mL, had favorable histopathological status.[24] Catalona et al described a multi-institutional experience using age-specific PSA. For men aged 50-59 years, there was a 45% increase in the number of prostate biopsies with a 15% increase in prostate cancer detection. In men older than 70 years of age, however, fewer biopsies (44%) were performed and 47% of organ-confined cancers were missed. The group concluded that the standard total serum PSA cutoff of greater than 4 ng/mL should be used as a guideline for biopsies in all age groups.[25] Littrip and associates compared ASRRs vs. a standard PSA range of 0-4.0 ng/mL for all age groups and concluded that the standard PSA reference range was more effective and less costly across all age groups.[26]

Although ASRRs increase cancer detection in younger men, they do so at a greater expense in terms of increased health costs and more unnecessary prostate biopsies. At the same time, they decrease cancer detection in older men. In summary, the routine use of ASRR is not currently endorsed by the AUA or the FDA; however, many clinicians employ the use of ASRR in men younger than 60 years of age, especially if they have any risk factors for prostate cancer. Since the data support increased cancer detection for this younger age group, these clinicians apply ASRRs at the expense of more negative prostate biopsies.

Other Proposed Screening Modifications

Lowering PSA Cutoff. Increased cancer detection in young men, illustrated by ASRRs, has raised interest in lowering the PSA threshold for performing a prostate biopsy from 4.0 ng/mL to 2.5 ng/mL in certain risk groups. Babaian's group identified prostate cancer in 24.5% of men with a benign DRE and total serum PSA in the range of 2.5-4.0 ng/mL.[27] Another group demonstrated a 27% likelihood of detecting cancer in men with total serum PSA between 2.5 ng/mL and 4.0 ng/mL.[28] Catalona et al demonstrated prostate cancer on biopsy in 22% of men with a benign DRE and serum PSA 2.6-4.0 ng/mL, with 81% of cancers detected being pathologically organ-confined.[29] A recent study by a multicenter group demonstrated that, because of an inherent verification bias in the PSA screening test when the disease status is not verified in all subjects, the sensitivity of the PSA screening test is overestimated and its specificity underestimated. Consequently, this group recommends lowering the PSA threshold level for recommending prostate biopsy to 2.6 ng/mL in men younger than 60 years to improve the sensitivity and the specificity of the PSA screening test.[30] Overall, these data suggest that it is reasonable to use 2.5 ng/mL as a cut-off for proceeding with a prostate biopsy in men aged 40-49 years and/or African-American men as these are groups in whom early detection and aggressive treatment would be beneficial. This practice, however, has not been universally adopted as insufficient data exist documenting improved long-term survival to justify the increased costs.

Optimizing the PSA Screening Interval. Although prostate cancer screening is recommended annually by the AUA and the American Cancer Society (ACS) as described later in this paper, collective data suggest that this protocol can be modified in the following ways: 1) Men with an initial total serum PSA less than or equal to 2 ng/mL and a normal DRE can be screened biannually, whereas men with an initial total serum PSA greater than 2 ng/mL should still be screened annually[31]; and 2) screening can be safely terminated in men 65 years of age or older with a total serum PSA of 1 ng/mL or less.[32] Other data suggest that screening can be performed biannually for men with a benign DRE and total serum PSA less than 2.5 ng/mL. It is clear, however, that men with a total serum PSA greater than 2.5 ng/mL require annual screening once screening has commenced.

Finally, the risk of dying of prostate cancer at 10 years with early localized disease is 8-20% vs. a 10-20% risk of dying of other disease in the same time period. Therefore, many physicians question the benefit of screening men with a life expectancy fewer than 10 years or men who are older than 75 years.[33] In fact, the AUA and ACS guidelines commence screening only if life expectancy is at least 10 years.

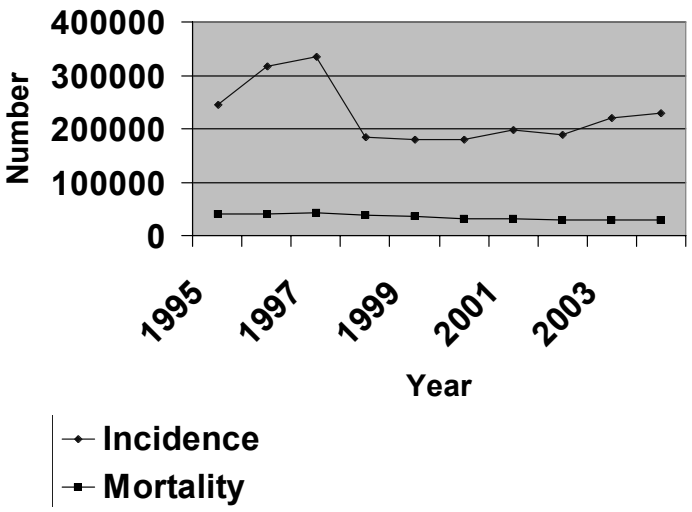
Results in the PSA Era

Trends in Incidence and Mortality. Since the clinical application of PSA screening, the Surveillance, Epidemiology, and End Results (SEER) program data illustrate a 20% age-adjusted increase in prostate cancer incidence per year from 1989 to 1992. Between 1986 and 1991, the detection of prostate cancer rose by 82% in men older than 65 years.[4] The incidence then decreased at 10.8% per year and stabilized after 1994.[34]

