

Evaluation of Prostate Specific Antigen as a Tumor Marker in Cancer Prostate

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Abstract

The present study was undertaken to evaluate the prostate specific antigen (PSA) alongwith other diagnostic methods as an application for a screening test, tumor marker and its relation to post surgical situation, The PSA has shown a sensitivity of 73.3% and specificity of 77.2%. The predictive value for positive PSA was 57% and for negative test was 66,6%. Local standards for PSA values in Pakistani community need to be established. The PSA test, inspite of its low specificity holds good promise for its contributory role as a tumor marker in prostate cancer (JPMA 48: 360,1998).

Introduction

The estimated incidence of 317,000 cases and 41,000 deaths due to prostate cancer during 1996 for U.S.A. suggests that prostate cancer (Ca) is the most common cancer and second leading cause of death from cancer among men in United States¹. The magnitude of the problem is not known for Pakistan, but due to improved life expectancy and socio-economic conditions, more and more males of senior ages will be exposed to this malignancy.

Prostate cancer can be detected by various methods. Digital Rectal Examination (DRE) is one of the oldest and relatively least invasive technique, but it fails to detect many cases of Ca Prostate in their earliest stages. Various studies carried out in West showed that DRE detected Ca Prostate in the range of 0.1-1.7%², Digital guided biopsy has an accuracy of diagnosing Ca Prostate in 30-40% cancer cases^{3,4}. Trans-rectal ultra sonography (TRUS) particularly random sextant biopsies also has facilitated detection of Ca prostate^{5,6}. For over 50 years, a protein manufactured by prostate called Prostatic Acid Phosphatase (PACP) has been used as a marker for prostatic disease. Prostate specific Antigen (PSA) has emerged as a very useful marker of Ca Prostate and monitoring the effect of therapy^{3,4,7}.

PSA was first identified in 1971⁸ and called Y semino-protein. In 1978 the protein was purified from seminal plasma and characterized as a potential semen marker⁹. In 1979 the protein was purified from all types of prostate tissue and was found specific in humans only, it was called Prostate Specific Antigen (PSA)¹⁰. PSA is a protease, making complexes with inhibitors in serum. The predominant complex is with "α antichymotrypsin (ACT), with the minor complexes and a small free form¹¹. Most of the commonly available immunoassay kits for PSA appear to detect both free and ACT complexes¹². The normal range of PSA is known to increase with age, probably due to increase in the prostate tissue mass, which can be assessed by ultrasonography. The PSA density or index does not refer to the 'density' of PSA within the prostate, but rather to an index that corrects the serum PSA for the contribution from BPH. Most of the increase in PSA with age is due to increase in prostate volume. PSA density = PSA result in serum

Volume of Prostate gland

The estimates of prostate volume are often imprecise and more expensive than the PSA assay itself. The benefits in specificity described to date are usually marginal at best. However, values above the normal range 0-4 ng/ml are one of the earliest signs of prostate cancer, in many cases allowing

diagnosis while the cancer is still confined to the gland^{13,14}.

Based on the simplicity of procedure and reliability, American Cancer Society has recently recommended annual screening of men over 50 years of age¹⁵. Different immunoassay kits may give different results in the same patient¹⁶⁻¹⁸. This raises the need to standardize PSA assay. Patients with greater than 10 ng/ml should be evaluated by ultrasound and needle biopsy to rule out prostate cancer¹⁹⁻²¹. In one study a reference interval of <4 ng/ml was defined as an upper limit that was observed in all men under the age of 40 years and 97% of men over 40 years²⁰.

Diurnal variations of PSA due to physical activity, exercise and diet have not been found. There are some racial differences in PSA levels. Ejaculation causes significant changes, PSA falls after ejaculation. Ideally PSA levels should be collected after 1-2 days of sexual abstinence. Digital rectal examination increases PSA levels, therefore one week gap is suggested following prostatic manipulation and PSA testing.

Subjects and Methods

A group of 144 males in the age range between 40 to 92 years were included in the study. The cases had at least one symptom of prostatism, including frequency, urgency, weak urinary stream, dysuria or microscopic hematuria. These cases were registered at the Urology Departments of Jinnah Hospital, Shaikh Zayed Hospital and National Health Research Complex Lahore, from November, 1996 to March 1997. All subjects (100%) had neither undergone any prostate surgery nor were diagnosed as cases of cancer prostate earlier.

