

PROSTATE-SPECIFIC ANTIGEN (PSA): AN OVERVIEW

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None of the tests currently used in clinical medicine can be described as being perfect. Every test can give a false-positive or false-negative result. This also applies to tumor markers used in the diagnosis and management of malignancies. In spite of extensive research in medicine, the "ideal" tumor marker is not yet available and likely does not exist. Thus, judgment and experience are required in the interpretation of any particular tumor marker. If the ideal tumor marker were to exist, it would be accurate, reliable, tumor specific, predictive of the presence of early, low-volume organ-confined disease, and would accurately predict the response to treatment.

Over the past decade, clinical experience has led to the identification of a tumor marker, currently considered to be the best yet, for the diagnosis of prostate cancer.¹⁻³ This tumor marker is prostate-specific antigen (PSA). Like all tests in medicine, however, it is not perfect and requires experienced clinical interpretation and judgment in its application to individual patients.

PSA was originally discovered in seminal plasma in Japan.⁴ A protein produced in the prostate was isolated and purified by Wang et al.⁵ in 1979. It was produced only in prostate epithelial cells, hence the name prostate-specific antigen. It is a serine protease which is produced exclusively by human prostatic epithelium,⁶ and is detectable only in the epithelium of normal prostate, benign prostatic hyperplasia (BPH) tissue, and in both primary and metastatic prostate cancer tissues.⁷ It is secreted into the prostate ducts and presents in the seminal fluid. It is involved in the liquefaction of seminal coagulum which is formed at ejaculation.

The clinical characteristics of PSA indicate no variation of concentration during the day, and studies in men with no prostate disease, BPH or prostate cancer indicate minimal fluctuation during the day.⁸ This enables blood samples to be obtained at any time of the day.

Various procedures are known to affect blood PSA levels. The evidence concerning the effect of digital rectal examination (DRE) on serum levels of PSA is mixed. One study showed no immediate change,⁹ while another showed a definite increase in the levels of PSA.¹⁰ Serum PSA concentration increases fourfold following cystoscopy procedure.¹⁰ Needle biopsy is said to increase the concentration of PSA from 2.6-fold¹¹ to 57-fold.¹⁰ Following transurethral resection of prostate (TURP) in patients with BPH, serum PSA gets elevated substantially

first, but then falls.¹² The median time for a return to stable baseline PSA value is 15 days for prostate patients, 17 days for men without cancer who have undergone biopsy, and 18 days for men who have undergone TURP. However, it has been shown that it can take more than 30 days for PSA to return to baseline in certain men who have had biopsy or TURP. Thus, following prostate procedure, it is important to wait at least six weeks before blood samples are drawn and results of serum PSA (half-life of days) are interpreted. Infection of urinary tract, prostatitis and urinary retention also affect serum PSA values.

As men get older, the prostate gland enlarges, and the most common disease process they are afflicted with is benign prostatic hyperplasia. By 80 years of age, 80% of men will have BPH, and 25% of them will require surgery. In USA, BPH constitutes one of the most substantial cost of Medicare reimbursement. Similarly, prostate cancer has become the biggest cancer problem in the West. The annual incidence of BPH in the West is said to increase from 0.2 per 100,000 at the age 40 years to 100 per 100,000 at the age 70, and to 1000 per 100,000 at age 80 years. It exceeds lung cancer in its incidence, and is the second leading cause of death after lung cancer in men.

The normal range of PSA test is a value of less than 4 ng/mL. With elevated values in the range of 4-9.9 ng/mL, 22% of men may have prostate cancer. When the value rises to more than 10 ng/mL, the percentage of men who may have prostate cancer increases to about 65%. It should be noted that the PSA test is not an absolute in ruling out or confirming the presence of cancer in the prostate. About 25% -50% of men with BPH or prostate infection may show elevated levels of PSA but no cancer.

Since PSA was identified, various methods have been developed in the search to improve its ability to predict the presence of early prostate cancers while reducing the number of false-positive assays. These include: 1) age-specific PSA levels; 2) PSA velocity; 3) PSA density; and 4) free-to-total PSA ratio.

Age-Specific PSA Levels

It has been noted that older men have higher baseline PSA levels as a result of age-dependent growth and PSA secretion and production variations. Thus, as man gets older, PSA rises even if there is no evidence of malignancy. In contrast, in younger men, the upper ranges of normal PSA levels may harbor occult malignancy. Oesterling et

al.¹³ and Dalkin et al.¹⁴ established normal levels of PSA for men without clinical evidence of prostate cancer. Based on their data, the upper limit of normal PSA were established at 0-2.5 ng/mL in the 40-49 year range, 0-3.5 ng/mL in the 50-59 year range, 0-4.5 ng/mL in the 60-69 year range, and 0-6.5 ng/mL in the 70-79 year range. These guidelines help to increase the sensitivity of PSA in men who are less than 60 years of age.

PSA Velocity

It is a serial measurement of PSA over time in an individual. It provides a reflection of longitudinal pathological changes within the prostate gland, and thus increases the positive-predictive value of PSA, and the likelihood of diagnosing prostate malignancy early while it is still confined to the prostate gland. When a rising trend in PSA levels is detected, prostate biopsy is to be considered. A rise of 0.75 ng/mL or greater per year is a reason for concern, and further investigation is warranted.¹⁵ The problem with this method is individual variation from one test to another, knowing the optimal utilization in the way of intervals between tests, the number of times test is to be done, etc.