Mortality rates have declined during this same time period which has correlated with a decrease in local and metastatic prostate cancer. The SEER data reflect a 52% decrease in the rate of distant (Stage D) prostate cancer between 1990 and 1994.[35] This decreased mortality has been attributed not only to earlier detection of prostate cancer when disease is still organ-confined, but also to advances in the various therapeutic options (radical prostatectomy, radiation therapy, and androgen deprivation therapy). The greatest increase in the number of radical prostatectomies performed has been in men age 60-79 years old between 1983 and 1991.[36] This very group also had experienced the greatest decline in mortality due to prostate cancer with the mortality rate reaching its lowest nadir in 1997 which it has not enjoyed since 1950.[37] Overall, radical prostatectomy rates have increased from 17.4/100,000 in 1988 to 54.6/100,000 in 1992.[35]

Screening Controversies. *Does PSA meet the criteria for a screening test?* Controversy exists as to whether total serum PSA meets the criteria of a screening test. The first prerequisite is that the disease should be common and/or aggressive enough to justify mass screening. As the most common cancer in men and the second leading cause of cancer death among men in the United States, prostate cancer certainly meets this requirement. In fact, the lifetime risk of dying of prostate cancer is 3%. Second, the screening test must detect disease at an early, presymptomatic stage when the disease is still localized and amenable to treat-

Figure 2. Prostate Cancer Incidence and Mortality Over Time



Adapted from: http://www.cancer.org; Wingo PA et al. Cancer statistics, 1995. *CA Cancer J Clin* 1995;45:8-30; and Packer SL et al. Cancer statistics, 1996. *CA Cancer J Clin* 1996;65:5-27.

ment. Approximately 50% of prostate cancers detected today are clinically localized and potentially curable with definitive therapy. A large multi-institutional study revealed that at least 60% of stage T1c cancers were pathologically organ confined.[38] Third, the screening test must be low in cost. Although the cost-effectiveness of PSA testing depends on screening strategy, routine annual screening is not drastically different from screening for other malignancies. In fact, compared to annual mammography with radiology costs and interpretive costs, PSA tests are considerably cheaper. The average quoted national cost for the Hybridtech PSA test is $65.[39] Many hospitals and large health care systems have negotiated lower costs. For example, the cost for a PSA test at one institution is $38.58. Fourth, the effects of false-positive screening must result in low morbidity. A false-positive test result will lead to an unnecessary prostate biopsy. The average cost of a transrectal ultrasound guided prostate biopsy is approximately $1500.[39] Prostate biopsy is a safe outpatient procedure that takes fewer than 10 minutes to perform and results in minimal morbidity. A recent review of approximately 6000 prostate biopsies found a mortality rate of 0%, infection rate of 0.8%, and a 0.6% rate of rectal bleeding greater than two days that may or may not have required intervention.[40] The treatments for diagnosed prostate cancer, however, may result in more significant morbidity, which will be discussed later.

PSA meets the above requirements of a mass screening test. The final criterion, however, requires evidence that treatment after early detection will reduce disease morbidity and/or mortality to justify mass screening.[5] This last criterion is a source of debate, as there is an absence of randomized trials documenting that early detection and treatment of prostate cancer can reduce overall mortality. In addition, curative prostate cancer treatment with either radical prostatectomy or radiation therapy is associated with a significant risk of developing impotence and/or urinary incontinence. These risks must be weighed against the benefits of treatment in making an informed decision to proceed with treatment. As a result, different medical societies offer different positions on PSA screening. Those that do not support screening await the results of two ongoing randomized trials: the Prostate, Lung, Colon, and Ovary Screening Trial in the United States and the European Randomized Study of Screening for Prostate Cancer. Both of these trials are expected to be completed by 2009. For the purposes of this paper, we recommend following the guidelines issued by the AUA and the ACS, which are discussed later.

Potential Biases. Critics of PSA screening cite two important biases in the interpretation of survival data for prostatic cancer. These biases are a reflection of the fact that prostate cancer is an indolent, slow-growing cancer. First, the perceived survival advantage with PSA testing is an artifact of lead-time bias. Lead-time bias refers to the bias of increased survival created by diagnosing a disease at an earlier point of time without affecting the time of death. In other words, screening does not alter the natural history of the disease and the patient dies at the same point in time. Instead, the increased survival merely reflects the earlier detection of an indolent disease without affecting its course. Second, increased cancer detection is due to length-time bias. Length-time bias refers to the bias that periodic screening only identifies slow-growing indolent cancers and not fast-growing aggressive cancers that screening is intended to detect. Therefore, screening leads to an increased identification of clinically insignificant tumors.

Merits of PSA Screening. *Demonstrable Reduction in Mortality.* Although increased survival after prostate cancer therapy might reflect some degree of lead-time bias, the introduction of PSA as a screening test has resulted in a proven decrease in prostate cancer mortality. Untreated men with a life expectancy of 10-15 years will have a 60-80% chance of dying of prostate cancer as compared to an 80% chance of being cured of prostate cancer after a radical prostatectomy in men with organ-confined prostate cancer.[41] Beginning in 1992 and 1993, there has been a 16.1% reduction in age-adjusted prostate cancer mortality rates among white men while there has been a 10.9% reduction in age-adjusted prostate cancer mortality rates among African-Americans respectively.[37] The estimated number of deaths from prostate cancer has declined from 40,400 in 1995 to 30,200 in 2002.[42] *(See Figure 2.)* In fact, since 1997 the incidence of prostate cancer has declined and plateaued, while the number of patients dying of prostate cancer each year is steadily decreasing. *(See Table 2.)* In addition to reducing prostate cancer mortality, PSA screening also reduces morbidity from bleeding, urinary tract obstruction, and painful metastases by identifying prostate cancer at an earlier stage.