A comparison group of 127 subjects was included after matching for age and socio-economic standards. These subjects did not have any urinary symptoms. Serum PSA levels were measured in each subject (total of 241 cases).

All 114 cases with symptoms of prostatism underwent Transurethral Resection of Prostate (TLJRP) or Millen's prostatectomy for verification of diagnosis as BPH or Ca prostate. None of the control subjects underwent TURP or other procedures.

Serum PSA was measured by Immunoradiometric assay (Netna, UK). Study of the specimens was carried out by single histopathologist in the department of histopathology at Shaikh Zayed Hospital Lahore. The prostatic tissue was embedded in paraffin and stained by Hematoxylin and Eosin staining method.

Results

The mean PSA levels of all 241 subjects is shown in Figure 1.

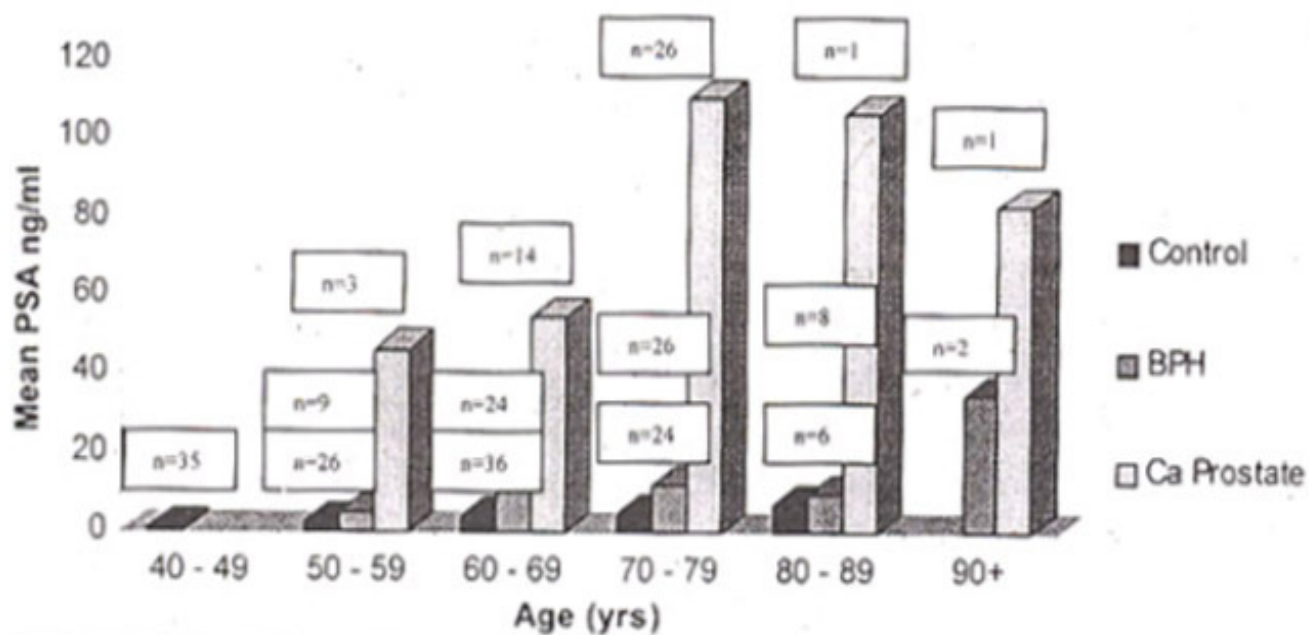


Figure 1. Mean serum prostatic specific antigen (PSA) levels by age and groups.

This figure shows that among the control group the mean PSA values ranged from 0.95-6.9 ng/ml. As PSA has a direct association with age, the six cases in the age group of 80-89 years had a PSA of 6.9 ng/ml. In BPH cases the PSA was higher than 4 ng/ml in all the age groups and generally increased with age. The range was 4.5-34.7 ng/ml. Only two cases showed the mean PSA as 34.7 ng/ml while the remaining were all below 12 ng/ml. In Ca prostate cases the PSA was generally quite high ranging from 46-110.8 ng/ml. In general all groups showed progressive increase in PSA levels by age.

