What to Do with an Abnormal PSA Test

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Take advantage of the use of total PSA thresholds for predicting prostate cancer risk and determining the need for prostate biopsy.
2. Distinguish prostate cancer from benign conditions based on the relative proportions of complexed and free forms.
3. Use PSA density as a means to correct for the effect of prostate volume on the PSA level.
4. Explain the evolving role of PSA kinetics in the prediction of aggressive prostate cancer.
5. Perform the calculations for PSA velocity and PSA doubling time.

ABSTRACT

For more than a decade, prostate-specific antigen (PSA) has been used for prostate cancer screening. Over the years, this screening has been continually refined, including investigation into the use of lower total PSA thresholds, PSA isoforms, and PSA kinetics. This review describes the evolution of prostate cancer screening and provides clinical insights into the informed use of PSA and its adjunctive measurements. The Oncologist 2008;13:299–305

INTRODUCTION

It was estimated that there would be 218,890 new cases of and 27,050 deaths from prostate cancer in 2007 [1]. Because of its high prevalence in the adult male population, the optimal protocol for prostate cancer screening continues to be the subject of considerable research and debate.

HISTORY OF PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen (PSA) is a serine protease found in the seminal coagulum that was first used by forensic scientists as a marker for human semen. In the late 1970s, the initial laboratory studies were conducted to evaluate the relationship between PSA and prostatic disease. Wang et al. [2] showed that PSA could be measured in human serum, and Stamey et al. [3]
subsequently reported that PSA diffused into the bloodstream from prostate cancer tissue at a 10-fold higher amount per gram of tissue than from benign prostatic tissue.

However, the initial use of PSA in clinical medicine was not for prostate cancer screening but rather as a marker for recurrence after definitive treatment. In 1986, the U.S. Food and Drug Administration (FDA) approved the PSA test for this indication.

It was not until the late 1980s that the first clinical studies were initiated to examine the role of PSA in prostate cancer screening. Previously, most prostate cancer cases were diagnosed either through a suspicious digital rectal examination (DRE) or as an incidental finding in the prostate chips from transurethral resection for presumed benign prostatic hyperplasia (BPH).

**TOTAL PSA MEASUREMENT**

The largest study on PSA for prostate cancer screening, led by the senior author, enrolled 36,000 men from 1989–2001. In the first phase of the study, 1989–1991, a PSA level >4 ng/ml prompted further evaluation with DRE and transrectal ultrasound (TRUS), and biopsy was then recommended if either was abnormal [4]. That portion of the study clearly demonstrated that the use of PSA in conjunction with DRE performed better than DRE alone. As a result, in 1991 the study protocol was revised such that all men received both a PSA test and DRE, with abnormalities in either test leading to a recommendation for biopsy. This study ultimately showed that PSA-based screening led to cancer detection at an earlier and more curable stage [5]. Following the publication of a large multi-institutional trial [6], PSA was approved by the FDA in 1994 as an aid to the early detection of prostate cancer, using a threshold of 4 ng/ml as the upper limit of normal.

Nevertheless, subsequent studies have demonstrated that a considerable proportion of men with total PSA levels <4 ng/ml have histological evidence of prostate cancer. For example, the Prostate Cancer Prevention Trial randomized 18,882 men to either finasteride or placebo for a 7-year period to evaluate the differences in prostate cancer detection between the groups [7]. According to their protocol, men who had a PSA <4 ng/ml and negative DRE on the annual screenings during the study were offered an empiric end-of-study biopsy. Among men with serum PSA levels ≤0.5, 0.6–1.0, 1.1–2.0, 2.1–3.0, and 3.1–4.0 ng/ml, prostate cancer was detected in 6.6%, 10.1%, 17.0%, 23.9%, and 26.9%, respectively.

Not only is there a strong relationship between the total PSA level and the presence of prostate cancer, but the PSA level also correlates directly with prostate cancer aggressiveness. In a large radical prostatectomy series, Antenor et al. [8] reported 10-year progression-free survival rates of 88%, 80%, 76%, and 61% in men with a preoperative PSA level of 2.6–4.0, 4.1–7.0, 7.1–10.0, and >10 ng/ml, respectively. The corresponding rates of organ-confined disease were 81%, 74%, 72%, and 60%, respectively (p < .0001). Thus, the PSA level at diagnosis has obvious implications for treatment with curative intent.