Radical prostatectomy has been shown to reduce prostate cancer mortality compared with "watchful waiting" among men with symptomatic and localized tumors. In this important study, 75% of patients had palpable tumors and only 10% of patients

had T1c disease (the most prevalent presentation of prostate cancer since the introduction of PSA testing). Patients were followed for eight years, and the "watchful waiting" group was only given treatment if they developed progressive or symptomatic disease. After eight years, 7.1% of the radical prostatectomy group died, vs. 13.6% of the "watchful waiting" group. Radical prostatectomy was shown to reduce the risk of death due to prostate cancer vs. "watchful waiting" alone. However, no statistical difference in overall survival was noted.[43] One problem, however, was the predominance of patients with locally advanced and palpable prostate cancer in this series. In reality, most patients present with T1c disease because of PSA screening tests. If this study had enrolled a more contemporary mix of patients, a statistically significant survival advantage of radical prostatectomy over "watchful waiting" probably may have been observed.

Detection of Clinically Significant Tumors. Although concerns about length-time bias and the identification of clinically insignificant tumors are legitimate, these tumors are detected by PSA testing less than 20% of the time.[44] In fact, fewer than 10-15% of all prostatectomy specimens contain clinically insignificant tumors (similar to those found at autopsy).[45] An argument in favor of detecting significant tumors can be made by analyzing the trends in prostate cancer incidence rates. Although incidence rates initially rose with the introduction of PSA screening, they eventually fell and, subsequent to 1992, they have remained only slightly higher than the incidence rates observed prior to the PSA-era. This fact corroborates the detection of significant disease because if the test detected insignificant disease, then incidence rates would continue to be substantially higher than prior to the introduction of the screening test. Finally, at least one biologic sign of aggressiveness is present in 34% of the prostate cancers detected by PSA screening. These signs include a high proliferation rate, the immunohistochemical observation of p53 accumulation, detection of aneuploidy by fluorescence in-situ hybridization (FISH), and a high Gleason grade (Gleason 8-10).[46] In those with detected cancer, approximately 92% had Gleason grade of 7 or less, implying tumors that would be amenable to definitive localized prostate cancer therapy. Therefore, these aggressive and substantial cancers are found at a more treatment-responsive stage by PSA screening.

Stage Migration. A good screening test predominantly identifies moderate-grade tumors, since the impact of therapy will be greatest in this group. The utility of identifying high-grade tumors is limited as the prognosis is already poor. Similarly, the diagnosis of low-grade tumors is equally fruitless as these tumors do not require any treatment. In the pre-PSA era, 24% of tumors detected were low-grade; 35% were moderate-grade; and 33% were high-grade. In 1999, 58% of cancers diagnosed were moderate-grade, and 17% were high-grade.[47] This stage migration from more aggressive prostate cancers to moderate-grade cancers responsive to therapy is a direct result of PSA screening. The study by Catalona et al comparing radical prostatectomy specimens from the pre-PSA era to those in the PSA era also illustrates this phenomenon. They demonstrated that 70-80% of men diagnosed with prostate cancer in the PSA era have tumors that are still pathologically organ-confined compared with fewer than 30% of men diagnosed in the pre-PSA era.[48]

Table 2. Prostate Cancer: Incidence and Deaths

YEAR	INCIDENCE	DEATHS
1995	244,000	40,400
1996	317,100	41,400
1997	334,500	41,800
1998	184,500	39,200
1999	179,300	37,000
2000	180,400	31,900
2001	198,100	31,500
2002	189,000	30,200
2003	220,900	28,900
2004	230,110	29,900

Adapted from http://www.cancer.org; Wingo PA et al. Cancer statistics, 1995. *CA Cancer J Clin* 1995;45:8-30; and Packer SL et al. Cancer statistics, 1996. *CA Cancer J Clin* 1996;65:5-27.

The effects of PSA screening are not exclusive to the United States as the recent introduction of PSA screening in the Austrian state of Tyrol led to a reduction in prostate mortality in a short period of time.[49] This finding, however, reflects the effect of aggressive downstaging (by identifying tumors at an earlier, more treatable stage) and successful treatment.

Different Guidelines from Different Medical Societies

Screening Recommended. Both the AUA and the ACS recommend annual screening. The AUA recommends an annual serum total PSA and a DRE beginning at 50 years of age in men with at least a 10-year life expectancy. Screening is started at 40 years of age if the patient is African-American or there is a positive family history of prostate cancer. The AUA also recommends a bone scan if serum total PSA is greater than 20 ng/mL. The ACS recommendations are similar but slightly modified.[50] Screening also commences at the age of 50 years if life expectancy is at least 10 years and begins with an annual serum total PSA and DRE. Screening is started at the age of 45 years if the patient is of African descent (sub-Saharan) and/or has a first-degree relative (e.g., brother or father) with prostate cancer. If the patient has multiple first-degree relatives with prostate cancer, annual screening begins at age 40 with an annual serum total PSA and a DRE. This protocol is modified depending on the initial serum total PSA as follows: 1) no annual testing until the age of 45 years if the serum total PSA is less than 1.0 ng/mL; 2) continue annual testing if serum total PSA is between 1.0 and 2.5 ng/mL; and 3) obtain a prostate biopsy if serum total PSA is greater than 2.5 ng/mL. Finally, the ACS also recommends annual PSA testing if the patient asks the clinician to make a decision for them.

