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# FREE AND TOTAL PROSTATE SPECIFIC ANTIGEN IN BENIGN PROSTATE HYPERPLASIA AND PROSTATE CANCER

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ORIGINAL ARTICLE

# FREE AND TOTAL PROSTATE SPECIFIC ANTIGEN IN BENIGN PROSTATE HYPERPLASIA AND PROSTATE CANCER

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## ABSTRACT

**Objective:** To record the levels of PSA in the sera of prostate cancer (CaP) and benign prostatic hyperplasia (BPH) cases. Free PSA/total PSA as percentage was also calculated in order to evaluate its utility in differentially diagnosing BPH and CaP.

**Design:** A cross-sectional, case control study.

**Place and Duration of Study:** Shaikh Zayed Hospital and Mayo Hospital, Lahore from August 2002 to March 2003.

**Materials and Methods:** A group of 108 male subjects, including one-third of each of biopsy-confirmed prostate cancer cases, BPH cases and asymptomatic controls of matching age were studied. PSA and Free PSA were determined by ELISA using commercially available assay kits.

**Results:** Mean PSA was found to be highest in CaP cases (41.9 ± 38.7 ng/ml), lower in the BPH cases (13.5±10.5 ng/ml), while it was lowest in the control subjects (5.7 ± 4.4 ng/ml). Moreover, it was observed that a majority of the CaP cases had serum PSA >20 ng/ml, 50% of BPH cases had serum PSA in the 'gray zone' (4.1-20 ng/ml), while majority of controls had serum PSA in the 'normal' range (0 - 4 ng/ml). Using a free-PSA "cut-off" of 18% to differentiate between benign and malignant prostate enlargement, it was found that 80% of the CaP cases had F/T% <18, while 75% of the BPH cases had F/T%>18. The percent free-PSA test to differentially diagnose BPH and CaP in the 'gray zone' was found to have a sensitivity of 86% and a specificity of 94%.

**Conclusion:** Using a cutoff of 18%, the free-PSA test significantly improved the differential diagnosis of BPH and CaP in the 'gray zone' as compared to the use of total PSA alone in the study group.

**KEY WORDS**: *Prostate specific antigen (PSA). Free PSA. Benign hyperplasia. Prostate cancer.*

## INTRODUCTION

Human prostate-specific antigen (PSA) is a 33 KD serine protease. The normal range of serum PSA is known to increase with age[1], probably due to an increase in the prostate tissue mass. Elevated serum PSA concentrations have been reported in patients with prostate cancer, as well as in benign prostatic hyperplasia (BPH) and prostatitis, leading to a large percentage of false positive screening results.[2] However, values above the normal range 0-4 ng/ml are one of the earliest signs of prostate cancer, allowing diagnosis in many cases while the cancer is still confined to the gland.[3,4]

Serum PSA values >20 ng/ml are strongly indicative of prostate cancer. However, values in the intermediate range 4-20 ng/ml constitute a diagnostic 'gray zone', in which differentiation between benign and malignant enlargement poses a dilemma.[5] Studies suggest that a lower percentage of free-PSA is observed in patients with prostate cancer than in those with BPH.[6,7] In BPH free-PSA level is highest. Determination of percent free-PSA is a potential marker for early detection of CaP. This study was undertaken to evaluate the significance of PSA and percent free-PSA measurements in the differential diagnosis of prostate cancer and BPH.

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## PATIENTS AND METHODS

SETTING: It was a multicentre study conducted at the Urology Wards of Shaikh Zayed Hospital, Jinnah Hospital, and Mayo Hospital from August 2002 to March 2003. The asymptomatic matched controls were selected at National Health Research Complex (NHRC), Lahore.

Diseased cases were selected on the basis of lower urinary tract symptoms (urgency, frequency and dribbling) and digital rectal examination (DRE) results (hard consistency, adherent mucosa overlying prostate gland, etc.), which were further confirmed as malignant and BPH on biopsy. While the control subjects displayed none of these symptoms.