Table I. Distribution of cases by PSA 'Cutoff' groups.

| Age range (years) | Control PSA levels | | | BPH PSA levels | | | Ca Prostate PSA levels | | |
|--------------------|--------------------|--------------|-----------|----------------|--------------|-----------|------------------------|--------------|-----------|
| | 0-4 ng/ml | 4.1-10 ng/ml | >10 ng/ml | 0-4 ng/ml | 4.1-10 ng/ml | >10 ng/ml | 0-4 ng/ml | 4.1-10 ng/ml | >10 ng/ml |
| 40-49 | 34 | 1 | - | - | - | - | - | - | - |
| 50-59 | 20 | 6 | - | 5 | 2 | 2 | - | - | 3 |
| 60-69 | 25 | 4 | 7 | 12 | 5 | 7 | 3 | 3 | 8 |
| 70-79 | 15 | 2 | 7 | 17 | 1 | 8 | 4 | 2 | 20 |
| 80-89 | 4 | - | 2 | 2 | 3 | 3 | - | - | 1 |
| 90+ | - | - | - | 1 | - | 1 | - | - | 1 |
| Total | 98 | 13 | 16 | 37 | 11 | 21 | 7 | 5 | 33 |
| Grand total | | 127 | | | 69 | | | 45 | |

Table I shows the distribution of cases by the three internationally recognized *cutoff* groups of PSA values i.e., upto 4 ng/ml, 4.1 -10 ng/ml and above 10 ng/ml. The distribution shows that majority of control subjects (77.2%) had PSA value upto 4 ng/ml, 10.2% were in the 4.1-10 ng/ml range and only 12.6% were in the above 10 ng/ml group. The majority of BPH cases (53.6%) had PSA values upto 4 ng/ml, while 15.9% had PSA values in the 4.1-10 ng/ml range and 30.4% were above 10 ng/ml. 73.3%

of the Ca prostate cases were in the above 10 ng/ml group while only 15.6% and 11.1% were in the upto 4 ng/ml and 4.1-10 ng/ml groups respectively.

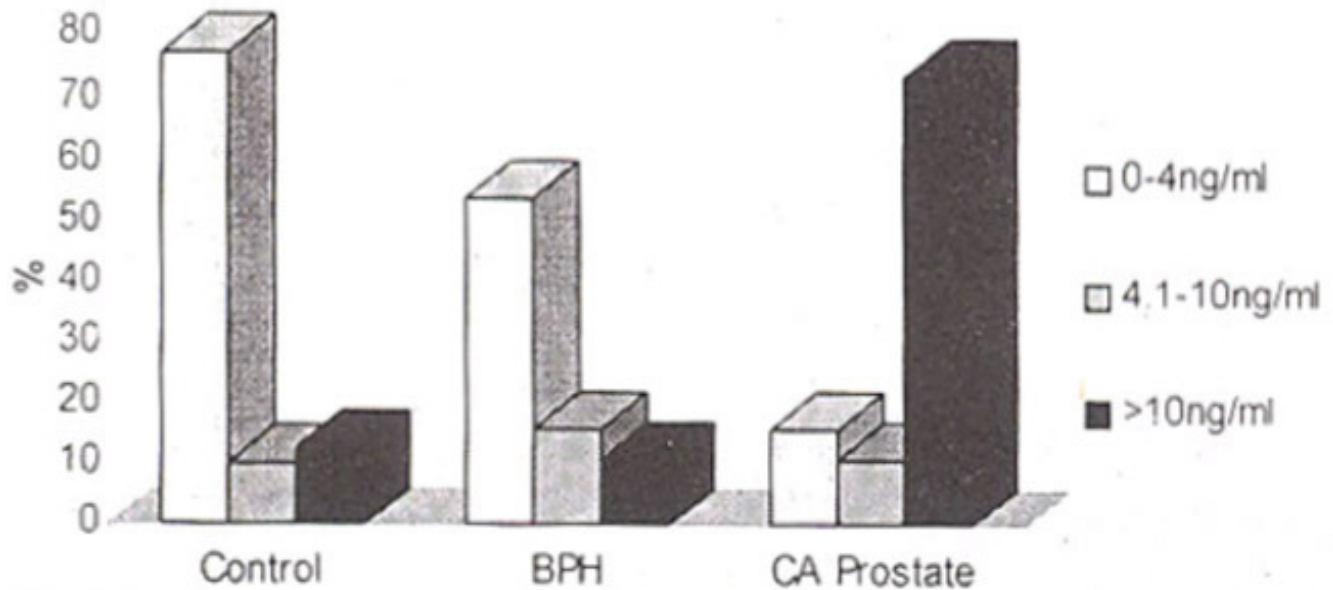


Figure 2. Percentage of cases in the study groups by PSA cutoff points.