Although we follow the guidelines of the AUA, the recommendations of the ACS are important to consider as they factor in the initial total serum PSA. It is not unreasonable to pursue a

Table 3. Prostate CA: Autopsy Prevalence in Asymptomatic Men

AGE GROUP	PREVALENCE
30-49	30%
50-59	10-42%
60-69	17-33%
70-79	25-66%
80+	18-100%

Source: U.S. Preventive Services Task Force, 1996

Table 4. Dynamic PSA and Determination of Recurrence

	NED	Local failure	Metastatic disease
PSA nadir	≤ 0.5	2.0-3.0	≥ 5.0
Time to nadir PSA	22-23 mos	17-20 mos	10-12 mos
PSADT	n/a	11-13 mos	3-6 mos

Key: NED = no evidence of disease; PSA = prostate-specific antigen; PSADT = PSA doubling time

prostate biopsy in a patient in his forties with a serum total PSA greater than 2.5 ng/mL, especially if he is African-American or has a family history of prostate cancer.

Screening Not Recommended. The U.S. Preventive Services Task Force (USPSTF) does not recommend PSA testing. Prior to 2002, their stance was that the net benefit of screening cannot be established without the results of any randomized controlled trials.[51] In September 2002, the Holmberg study (as mentioned earlier) was the first randomized controlled trial comparing radical prostatectomy vs. watchful waiting prospectively. This study did not demonstrate a reduced overall mortality among the treated group even though prostate cancer related mortality was reduced among the treated group.[43] Although the USPSTF admits that radical prostatectomy can reduce disease-specific mortality for localized prostate cancer; they argue that there is no good evidence documenting the benefits of other forms of therapy, including brachytherapy, external beam radiation therapy (EBRT), and androgen deprivation therapy. Furthermore, they cite the results of autopsy studies from men dying of causes unrelated to prostate cancer. These studies demonstrate a large prevalence of asymptomatic prostate cancer in men of all ages suggesting that although many men harbor prostate cancer, they rarely die from it. *(See Table 3.)* As a result, the UTPSTF still does not recommend PSA screening and awaits the results of the large-scale randomized trials described earlier to revisit their recommendation.

Screening Individualized. The American College of Physicians-American Society of Internal Medicine and the American Academy of Family Physicians recommend that screening be individualized for each patient. These societies recommend a discussion of the potential harms and benefits of PSA screening, prostate cancer diagnosis, and available treatment options before proceeding with PSA testing.[33]

PSA Monitoring After Treatment

PSA has an invaluable role as a tumor marker in the management and long-term follow-up of patients after definitive localized therapy (brachytherapy, external beam radiation therapy, and radical prostatectomy). PSA functions as a surrogate or endpoint by which to judge the response to therapy. PSA elevations provide evidence for biochemical recurrence of disease prior to the development of symptomatic or metastatic disease.

Brachytherapy. Prostate brachytherapy is a site-specific form of radiation therapy that involves the implantation of radioactive seeds into the prostate gland. At this time, this is a relatively new technology with little data on PSA kinetics and changes in response to therapy to make any definitive statements. The serum half-life of PSA is 1-3 months after brachytherapy. The results of a recent longitudinal study reveal that the greatest decline in PSA occurs during the first year after treatment. Furthermore, a one-year total serum PSA greater than 1.0 ng/mL is highly predictive of eventual PSA failure. Most failures occurred 18 months after brachytherapy.[52]

External Beam Radiation Therapy. The serum half-life of PSA is 1.9 months after external beam radiation therapy (EBRT), vs. a serum half-life of 3.2 days after radical prostatectomy. This difference is due to two factors: 1) death of cancerous cells may not be complete until 18-24 months after radiation therapy; and 2) residual benign prostate tissue that remains after radiation therapy still makes PSA.[53] Therefore, it is important to remember that PSA will still be detectable after radiation therapy. The PSA nadir after radiation therapy is important to document as it is predictive of biochemical disease-free survival. For instance, a total serum PSA nadir of less than or equal to 0.5 ng/mL is associated with an 83% biochemical disease-free rate at 5 years.[54]

After EBRT for localized prostate cancer, PSA should be checked immediately (as a baseline) and then every three to four months in the first two years to detect meaningful results, and every six months thereafter. Biochemical failure after radiation therapy is defined as three consecutive rises in PSA separated by 3-4 months each, as per the American Society of Therapeutic Radiation Oncology (ASTRO) criteria in 1997.[55]

In the absence of biochemical failure, dynamic PSA values can help differentiate between no evidence of disease (NED), local recurrence, and metastases after radiation therapy.[56] *(See Table 4.)*

Dynamic PSA values include the PSA nadir, time to nadir PSA, and the PSA doubling time (PSADT). The time to nadir PSA may take two years or longer to be achieved, however, it is directly related to disease-free survival. For example, one group reported that 92% of men whose time to nadir PSA was at least 36 months remained disease-free as compared to 30% of men whose time to nadir PSA was fewer than 12 months.[57] The

Table 5. Risk Factors for Local vs. Metastatic Recurrence

	GLEASON	SEMINAL VESICLE INVOLVEMENT	LYMPH NODE INVOLVEMENT	TIME TO DETECTABLE PSA	PSADT	PSA VELOCITY
Local	≤ 5	Negative	Negative	> 1 yr after RP	> 6 mos	< 0.75 ng/mL
Distant	> 7	Positive	Positive	< 6 mos	< 6 mos	> 0.75 ng/mL

PSADT can differentiate local from metastatic recurrence. A PSADT of fewer than eight months predicts metastatic relapse, especially if the rise begins within one year of radiation therapy.[58] In summary, PSA nadirs at a higher level, begins to rise sooner after radiation therapy, and rises (doubles) more rapidly with metastases.