Based upon the growing evidence that prostate cancers detected at lower total PSA levels have more favorable characteristics, the senior author lowered the PSA threshold for recommending biopsy to 2.5 ng/ml in 1995. Similarly, many other groups in the U.S. and internationally are currently using thresholds in the range of 2.5–3.0 ng/ml to recommend prostate biopsy.

Finally, PSA is also useful to predict future prostate cancer risk. Using long-term follow-up data from the Physician’s Health Study, Gann et al. [9] showed that, compared with the reference group (baseline PSA level <1 ng/ml), men with baseline PSA levels of 1.01–1.5, 1.51–2.0, 2.01–3.0, 3.01–4.0, 4.01–10.0, and >10 ng/ml had a 2.2-, 3.4-, 5.5-, 8.6-, 22.2-, and 145.3-fold higher risk for a prostate cancer diagnosis in the next 10 years [9]. In 796 men from the Baltimore Longitudinal Study on Aging, Fang et al. [10] showed that men in their 40s with a PSA level ≥0.6 ng/ml (the age-specific median) were significantly more likely to subsequently develop prostate cancer. Specifically, the 25-year prostate cancer–free probability was 89.6% for men with a baseline PSA level <0.6 in their 40s, compared with 71.6% in men with a higher baseline PSA. Similarly, men in their 50s with a median PSA level below the age-specific median had an 83.6% 25-year prostate cancer–free probability, compared with 58.9% for men who had a higher baseline PSA. In a later study, our research group showed that men in their 40s and 50s from our prostate cancer screening study with a baseline PSA level above the age-specific median had a 14.6- and 7.6-fold higher risk for subsequent prostate cancer detection, respectively [11]. In light of these collective findings, some professional organizations are now recommending that all men undergo a baseline PSA measurement at age 40, which can provide useful information about their risk profile and help to individualize the subsequent screening protocol [12].

Despite these multiple applications of PSA testing, there are several problems that complicate its use in daily practice. First, PSA can also be elevated in benign prostatic conditions, limiting its specificity for prostate cancer. Even certain medications (e.g., finasteride), ejaculation, and prostate manipulation (e.g., catheterization, cystoscopy, prostatic massage) can alter PSA levels.

Also, because PSA correlates closely with prostate cancer risk along the full spectrum of PSA levels, there is really...
no threshold below which the risk for prostate cancer is zero. Thus, the determination of PSA cutpoints to be used in clinical practice has remained controversial.

To further complicate matters, the initial studies on PSA used assays that were standardized to the Hybritech standard. These studies were used to establish many of the thresholds and PSA parameters that continue to be used in practice today. Nevertheless, in 1999, the Expert Committee on Biological Standardization of the World Health Organization (WHO) introduced alternate reference material for PSA (the so-called 96/670 standard material). Today, about half of the commercially available PSA tests are standardized to Hybritech and the other half to the WHO standard. Yet the PSA results are approximately 23% different between the two [13, 14]. Patients and physicians are largely unaware of which PSA standard has been used when interpreting individual measurements, and the effect that this may have had on clinical outcomes is unknown. Certainly greater awareness of this issue and the use of the same assay on a serial basis could help prevent such problems. As a result of these difficulties, numerous variations on the PSA measurement have evolved to further enhance its utility for the prediction of prostate cancer risk and prognostication. These adjunctive measures are described in the sections to follow.

**FREE PSA**

PSA circulates in the bloodstream in several different forms, and the relative proportion of these forms is highly variable. In general, PSA can bind to natural substrates like α-1-antichymotrypsin (complexed PSA) or circulate in unbound (free) forms [15].

For more than a decade, the proportion of PSA circulating in the free form (percent free PSA) has been used to help distinguish BPH from prostate cancer. For example, a large multi-institutional study showed that 56% of men with <10% free PSA had prostate cancer, compared with only 8% of men with >25% free PSA [16]. Free PSA was approved by the FDA in 1998 as an aid to prostate cancer detection in men with total PSA levels of 4–10 ng/ml and is usually reported together with the total PSA level to help guide clinicians as to what is causing the PSA elevation.