Patients who had previously undergone any surgical intervention were excluded.

Conveniently selected group of 108 male subjects in the age range of 50-85 years were studied. They included 36 subjects each of biopsy-confirmed prostate cancer cases, BPH cases and asymptomatic controls. Blood samples were collected from each subject. Sera were separated and stored at -80$^0$C. Enzyme-linked immunosorbent assay (ELISA) for PSA and free-PSA was performed using commercially available test kits from NETRIA, UK. Percentage of free-PSA was calculated. Analysis of data was carried out by using SPSS software version 10. The quantitative data was subjected to t test for significance at $< 0.05$.

## RESULTS

Mean PSA was seen to increase with age in control subjects as well as in BPH and CaP cases, except in elderly cases of over

80 years of age, probably because of fewer number of subjects. (Figure 1).

The three study groups did not differ significantly in their age composition ($p > 0.05$) but the PSA levels varied significantly by diagnosis. The level of PSA in BPH cases was approx. 2 times higher and that in CaP cases, 8 times higher than in the control subjects.

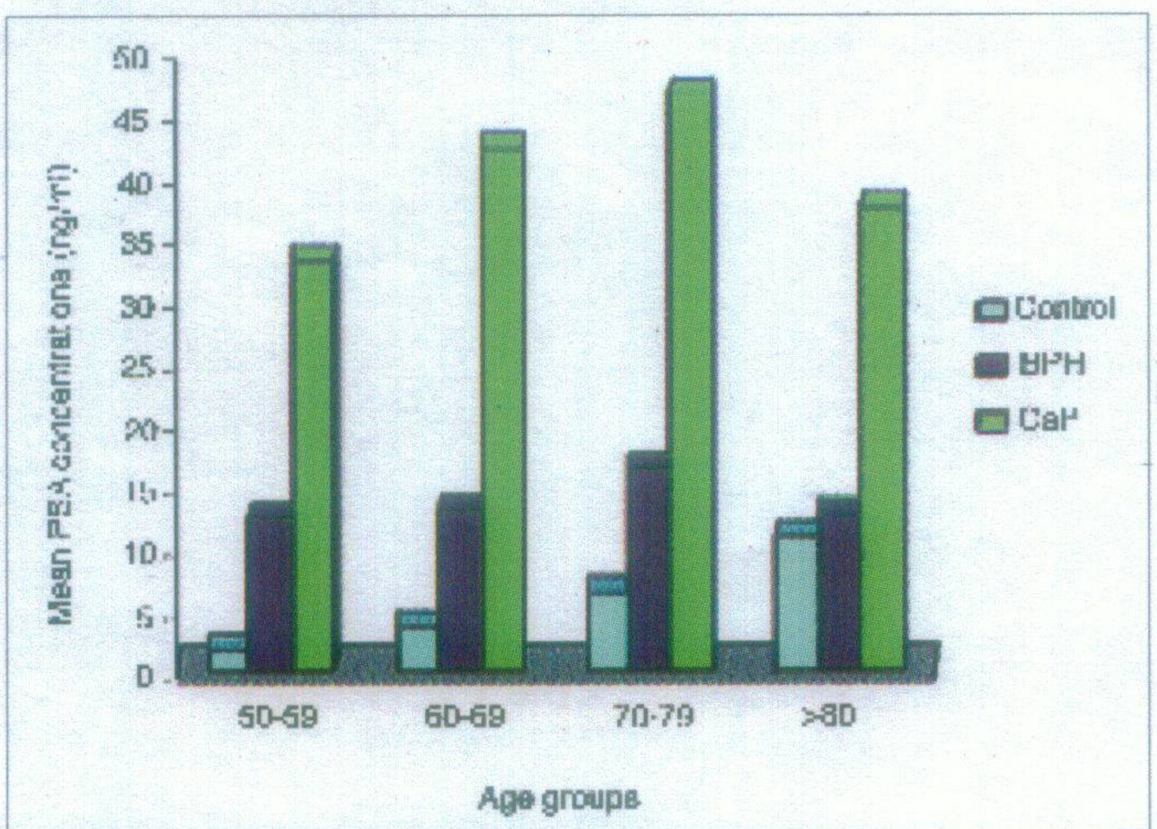


**Figure 1:** Distribution of PSA levels by study groups and ages.

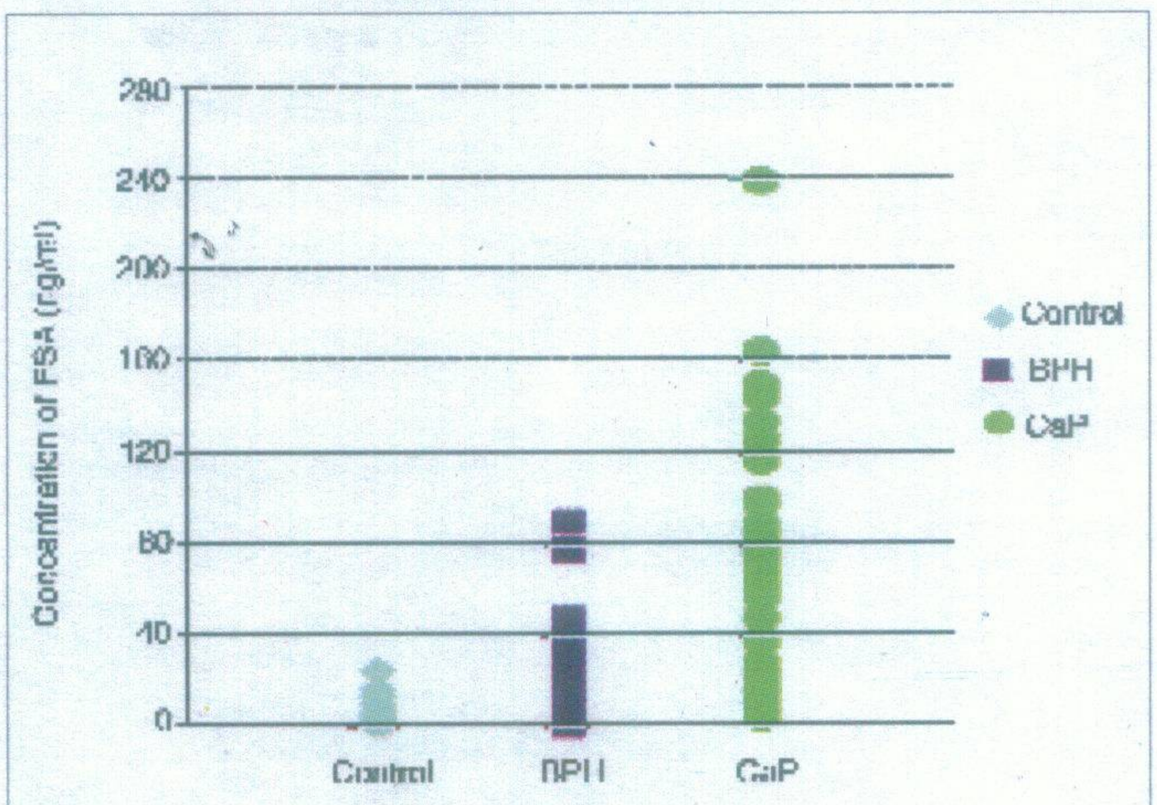


**Figure 2:** Comparison of PSA levels in the study groups.

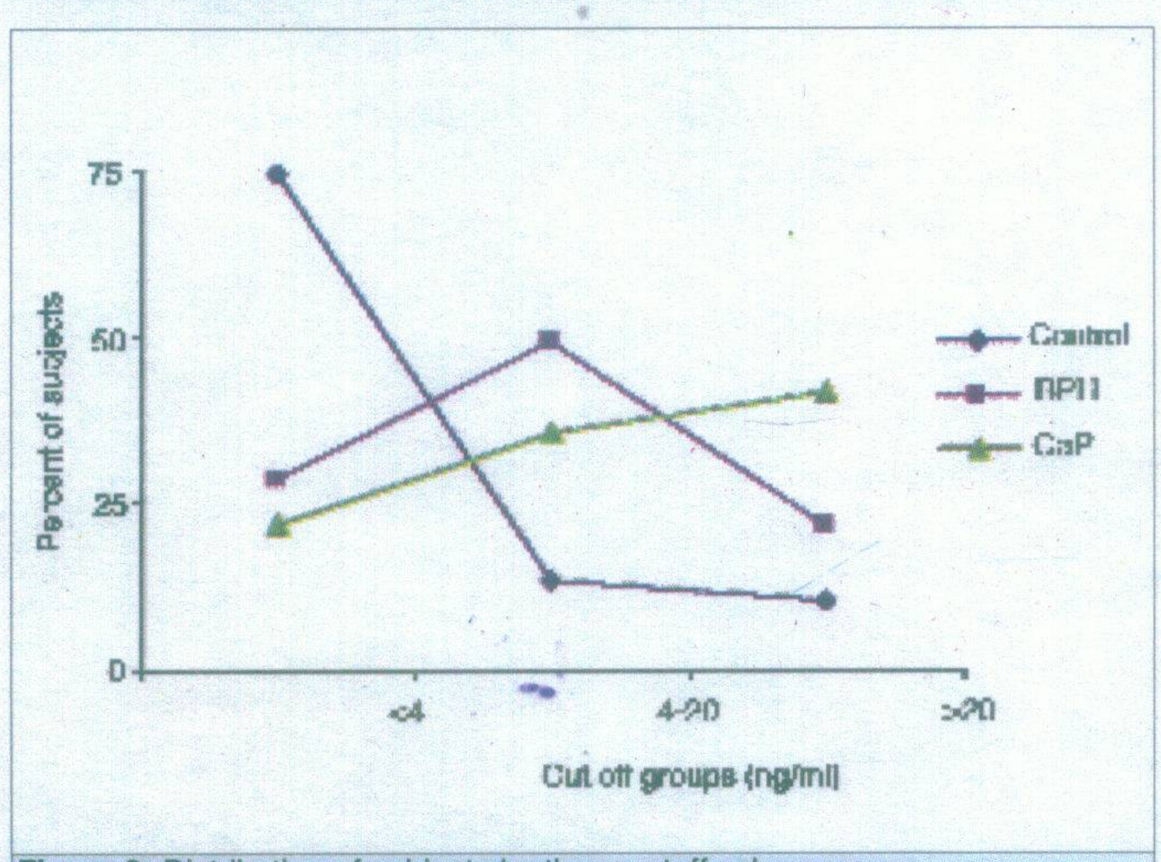