Finally, the phenomenon of "PSA bounce" must be kept in mind when interpreting serial PSA levels after radiation therapy. "PSA bounce" is a transient rise in PSA ranging from 0.3 to 3.4 ng/mL that is observed 18-24 months after radiation therapy. It reflects radiation-induced prostatitis and is not associated with an increased risk of disease recurrence.[53]

Radical Prostatectomy. Biochemical failure after radical prostatectomy is defined as the appearance of detectable PSA. Using conventional PSA immunoassays that have a lower limit of detection of 0.1 ng/mL, detectable PSA, and hence biochemical failure, is consistent with the detection of serum levels greater than 0.2 ng/mL on two or more occasions.[59] Failure of PSA to become undetectable after surgery reflects residual or persistent disease. Identification of biochemical failure is essential as the average time from biochemical failure to the development of clinical disease after radical prostatectomy is eight years.[60] As with post-EBRT, dynamic PSA values and other pathologic factors can help differentiate between the likelihood of local vs. metastatic recurrence.[61,62] *(See Table 5.)*

In men who have developed biochemical recurrence after radical prostatectomy, androgen deprivation therapy (ADT) is one of many treatment options. Nadir PSA and percentage of PSA decline at 3-6 months, following the institution of ADT, predict progression-free survival in this group. In fact, prolonged progression free survival is associated with an undetectable PSA or a 90% or greater decline in PSA at 3-6 months.[63]

Future Tumor Markers. Recently, Partin et al demonstrated that complexed PSA as a single test increases specificity for prostate cancer over total PSA. Using cutoffs of complexed PSA (1.5-8.3 ng/mL) and total PSA that provided a sensitivity of 80-95% for prostate cancer, this multicenter prospective study demonstrated increased specificity of complexed PSA over total PSA by 6.2-7.9%.[64] However, a prior study led by Partin as well revealed that complexed PSA was equivalent to total PSA in predicting organ-confined disease.[65] Currently, complexed PSA is not routinely used but may serve as an important tumor marker in the future. Likewise, other investigators are developing immunoassays that can detect the amount of PSA bound to AMG in the hopes that this fraction of bound PSA might have some clinical application.

Other directions for tumor markers include the search for novel molecular markers such as nuclear morphometry and DNA ploidy. Preliminary results reveal a correlation between abnormal findings and the response to ADT, the risk of tumor progression, overall survival, and the development of metastases. Two actively researched proteins are human glandular kallikrein 2 protein (hk2) and prostate-specific membrane antigen (PSMA). Hk2 is a serine protease that shares 80% homology with PSA and cleaves pro-PSA to produce enzymatically active PSA.[66] It demonstrates increased staining intensity with more aggressive prostate cancers and may have a role in increasing specificity for prostate cancer detection in men with elevated PSA and increasing sensitivity for early detection of cancer in men with normal PSA levels. Further research is being conducted. PSMA is a transmembrane glycoprotein that is more frequently expressed by prostatic epithelium in more aggressive prostate cancers. It is currently being used in ProstaScint scans which identify PSMA expression locally at the prostatic fossa or distantly in the body. These scans are an effort to detect recurrent and/or persistent disease after prostate cancer treatment. Although ProstaScint scans enhance the ability to diagnose disease over conventional modalities (e.g., MRI, CT, and PET scans), they still lack tremendous sensitivity (only 72%) and accuracy (only 82%).[67] Active efforts, however, are underway to improve the utility of PSMA as a tumor marker. Finally, epidemiologic evidence has linked increased plasma levels of insulin-like growth factor (IGF)-1 and decreased plasma levels of IGF binding protein-3 with an increased risk of prostate cancer. Recent evidence, however, suggested that levels of these substances do not predict evidence of cancer in prostate biopsies. Therefore, although they may be linked to increased prostate cancer risk, they cannot be used as tumor markers for prostate cancer themselves.[68]

Summary

The AUA advocates prostate cancer screening in men with an annual PSA test and a DRE starting at 50 years of age or at 40 years of age if they are African-American or have a family history of prostate cancer. PSA is organ-specific but not cancer-specific, and as a result, has lower specificity in men with BPH and older men. Currently, the AUA recommends that all men with a serum PSA greater than 4.0 ng/mL should undergo a prostate biopsy. Numerous strategies, however, have evolved to improve PSA's sensitivity in younger men and its specificity in older men that may become part of routine clinical practice in the future. Trends that are becoming popular include use of percentage free PSA (less than 15-25%) in serum to determine

whether or not to perform an initial or repeat biopsy in someone with an elevated PSA (4-10 ng/mL) and a benign DRE or in someone at increased risk of prostate cancer (African-American, positive family history, and/or younger than 60 years) with a serum PSA 2.5-4.0 ng/mL and a benign DRE; use of PSA velocity greater than 0.75 ng/mL/year to determine whether or not to perform an initial or repeat biopsy in someone with a normal serum PSA and a benign DRE; applying age-specific reference ranges of PSA to men younger than 60 years in determining whether or not to perform a prostate biopsy; screening men biannually if their DRE is benign and their initial serum PSA is less than or equal to 2.0 ng/mL; and terminating screening after 65 years of age if the total serum PSA is less than or equal to 1.0 ng/mL.

These trends have not been endorsed or recommended universally by any medical societies, but some physicians have adopted these screening strategies into their practice.