More recently, the use of free PSA has been further refined by the discovery that it is actually comprised of three different isoforms. Two forms—“B” (BPH-PSA) and “i” (inactive-PSA) appear to be relatively greater with BPH [17], while proenzyme (pro-PSA) isoforms are found in a greater proportion in men with prostate cancer. For example, Sokoll et al. [18] reported that, in men with total PSA levels of 2.5–4.0 ng/ml, the percentage of pro-PSA was 50.1% in men with prostate cancer versus 35.5% in men with a negative prostate biopsy. A higher percentage of pro-PSA also has been associated with a higher risk for prostate cancer in men with total PSA levels of 4.0–10 ng/ml [19]. Finally, there is preliminary evidence that a higher proportion of pro-PSA may be associated with higher Gleason grade and a greater likelihood of extracapsular tumor extension [20]. Additional studies are needed to further elucidate the role of these PSA isoforms in prostate cancer screening and management.

**PSA DENSITY**

Because PSA is produced by prostatic epithelial cells, it makes sense that larger prostate glands produce more PSA. Thus, an evaluation of the PSA level in relation to the size of the prostate is another useful way to differentiate prostate cancer from benign enlargement. To calculate PSA density (PSAD), the PSA level is simply divided by the prostate volume, typically measured by TRUS.

Benson et al. [21, 22] reported that the mean PSAD was significantly higher in men with prostate cancer than in those with BPH (0.581 versus 0.044, respectively; p < .002). One difficulty with the use of PSAD is that prostate volume assessment by DRE is particularly unreliable [23], necessitating the use of ultrasonography. Because ultrasonography is more invasive than a simple serologic test, it is typically performed only at the time of prostate biopsy, and therefore may be less useful in determining the need for prostate biopsy. This notwithstanding, among men with a positive prostate biopsy, PSAD is useful for prognostication. In a multi-institutional trial of 773 men treated with radical prostatectomy, 74% of men with a preoperative PSAD <0.15 had favorable pathology compared with only 36% of men with a higher PSAD [16]. Thus, PSAD is now among the parameters being used as a surrogate marker for prostate cancer aggressiveness to help determine whether active surveillance is a reasonable strategy for men with otherwise low-risk, low-volume prostate cancer [24].

**PSA KINETICS**

An increasingly popular way to use the total PSA measurement is by evaluating changes over time. Indeed, a rapidly rising PSA is significantly more likely to occur with prostate cancer than with BPH.

One way to express longitudinal PSA trends is called PSA velocity (PSAV). A simplified equation for PSAV is: (PSA2 − PSA1) ÷ (time elapsed between measurements). However, some experts believe that it is most reliable when at least three component PSA measurements are used in the calculation, to help reduce background variability resulting from short-term physiologic PSA fluctuations.

In 1992, Carter et al. [25] showed that, in men with PSA
levels of 4–10 ng/ml, a PSAV >0.75 ng/ml per year was a significant predictor of prostate cancer. However, the majority of men have total PSA levels <4 ng/ml, and the annual PSA changes in men with BPH are actually very small (~0.1 ng/ml per year). Furthermore, Carter and colleagues recently reported that men with a PSAV >0.35 ng/ml per year many years prior to diagnosis were significantly more likely to die from prostate cancer over a decade later [26]. Several other research groups have also suggested that a PSAV threshold of approximately 0.4 ng/ml per year is useful for early prostate cancer detection in conjunction with the total PSA level, particularly in young men [27, 28]. As a result of these studies, in its 2007 guidelines the National Comprehensive Cancer Network may recommend that men with a PSA level <2.5 ng/ml should undergo prostate biopsy if their PSAV exceeds 0.35 ng/ml per year to aid in the detection of curable disease [12].

On the other end of the spectrum, men with a PSAV >2 ng/ml per year in the year prior to diagnosis have a significantly higher prostate cancer–specific mortality rate after both radiation therapy and radical prostatectomy [29, 30]. Thus, PSAV appears to be a surrogate marker for prostate cancer aggressiveness.