**Figure 3:** Distribution of subjects by three cutoff values groups.

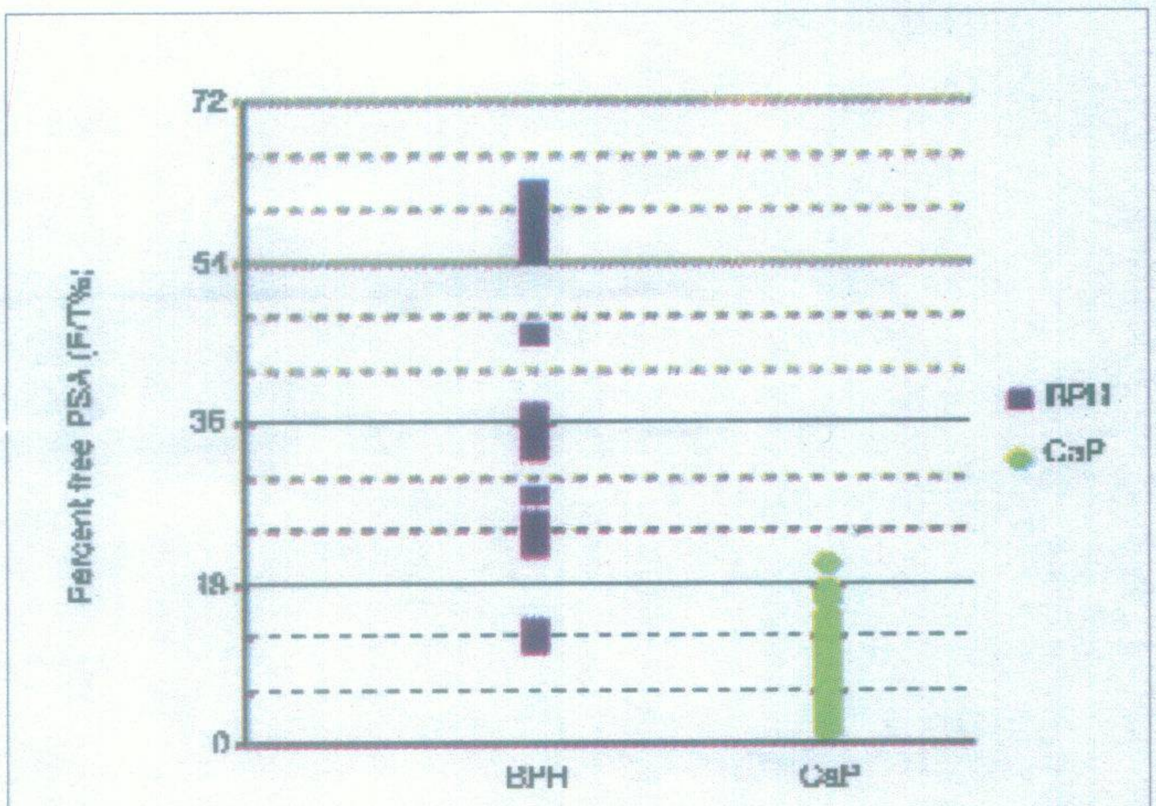


**Figure 4:** Comparison of F/T% in BPH and CaP cases.

**Table I:** Comparison of PSA levels by cutoff in controls, BPH and CaP cases.

| Study groups | PSA cutoff ranges 0-4 ng/ml n | % | 4.1-20 ng/ml n | % | >20 ng/ml n | % | Total n | % |
|---|---|---|---|---|---|---|---|---|
| Control | 27 | 75 | 5 | 14 | 4 | 11 | 36 | 33.33 |
| BPH | 10 | 28 | 18 | 50 | 8 | 16 | 36 | 33.33 |
| CaP | 8 | 22 | 13 | 36 | 15 | 42 | 36 | 33.33 |
| Total | 45 | 42 | 36 | 33.3 | 27 | 23 | 108 | 100 |

Significant value = $p<0.05$

**Table II:** Outcome of PSA against gold standard.

| PSA test results | BPH and CaP cases | Healthy group | Total |
|---|---|---|---|
| +ve (>4 ng/ml) | 33 | 9 | 42 |
| -ve (<4 ng/ml) | 39 | 27 | 66 |
| Total | 72 | 36 | 108 |

Significant value = $p<0.05$
Therefore Sensitivity for combined
BPH and CaP = 33/72x100 = 45.8%
Specificity = 27/36 x 100 = 75%
Predictive value for +ve PSA test = 33/42 x 100 = 78.6%
Predictive value for - ve PSA test = 27/60 x 100 = 40.9%

**Table III:** Differential diagnosis of BPH and CaP cases in "gray zone" using F/T%.

| Study groups | N | Mean PSA ng/ml | Cutoff of *F/T% F/T%>18 n | F/T% | F/T%<18 n | F/T% |
|---|---|---|---|---|---|---|
| BPH | 18 | 10.1 | 16 | 33.7 | 2 | 15.6 |
| CaP | 13 | 14.9 | 1 | 23.3 | 12 | 10.9 |
| Total | 31 | 12.5 | 17 | 28.5 | 14 | 13.2 |