Prostate cancer is the most common non-cutaneous malignancy in the world afflicting men today and the second leading cause of cancer death in the United States. Prior to the advent of PSA, prostate cancer was usually detected at a clinically advanced stage with little hope of a cure with treatment. The introduction of PSA allowed for the early detection of prostate cancer. This initially corresponded to an initial rise in the incidence of prostate cancer which subsequently decreased and has now plateaued. Critics argue that the cancers diagnosed are clinically insignificant and that current treatments do not improve survival as no randomized controlled clinical trials have been conducted that demonstrate greater survival with early detection and treatment of prostate cancer. PSA screening, however, has led to a reduction in the mortality and morbidity associated with prostate cancer. The tumors that are detected are clinically significant and amenable to therapy. In addition, radical prostatectomy has been shown to reduce prostate cancer mortality over watchful waiting. As a tumor marker, PSA is also useful in the monitoring of patients after they have received localized therapy. Trends in PSA dynamics can help differentiate between local or distant recurrence. Finally, other potential tumor markers are being investigated that may someday provide greater sensitivity and specificity over PSA. Until that day, however, PSA will remain the best tumor marker for prostate cancer. It is important for the primary care clinician to be aware of potential risks and benefits relevant to PSA testing, and to so inform their patients. Concerning trends in serial PSA tests may herald earlier referral to a urologist.

References

1. Jemal A, et al. Cancer statistics, 2002. *CA Cancer J Clin* 2002;52: 23-47.
2. Scardino PT. The prevention of prostate cancer—The dilemma continues. *N Engl J Med* 2003; 349: 297-299.
3. Gann PH, et al. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;273:289-294.
4. Potosky AL, et al. The role of detection in the rising incidence of prostate cancer. *JAMA* 1995;273:548-552.
5. Cookson MS. Prostate cancer: Screening and early detection. *Cancer Control* 2001;8;133-140.
6. Crawford D, et al. The history of prostate specific antigen. In: Brawer MK, ed. *Prostate Specific Antigen*. 1st ed. New York: Marcel Decker; 2001:2.
7. Crawford D, et al. The history of prostate specific antigen. In: Brawer MK, ed. *Prostate Specific Antigen*. 1st ed. New York: Marcel Decker; 2001:2-5.
8. Stenman UH. Biochemistry and basic science. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:11.
9. Herschman JD, et al. Effect of ejaculation on serum total and free prostate-specific antigen concentrations. *Urology* 1997;50:239-243.
10. Stenman UH. Biochemistry and basic science. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:16-8.
11. Catalona WJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; 324:1156-1161.
12. Brawer MK. Prostate-specific antigen: Current status. *CA Cancer J Clin* 1999;49:264-281.
13. Miller GJ, et al. Prostate cancer: Serum and tissue markers. *Rev Urol* 2001;3:S11-S19.
14. Catalona WJ, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: A prospective multicenter clinical trial. *JAMA* 1998;279:1542-1547.
15. Li PE and Lange PH. Free and total PSA. In: Brawer MK, ed. *Prostate Specific Antigen*. 1st ed. New York: Marcel Decker; 2001:106-107.
16. Jhaveri FM. PSA velocity. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:63.
17. Oesterling JE, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860-864.
18. Richardson TD, et al. Age-specific reference ranges for serum prostate-specific antigen. *Urol Clin North Am* 1997;24:339-351.
19. Morgan TO, et al. Age-specific reference ranges for prostate-specific antigen in black men. *N Engl J Med* 1996;335:304.
20. Oesterling JE, et al. Serum prostate-specific antigen in a community-based population of healthy Japanese men: Lower values than for similarly aged white men. *BJU* 1995;75:347.
21. Partin AW, et al. Standard versus age-specific prostate specific antigen reference ranges among men with clinically localized prostate cancer: A pathological analysis. *J Urol* 1996;155:1336-1339.
22. Reissigl A, et al. Comparison of different prostate-specific antigen cutpoints for early detection of prostate cancer: Results of a large screening study. *Urology* 1995;46:662.
23. Oesterling JE, et al. The use of age-specific reference ranges for serum prostate specific antigen in men 60 years old or older. *J Urol* 1995;153:1160-1163.
24. Blake O, et al. Age-specific PSA. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:72.