An alternate way to describe PSA kinetics is the PSA doubling time (PSADT). This can be calculated by the formula: \[ \frac{\log 2 \times dT}{\log PSA2 - \log PSA1} \]. For many years, PSADT has been used in the setting of biochemical recurrence after prostate cancer treatment. Pound et al. [31] showed that a postoperative PSADT <10 months was significantly associated with metastatic disease. More recently, Freedland et al. [32] reported on 379 patients with biochemical progression after radical prostatectomy. They showed that a shorter postoperative PSADT was significantly associated with both cancer-specific and overall mortality. Moreover, men with a postoperative PSADT <15 months represented a particularly high-risk population in which prostate cancer accounted for 90% of all deaths at 15 years [32].

Some groups have attempted to instead apply PSADT in the pretreatment setting. For instance, in a large Canadian active monitoring cohort, a PSADT >3 years is considered a sign of more aggressive disease and is used to trigger intervention [33]. Nevertheless, the PSADT calculation is much simpler in recurrence after radical prostatectomy, wherein the PSA starts at zero and subsequently rises. In the pretreatment setting, men start out with very different PSA levels, and the PSADT calculation is strongly influenced by the baseline PSA level (i.e., patients who start with a higher PSA level have to have a greater increase in PSA for it to double). Overall, most clinicians are more facile with the application of PSAV among men with newly diagnosed prostate cancer.

**DISCUSSION**

Patients and physicians alike have been receiving mixed messages about the advisability of PSA-based prostate cancer screening from various professional organizations. Those that favor offering PSA screening are the American Cancer Society, the American Urological Association, and the National Comprehensive Cancer Center Network, whereas the American College of Physicians and the U.S. Preventive Services Task Force are less enthusiastic about PSA screening or feel there is insufficient evidence to recommend it. The National Cancer Institute and the Center for Communicable Diseases are fairly neutral while awaiting additional evidence.

Despite these disparate recommendations, prostate cancer screening with PSA is very widespread in the U.S. Between 2001 and 2004, >50% of men >50 years old and 87% of male physicians had a PSA test [34].

PSA screening was introduced in the early 1990s, and there followed a striking increase in the incidence rates of prostate cancer, as the inventory of previously undiagnosed cases were discovered. Since then, the incidence rates have returned to lower levels but have continued to rise gradually at a level higher than before the introduction of PSA screening.

The first sign of success of PSA screening was a 70% reduction in the proportion of men who presented with metastatic disease at the time of diagnosis. The prostate cancer mortality rates that had been rising steadily for decades leveled off in 1995, and from then through 2003 (the latest figures available), there has been a 32.5% reduction in the age-adjusted prostate cancer–specific mortality rate [35].

Perhaps the most convincing evidence of the success of PSA screening is the report by Jemal et al. [36] examining the relationship between PSA screening and the stage of prostate cancer at diagnosis and the prostate cancer death rates in population-based regions of the U.S., representing nearly two thirds of the U.S. population. They found that, in regions where PSA testing was most prevalent, there was a correspondingly lower proportion of men that presented with metastatic disease and a lower prostate cancer mortality rate.

In recent years, the question has been raised about whether PSA has fallen victim to its own success, resulting in the detection and treatment of harmless prostate cancers that would not have been detected without PSA screening nor caused suffering or death for the patient. The concerns about overdiagnosis of prostate cancer have become increasingly more resonant.
There are different ways of defining and estimating the rate of so-called overdiagnosis: (a) epidemiologic, in which the number of new cancer cases detected is compared with the expected number; and (b) clinical and pathologic, in which the features of the cancers detected are scrutinized for the parameters of “clinically insignificant” disease (i.e., low-volume, organ-confined, and low Gleason grade) [37]. Using epidemiologic criteria, it has been estimated that 25%–50% or more prostate cancers are overdetected [38, 39]. In contrast, using clinical and pathologic criteria, approximately 5%–30% of cancers would fit the published criteria for being harmless [37, 40–42].