Figure 2 shows the distribution of PSA levels in the various study groups. Among Ca prostate cases there were 73% subjects with PSA levels over 10 ng/ml. Among BPH cases 46.4% had PSA more than 4 ng/ml. Among the control group less than 4 ng/ml PSA was observed in 77.2% of cases.

Table II. The diagnostic potential of PSA in the three study groups by the arbitrary PSA cutoff points.

| Study groups (%) | Cutoff points for PSA | | | Diagnostic potential | Total No. of cases |
|--------------------|-----------------------|---------------------|-------------------|----------------------|--------------------|
| | 0-4 ng/ml | 4.1-10 ng/ml | 10 ng/ml | | |
| Control Status | 77.2 True -ve | 10.2 Border line | 12.6 False +ve | 77.2% Specificity | 127 |
| BPH status | 53.6 False -ve | 15.9 True +ve | 30.4 High +ve | 46.3% Sensitivity | 69 |
| Ca Prostate status | 15.6 False -ve | 11.1 Borderline | 73.3 True +ve | 73.3% Sensitivity | 45 |

Sensitivity

Out of 45 cancers cases, 33 were detected suggesting an overall sensitivity of 73.3% with 26.7% of cancers failing to demonstrate elevated PSA. For the BPH cases the PSA values have shown that 53.6% were less than 4 ng/ml and 46.4% were more than 4 ng/ml. There were 21 cases (30.4%) who showed PSA values over 10 ng/ml. However, the values ranged upto 34 ng/ml.

Specificity

Specificity refers to the proportion of truly non-diseased persons who were so identified by the test in

question. Out of 127 negative cases the PSA was found false positive in 29 cases. The specificity therefore was 77.2%.

The predictive value for a positive test was found to be 57.0% and for a negative test as 66.6%. Results of the studies elsewhere in this case have also suggested that improving specificity for PSA test is more important than improving sensitivity²². This is based on the fact that false negative cases could still be diagnosed by other techniques due to persistence of symptoms and managed effectively, while the psychological trauma for a false positive case may be cumbersome and entail unnecessary heavy costs for other tests.

Calculations

Ca Prostate Sensitivity = $33/45 \times 100 = 73.3\%$ Specificity = $98/127 \times 100 = 77.2\%$. Predictive value for positive PSA test = $65/114 \times 100 = 57.0\%$. Predictive value for negative PSA test = $98/147 \times 100 = 66.6\%$.

Discussion

This study has shown the importance of using PSA as an efficient screening test. It has not been studied for its monitoring role in the management of therapy.

Local standards for our population need to be established for suggesting more accurate Cut off values by expanding the number of subjects and including more general male population from ages 40 years and above. It has not yet been cleared as to what grade of PSA cut off value should be taken into account to suspect Ca prostate development and cases of BPH. It is possible that the PSA values for BPH are intermediate between the Ca prostate values and normal values. Thus we have to define the cut-off values for the three stages of prostate conditions (Normal, BPH and Ca prostate). In the present series 43% of Ca prostate cases were under 70 years of age who had PSA upto 4 ng/ml, while the remaining 57% of such cases were between 70-79 years of age; Among the 5 Ca prostate cases who had PSA values between 4.1-10 mg/ml, 60% were under 70 years of age. The behaviour of PSA value for BPH was much less specific and predictable, although very few cases had the PSA values more than 30 ag/mi. It therefore seems that while age is a significant factor for the prostatic volume, other factors independently influence the PSA values. To obtain higher sensitivity and specificity some adjustments may also have to be taken into consideration for determinants like aging, gonadal androgenic hormones, genetic predisposition, prostatic volume and prostatic velocity. PSA testing as used currently lacks sufficient sensitivity and specificity to be considered a 'perfect' tumor marker for the detection of early prostate cancer. Under the present situation, use of a combination of DRE, PSA and TRUS can be suggested to obtain better yields for BPH and Ca Prostate. For organ confined Ca prostate PSA based screening programme seems to hold better promise²³. To improve the clinical utility of serum PSA measurements. PSA density²⁴, PSA velocity²⁵ and age specific reference ranges²⁶ have been developed and evaluated. Perhaps risk assessment should be used instead of absolute cut off values, taking into account patient's age, DRE findings as well as the free and total PSA levels.

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