25. Catalona WJ, et al. Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: Receiver operating characteristic curves. *J Urol* 1994;152:2037-2042.
26. Littrup PJ, et al. Cost-effective prostate cancer detection. Reduction of low-yield biopsies. Investigators of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1994;74:31-46.
27. Babaian RJ, et al. The incidence of prostate cancer in a screening population with a serum prostate specific antigen between 2.5 and 4.0 ng/mL: Relation to biopsy strategy. *J Urol* 2001;165:757-760.
28. Smith DS, et al. Use of lower prostate specific antigen cutoffs for prostate cancer screening in black and white men. *J Urol* 1998;160: 1734-1738.
29. Catalona WJ, et al. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/ml and benign prostate examination: Enhancement of specificity with free PSA measurements. *JAMA* 1997;277:1452-1455.
30. Punglia RS, et al. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. *N Engl J Med* 2003;349:335-342.
31. Ornstein DK, et al. PSA and early detection. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001: 144.
32. Pearson JD, et al. When is PSA testing no longer necessary? *J Urol* 1998;159:178-180.
33. Barry MJ. Prostate-specific antigen testing for early diagnosis of prostate cancer. *N Engl J Med* 2001;344:1373-1377.
34. Hankey BF, et al. Cancer surveillance series: Interpreting trends in prostate cancer—part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. *J Natl Cancer Inst* 1999;91:1017-1024.
35. Stephenson RA. Population-based prostate cancer trends in the PSA era: Data from the Surveillance, Epidemiology, and End Results (SEER) Program. *Monogr Urol* 1998;19:3.
36. Wingo PA, et al. Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988-95. *Cancer Causes Control* 2000;11:497-512.
37. Tarone RE, et al. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. *Epidemiology* 2000;11:167-170.
38. Partin AW, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: A multi-institutional update. *JAMA* 1997;277:1445.
39. Http://www.beckman.com/products/applications/diseasemgmt/prostate.asp. Accessed 4/13/2004.
40. Berger AP, et al. Complication rate of transrectal ultrasound guided prostate biopsy: A comparison among 3 protocols with 6, 10, and 15 cores. *J Urol* 2004;171:1478-1480.
41. Gerber GS, et al. Results of radical prostatectomy in men with clinically localized prostate cancer. *JAMA* 1996;276:615-619.
42. Walsh PC. Surgery and the reduction of mortality from prostate cancer. *N Engl J Med* 2002;347:839-840.
43. Holmberg L, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347:781-789.
44. Epstein JI, et al. Pathologic and clinical findings to predict tumor extent of non-palpable (stage T1c) prostate cancer. *JAMA* 1994; 271:368.
45. Slawin KM, et al. Screening for prostate cancer: An analysis of the early experience. *CA Cancer J Clin* 1995;45:134-147.
46. Isola J, et al. Predictors of biological aggressiveness of prostate specific antigen screening detected prostate cancer. *J Urol* 2001;165: 1569-1574.
47. Perrotti M, et al. Trends in poorly differentiated prostate cancer 1973 to 1994: Observation from the Surveillance, Epidemiology, and End Results database. *J Urol* 1998;16:811-815.
48. Catalona WJ, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6630 men. *J Urol* 1994;151:1283-1290.
49. Bartsch G, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001;58:417-424.
50. Smith RA, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2002:52:8-22.
51. Harris R, et al. Screening for prostate cancer: An update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;137:917-929.
52. Iannuzzi CM, et al. PSA kinetics following I-125 radioactive seed implantation in the treatment of T1-T2 prostate cancer. *Radiat Oncol Investig* 1999;7:30-35.
53. Collins SM, et al. Prostate specific antigen as a predictor of progression after primary curative treatment for prostate cancer. *AUA Update Series* 2003;22 (Lesson 24):186-191.
54. Shipley WU, et al. Radiation therapy for clinically localized prostate cancer: A multi-institutional pooled analysis. *JAMA* 1999;281:1598.
55. Consensus statement: Guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035.
56. Crook J. PSA and radiation therapy. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:207.
57. Kestin LL, et al. Defining biochemical cure for prostate carcinoma patients treated with external beam radiation therapy. *Cancer* 1999; 86:1557-1566.
58. Zagars GK, et al. Kinetics of serum prostate specific antigen after external beam radiation for clinically localized prostate cancer. *Radiother Oncol* 1997;44:213.

CME Objectives

To help physicians:

- summarize the most recent significant primary care medicine-related studies;
- discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;
- evaluate the credibility of published data and recommendations; and
- describe the pros and cons of new testing procedures.

59. Lange PH, et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989;141: 873-879.
60. Pound CR, et al. Prostate specific antigen after radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin N Am* 1997;24:395.
61. Wonjo KJ, et al. Percent of free prostate-specific antigen values in men with recurrent prostate cancer after radical prostatectomy. *Urology* 1998;52:474.
62. Roberts SG, et al. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clin Proc* 2001;76:576.
63. Smith JA Jr, et al. Serum markers as a predictor of response duration and patient survival after hormonal therapy for metastatic cancer of the prostate. *J Urol* 1997;157:1329.
64. Partin AW, et al. Complexed prostate-specific antigen improves specificity for prostate cancer detection: Results of a prospective multicenter clinical trial. *J Urol* 2003;170:1787-1791.
65. Sokoll LJ, et al. Complexed prostate-specific antigen as a staging tool for prostate cancer: A prospective study in 420 men. *Urology* 2002;60:18-23.
66. Klee GG, et al. Human glandular kallikrein 2 Protein. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001: 283.
67. Holmes EH. Prostate specific membrane antigen. In: Brawer MK, ed. *Prostate Specific Antigen.* 1st ed. New York: Marcel Decker; 2001:303.
68. Ismail AH, et al. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. *J Urol* 2002;168:2426-2430.

Physician CME Questions

20. At what age should PSA screening begin for a Caucasian man with no family history of prostate cancer?
    A. Age 30
    B. Age 40
    C. Age 45
    D. Age 50
    E. At any age when he complains of bone pain

21. What has been the most common clinical presentation of prostate cancer in the last 10 years?
    A. T1c (nonpalpable, identified by needle biopsy)
    B. T2a (palpable, involves one lobe)
    C. T2b (palpable, involves both lobes)
    D. T3 (tumor extends through prostate capsule)
    E. T4 (tumor fixed or invades adjacent structures other than seminal vesicles)

22. Which circulating form of PSA in serum is *not* recognized by conventional PSA immunoassays?
    A. Free PSA
    B. PSA-ACT
    C. PSA-API
    D. PSA-AMG
    E. Total PSA

23. Which of the following interventions does *not* appreciably raise total serum PSA levels?
    A. Ejaculation
    B. Digital rectal exam
    C. Urethral catheterization
    D. Prostate needle biopsy
    E. Transurethral resection of the prostate

Answer Key:
20. D; 21. A; 22. D; 23. B.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

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Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Atherosclerosis Reversed With Lipid-Lowering Drugs