The corollary of this analysis is that prostate cancer is still underdiagnosed more frequently than overdiagnosed [41, 42]. By the time of diagnosis, the cancer has spread beyond the prostate in at least 20% of patients, and >30% of patients treated for localized disease require secondary treatment for cancer recurrence.

The concept of insignificant cancer is controversial, and in a young man with a long life expectancy, it is impossible to state with certainty that any cancer would remain indolent, because cancers can acquire genetic mutations and more aggressive behavior over time. Nevertheless, concerns about overdiagnosis have given rise to the concept of “active monitoring” rather than immediate treatment of men with possibly insignificant cancer, even in young patients [43]. Active monitoring is becoming more widespread in the U.S., although the senior author questions its wisdom in young patients. That notwithstanding, PSA testing (total PSA, percent free PSA, PSAD, and PSA kinetics) continues to play an important role in managing patients with this new approach.

The challenge to physicians is to avoid both overdiagnosis and underdiagnosis, if possible. In the senior author’s opinion, the informed use of PSA includes beginning PSA-based screening of men in their 40s. Baseline measurements not only screen them for prostate cancer at the moment, but also assess their future risk through comparisons of their PSA level with that of the median for their age group. PSA measurements in the 40s also provide useful longitudinal data to measure PSAV.

To obtain the most benefit from serial PSA testing, both patients and their physicians should maintain a flow sheet that records the date, the PSA value, and the assay used (to evaluate for possible confounding from differences in PSA assays and standardization). Figure 1 shows an algorithm

Figure 1. What to do with an abnormal PSA test: Clinical algorithm.

Abbreviations: ASAP, atypical small acinar proliferation; DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; PSAD, PSA density; PSADT, PSA doubling time; PSAV, PSA velocity.
for management of an abnormal PSA test. PSAD and percent free PSA may be used to estimate possible confounding from BPH. Moreover, in patients with a sudden PSA elevation, subclinical prostatitis can be ruled out with an empirical course of antibiotics and repeat PSA measurements. Finally, PSAV will help distinguish the more aggressive tumors that need to be diagnosed and treated from indolent tumors [26]. We recommend a PSAV threshold of 0.4 ng/ml per year, because this degree of PSA rise does not appear to result from biologic variability of PSA measurements, ejaculation, or prostate manipulation [28, 44].

Once prostate cancer is diagnosed, total PSA, PSAD, percent free PSA, and PSA kinetics are useful in addition to other clinicopathologic information (i.e., how much cancer is present in the biopsy specimens, the Gleason score, findings on DRE, and any imaging studies, such as ultrasonography, computed tomography, magnetic resonance imaging, and spectroscopy, if available) to estimate how aggressive the cancer is likely to be. There are numerous algorithms using different combinations of these features that can help to predict the extent of disease and the likelihood of finding “insignificant” cancer on the radical prostatectomy specimen.

For men who elect to undergo definitive treatment, the PSA level correlates with the volume of cancer present in approximately 90% of cases (excluding men with a very large prostate) [45]. If a patient is deemed to have potentially insignificant cancer and elects to be managed with active monitoring, PSA and its derivatives again may play an important role in determining whether the cancer is progressing (25%–50% have objective evidence of progression within 5–10 years) [33].

CONCLUSIONS

PSA and its derivatives are useful predictors of prostate cancer risk and aggressiveness. With regard to screening, men with a PSA >2.5 ng/ml, a suspicious DRE, or a PSAV greater than approximately 0.4 ng/ml per year have a significantly higher risk for prostate cancer, and prostate biopsy should be considered. In terms of prognosis, a PSAD >0.15 ng/ml per gram and a PSAV > 2 ng/ml per year are suggestive of more aggressive disease. These patients may not be appropriate candidates for active monitoring and have a greater risk for adverse outcomes after definitive therapy.

AUTHOR CONTRIBUTIONS

Conception/design: William J. Catalona, Stacy Loeb
Provision of study materials or patients: William J. Catalona
Collection/assembly of data: William J. Catalona, Stacy Loeb
Data analysis and interpretation: William J. Catalona, Stacy Loeb
Manuscript writing: Stacy Loeb
Final approval of manuscript: William J. Catalona

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