*Free PSA/Total PSA x100 = Percent Free PSA
$p < 0.05$
Sensitivity = 12/14 ¥ 100 = 86%
Specificity =16/17 ¥ 100 =94%
Predictive value of a Positive Test = 12/13x100 = 92.3%
Predictive value of a Negative Test = 16/18x100 = 88.8%

The three 'cutoff' values of less than 4 ng/ml, 4-20 ng/ml and over 20 ng/ml for PSA were applied to the results. At the under 4 ng/ml, 75% of controls were predominant group, while BPH were 28% and CaP 22%. In the range of 4-20 ng/ml, BPH was the leading group with 50% subjects, CaP cases were 36% and controls 14%. In the higher values of over 20 ng/ml, the CaP were highest, being 46%, to be followed by BPH as 16% and controls as 11% (Figure 3 and Table I).

The Table I suggests that 75% of healthy, 28% of BPH and 22% of CaP cases shared the normal zone area of PSA cutoff value 4 ng/ml. 50% of BPH cases, 14% of the healthy subjects and 36% of the CaP cases shared the grey middle area of BPH zone

(4-20 ng/ml). The cancer zone (>20 ng) was shared by 42% by CaP cases and 33% by healthy and BPH cases (11% and 22% respectively).

The bases of calculation for sensitivity, specificity and predictive values when the BPH and CaP cases were grouped as positive on "Gold Standard" and healthy group as the true negatives are shown below (Table II). Majority (88.8%) of the BPH cases fell in the area of cutoff >18% of ratio between free and total PSA while most (92.3%) of the CaP cases fell in the cutoff <18 % (Figure 4).

A free-PSA cutoff value of 18% improved the ability of the PSA test to differentiate between BPH and CaP cases in the diagnostic 'gray zone'. Sensitivity of the test to correctly diagnose BPH and CaP was 86%, while its specificity was 94%. The predictive values of positive and negative tests were 92.3% and 88.8% respectively.

## Discussion

The present study has confirmed the previous observations of many studies that total PSA increases with age and prostate mass, therefore, BPH and CaP cases show higher levels of PSA. The problem, however, is that in the initial stages of CaP when the prostatic growth is in the initial stages the total PSA does increase but differentiation between BPH and CaP is not obvious. Only in advanced stages of CaP the total PSA exceeds 20 ng/ml. Among controls, 4 subjects (11.1%) had PSA level higher than 20 ng/ml. Since such subjects were clinically healthy, nothing could be suggested about their prostate gland. If the cut-off value is raised to say 30 ng/ml, this would clearly differentiate the healthy from the unhealthy groups. But the preferred requirement is to differentially diagnose CaP at an early stage when the disease is still localized to the gland and carries better prognosis for early surgery. Out of prostate cancer cases 22% had serum PSA levels up to 4 ng/ml, which showed that PSA alone, cannot be considered the 'perfect' tumor marker for the early detection of prostate cancer. Results of the study elsewhere in this regard have also suggested that about 15.5% of men with prostate cancer have serum PSA levels upto 4 ng/ml.[8]

In this regard the free to total complexed PSA ratio has been found to help. It has been observed that in BPH the free PSA exceeded 18% cutoff value; but in CaP the free to total PSA was reversed. Our study has shown consistent results to the studies elsewhere. A percent free-PSA cutoff of 18% or less is a strong indicator of prostate cancer.[9] Percent free-PSA has its maximum utility to detect prostate cancer in the 'gray zone', i.e. when the serum PSA is in the range 4-20 ng/ml.[10,11] Reference standards for local population need to be established by increasing the number of subjects studied, in order to suggest more accurate cutoff values.

Considering this ratio of free to total proportionately the sensitivity, specificity and productivity values have been found to be very significant. This is superior to simple cutoff values of total PSA for differential diagnosis.

## Conclusion

Total PSA and the percentage free-PSA is useful marker for the early detection of prostate cancer cases. Percent free-PSA cutoff of 18% or less significantly improved the specificity and ability to differentiate BPH and prostate cancer cases, as compared to the use of total PSA alone.

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