When it comes to treating lipids in patients with heart disease, the mantra may be, "The lower the LDL, the better." Data from the multicenter Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial indicate that aggressive reduction of atherogenic lipoproteins prevents progression of disease. The study randomized 654 patients with coronary disease to pravastatin 40 mg/d (moderate lipid-lowering regimen) or atorvastatin 80 mg/d (intensive lipid-lowering regimen). After 18 months of therapy, 502 patients were evaluable with baseline and post-treatment intravascular ultrasounds. The primary outcome was percentage change in atheroma volume. Intensive lipid-lowering therapy with atorvastatin resulted in a decrease of LDL cholesterol from an average of 150 mg/dL to 79 mg/dL, while pravastatin therapy resulted in a decrease to 110 mg/dL. C-reactive protein decreased 36.4% with atorvastatin and 5.2% with pravastatin ($P < .001$). Progression of coronary atherosclerosis did not occur in the atorvastatin group, while coronary atherosclerosis progression did occur in the pravastatin group compared with baseline. The authors suggest that the data support aggressive lipid lowering, below the current national guidelines for secondary prevention in patients with coronary atherosclerosis (*JAMA*. 2004;291:1071-1080). It is of note that this study employed the relatively new technology of coronary ultrasound, which more effectively measures plaque volume as opposed to coronary angiography, which merely quantifies the lumen. Still, this technology is relatively new, as pointed out in an accompanying editorial, but the results appear to be valid. The editorial also points out that the moderate lipid-lowering regimen in the study did not achieve levels of LDL lowering recommended by national guidelines, which suggest lowering LDL below 100 mg/dL for secondary prevention. The authors recommend focus on all risk factors in patients with coronary disease, including LDL lowering at least to levels recommended in national guidelines (*JAMA*. 2004;291:1132-1134).

Positive Alendronate Data in Osteoporosis

Does alendronate prevent fractures after 10 years of therapy? According to a new multicenter placebo-controlled trial, the drug is effective and safe over 10 years in women with osteoporosis. Data from the study are from a follow-up of 2 identical 3-year trials of alendronate therapy followed for an additional 7 years. In this follow-up study, women were randomized to 3 daily doses of alendronate or placebo. The 3 active treatment groups included women who took alendronate 5 mg or 10 mg daily for the entire 10-year study. A third group took 20 mg of

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alendronate daily for 2 years and 5 mg daily in years 3, 4, and 5 followed by 5 years of placebo. This last group was called the "discontinuation group." Women in the original placebo group ended up receiving alendronate in years 4 and 5 and then were discharged. There were 247 women who participated in all 4 phases of the study. Treatment with 10 mg of alendronate daily for 10 years resulted in statistically significant increases in bone mineral density at the following sites: 13.7% increase, lumbar spine; 10.3%, trochanter; 5.4%, femoral neck; and 6.7%, proximal femur as compared with baseline values ($P < .001$; 95% CI for all groups). The percentage increases for the 5 mg group were 9.3%, lumbar spine; 4.8%, trochanter; 2.8%, femoral neck; and 2.9%, proximal femur. Alendronate also resulted in fewer fractures and lower rates of loss of stature over the 10-year period. Discontinuation of alendronate resulted in a gradual loss of bone density. The authors conclude that continued treatment with 10 mg of alendronate daily for 10 years was associated with a sustained therapeutic effect on bone density and bone remodeling. Concern over increase fracture rates with bisphosphonates over time was not validated by the study (*N Engl J Med*. 2004;350:1189-1199).

NSAIDs For Myocardial Infarction

Nonaspirin NSAIDs, especially ibuprofen and naproxen, may protect against myocardial infarction in patients who are not taking aspirin. Researchers from Pennsylvania conducted a case-control study with cases of first, nonfatal MI identified prospectively with random controls from the community. The use of a nonaspirin NSAID was associated with a significant reduction in MI compared to those not using aspirin (OR 0.53; 95% CI). The adjusted odds ratio for ibuprofen was 0.52 and for naproxen was 0.48. The odds ratio for aspirin alone in this study was 0.79. The combination of aspirin with a nonaspirin NSAID trended toward increased risk of MI and worsened as the frequency of nonaspirin NSAIDs use increased; however, the confidence intervals for this determination were very wide. The authors conclude that in patients who are not taking aspirin, a nonaspirin NSAID is associated with a reduced risk of MI. The concomitant use of aspirin for cardioprotection along with a nonaspirin NSAID needs further study (*J Am Coll Card*. 2004;43:985-993).

Four-Hour Window for CAP Patients

Medicare patients with community-acquired pneumonia (CAP) fare better if they receive their first dose of antibiotics within 4 hours of hospitalization, according to new study. The records of nearly 14,000 Medicare patients admitted for CAP, who had not received antibiotics as outpatients, were reviewed. The administration of an antibiotic within 4 hours of arrival to the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR] 0.85; 95% CI, 0.74-0.98), reduced mortality within 30 days of admission (11.6% vs 12.7%; AOR 0.85; 95% CI, 0.76-0.95), and reduced length of stay as measured by hospitalization exceeding the 5-day median (42.1% vs 45.1%; AOR 0.90; 95% CI, 0.83-0.96). Early administration of antibiotics also resulted in a 0.4-day shorter length of stay. The study did show that the majority of patients (60.9%) received antibiotics within 4 hours of arrival (*Arch Int Med*. 2004;164:637-644). Current CAP guidelines generally recommend initiation of an antibiotic within 8 hours of arrival, but this study suggests that those guidelines may not be aggressive enough.

FDA Actions

Rofecoxib (Vioxx) has been approved for the treatment of migraine attacks with or without aura in adults. The approval was based on a large study that showed that the single dose of rofecoxib, either 25 or 50 mg, effectively reduced migraine pain at 2 hours and reduced the use of rescue medications.

The FDA has issued a Public Health Advisory about the need for physicians, patients, and families to closely monitor adults and children with depression when beginning treatment certain antidepressants and has asked the manufacturers of these drugs to include new warnings in their labeling about the potential for increased suicidality. The antidepressant drugs are the serotonin reuptake inhibitors fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro); and the non-SSRI antidepressants bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). ■