PSA Density

PSA Density is a value of serum PSA divided by prostate gland volume. It is based on the concept that cancer on a gram-per-gram basis will produce more glycoprotein and thus increase serum PSA levels to a greater extent than normal prostate tissue or BPH.

Free-to-Total PSA Ratio

This is a new blood test currently under study and an area of considerable investigation and interest. It is believed to be a relatively more sensitive test. In the blood, there are two kinds of PSA; one is free, and the other is bound PSA. The majority of immunoreactive PSA (85% -90%) is bound to protease inhibitor alpha 1 antichymotrypsin (PSA-ACT). The PSA-ACT complex is the major molecular form of PSA in the serum, while a small proportion is in the free form. Initial studies have indicated that bound PSA may be higher in men with prostate cancer and that they have lower free PSA fraction. Low free-to-total PSA ratio (<10%) is suggestive of malignancy and a high ratio (>25%) is suggestive of BPH. Thus, the ratio of free-to-total PSA may be used to increase the specificity and positive-predictive value of PSA in the early detection of prostate cancer, especially when PSA levels are between 4 and 10 ng/mL. When patients have PSA levels greater than 10 ng/mL, it is appropriate to conduct further investigations. It is hoped that more laboratories would report the test in fractions, which would improve the accuracy in diagnosing prostate cancers in the early stages.

There is a good correlation of PSA with tumor volume and the clinical and pathological stage of prostate cancer, but accurate clinical staging is difficult as there is much overlap between stages, and it is not accurate enough as a

“staging” tool when used alone. The staging accuracy improves when used with digital rectal examination and grade of the tumor. However, PSA helps categorize patients into low versus high risk. When PSA levels are below 4 ng/mL in patients who have been diagnosed to have prostate cancer, up to 80% of the patients would have cancer confined to the prostate gland, about 60% when PSA levels are between 4 to 10 ng/mL, and when PSA is more than 10 ng/mL, over 50% of patients would have extraprostatic disease.

Elevated serum PSA level is a predictor of lymph node metastases as well. Patients with PSA levels above 50 ng/mL tend to have lymph node metastases. On the other hand, the risk of positive lymph node metastases in patients with low PSA levels is low. With PSA of less than 10 ng/mL and low-grade disease, the risk of positive nodes is negligible. Serum PSA also correlates with bony metastasis. Gleave et al found 0% positive bone scan at presentation when PSA was below 10 ng/mL, 4% when PSA was between 10-20 ng/mL, and 17% when PSA was >20 ng/mL.

Post-Radical Prostatectomy

Following radical prostatectomy, the PSA rapidly falls to undetectable levels in most patients. Serum PSA is the most useful test in predicting treatment failure. If there is detectable serum PSA within the first year, 50% of these patients will develop either local or distant metastases.¹⁶ According to a report by Lange et al.,¹⁷ all patients who have undergone radical prostatectomy and with post-operative PSA greater than 0.4 ng/mL will develop progressive disease.

Post-Radical Radiation Therapy

In patients treated with radiation therapy, unlike those treated with radical prostatectomy, PSA levels decrease more slowly and may never reach undetectable levels. Zagar et al.¹⁸ reported that over 95% of patients will have significant decrease in their PSA levels, and about 80% will be in the normal range within six months.

Little is known about the natural history of the irradiated prostate and whether residual or recovered normal tissue can manufacture PSA. After radiation treatment, nadir PSA (nPSA) is widely used as a predictor of treatment success or failure. However, different investigators choose different nPSA values as significant endpoints, ranging from 0.5 to 4 ng/mL. Secondly, in patients who were treated with radiation therapy whose PSA has reached the lowest level and then remained stable for a period, rising PSA is a marker of treatment failure or success. The rising PSA is an ominous sign and indicates either local recurrence or distant metastasis. As per guidelines of the American Society for Therapeutic Radiology and Oncology Consensus Panel, three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy.¹⁹

Screening

PSA is organ specific but not cancer specific, thus the use on its own as a screening tool for the early detection of prostate cancer is limited. Several factors favor its use as part of a screening program. Screening is fairly inexpensive and has widespread acceptance, and treatment options, i.e., surgery or radiation therapy, are available for the early stages of the disease.

The value of screening as an aid for the early detection of prostate cancer is controversial. It is not possible to state categorically that early detection and treatment lead to reduced mortality rates. It has not yet been established whether the value of screening outweighs the cost and morbidity associated with prostate cancer treatment (erectile dysfunction, incontinence and anxiety). The American Cancer Society and American Urological Association recommend the use of PSA and DRE (digital rectal examination) in an annual physical examination for men who are 50 years or older, and at age 40 years in high-risk men such as African-Americans and men who have first-degree relatives with prostate cancer. On the other hand, US Preventive Services Task Force and The Canadian Task Force on the Periodic Health Examination do not recommend routine PSA screening in asymptomatic males over 50 years. The National Cancer Institute concluded in 1994 that there was insufficient evidence at the time to recommend PSA for routine screening. There are however ongoing trials, one by the National Cancer Institute (NCI) in the US and another in Netherlands by the European Randomized Study of Screening. The results are expected by the year 2006 and 2008, respectively. Hopefully, the results of these trials will provide more definitive answers as to whether screening for prostate cancer is of value and is justified.

Since PSA was identified in the late seventies, it has been used extensively in the diagnosis, management and follow-up of patients with prostate cancer. However, we still have much to learn about PSA, and it will still require judgment and experience of the treating physicians in its use and interpretation.

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