

## Serum PSA level in Prostatic lesions with Histopathological correlation in Gujarat

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**Abstracts:** Background: Prostate specific antigen (PSA) has been widely used in the diagnosis and management of patients with prostate cancer. It may be elevated in other prostatic diseases and surgical procedures. PSA exists in two forms, a major bound form (cPSA) and a free form (fPSA). Objectives: The objective of the study was to determine the relationship between serum fPSA levels and histologic findings in biopsy specimens of men with prostatic disease. Material and methods: This study includes 80 cases of prostatic diseases and 20 controls for the study were taken from the patients admitted in surgical wards with no prostate related complain, in different age were planned for transurethral resection of prostate (TURP). All the cases and controls were evaluated by serum prostate specific antigen level. Results: The median serum fPSA values for control, malignant and nonmalignant lesions were  $3.66 \pm 0.029$  ng/ml,  $20.33 \pm 0.0106$  ng/ml and  $6.47 \pm 0.8127$  ng/ml respectively. Mean serum PSA values in cases of prostatic hyperplasia with or without dysplasia (PIN: Prostatic Intraepithelial Neoplasia I to III), prostatitis, well to moderately differentiated adenocarcinoma and poorly differentiated adenocarcinoma were 6.49 ng/ml, 5.35 ng/ml, 18.92 ng/ml and 31.6 ng/ml respectively. Cut off value of serum PSA 4 ng/ml the sensitivity, specificity and positive predictive value were 100 % and 14.28 % respectively while using 10 ng/ml the findings were 77.77 %, 92.95% and 58.33% respectively. Difference is highly significant between control cases and nonmalignant cases, ( $p < 0.001$ ) as well as between nonmalignant cases and malignant cases ( $p < 0.001$ ). Conclusions: In cases of prostatic hyperplasia, chronic prostatitis and prostatic malignancy serum fPSA value increases significantly ( $P < 0.001$ ) above the standard (0 to 4 ng/ml) as compare to control and nonmalignant group. Statistically there is significant difference in serum fPSA values between control cases and non malignant cases as well between nonmalignant cases and malignant cases of prostate, but when serum PSA values are between 4.0 to 10.0 ng/ml. [Goswami A et al. NJIRM 2011; 2(4) : 33-38]

**Key Words:** Benign prostatic hyperplasia, fPSA, prostate cancer, prostatic intraepithelial neoplasia.

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**Introduction:** Tumour markers are substances that can be detected in higher than normal amount in the blood, urine or body tissue of some patient with certain type of cancer. A tumour marker may be produced by a tumor itself or by the body in response to the presence of cancer.<sup>1</sup>

Prostate specific antigen is a protein produced by both normal and abnormal prostate cells. The prostate specific antigen level in the blood may be elevated in men who have prostatitis, prostatic hyperplasia or malignant growth in the prostate. While PSA does not allow doctor to distinguish between benign prostatic condition (which are very common in older man) and cancer, an

elevated serum PSA level may indicate that other tests are necessary to determine whether cancer is present.<sup>1</sup>

Wang M C et al<sup>2</sup> suggested the potential significance of PSA in clinical application, as initial results indicated that this prostate antigen, although a eutopic component of the prostate, may play a role in the detection of prostate cancer. This attention was turned to the development of the PSA blood test and they were developed a serological test allowing PSA to be measured in the serum. Catalona et al<sup>3</sup> reported in an expanded study that PSA screening is effective in detection of organ confined, early stage prostate cancer.

In Chu et al<sup>4</sup> confirmed by immunoelectrophoresis method and by ELISA method that only tissue of prostate origin contained significant amount of PSA and no statistically significant difference in PSA level was found among normal, benign and malignant prostatic lesions.

The American cancer society in 1992 recommended the use of PSA and DRE in the annual physical examination for men 50 years or older.<sup>5</sup> Study was conducted in mind keeping objective to assess the diagnostic accuracy of serum PSA in prostatic lesions. To correlate the serum PSA level findings with histopathological diagnosis.

**Material and Methods:** This prospective, observational, hospital-based cohort study was carried out after prior approval by Institutional Ethics Committee. In the present study 80 cases of prostatic disease and 20 controls in different age groups admitted to the general surgery wards of Guru Gobind Singh Hospital, Jamnagar, were enrolled in the study between January 2003 to October 2004.

The presenting complaints of cases with prostatic disease were hesitancy, dysuria, frequency, urgency, dribbling of urine after completing urination, incomplete emptying sensation etc. All patients were admitted in surgical wards of Guru Gobind Singh Hospital, Jamnagar. Controls for the study were taken from the patients admitted in surgical wards with no prostate related complaints. All patients were followed up in wards till discharge from the hospital. In all the cases detailed history was taken and physical examination was performed, which included digital rectal examination. Control group had normal digital rectal examination. Consent of all the patients was taken. All the cases and controls were evaluated by serum prostate specific antigen level. The test kit of monobind from LILAC, based on principle of ELISA was used and were investigated for routine hematological investigations, radiological investigations including volume and size of prostate measured by Ultrasonography.

Specimens of both study and control group were received for histopathological study in Pathology

Department of Shri M. P. Shah Medical College, Jamnagar. Histological classification of prostate tumours is according to WHO classification.<sup>6</sup> Statistically  $P < 0.05$  is significant.

**Result:** Out of 80 patients studied, age distribution in cases of prostatic disease group, the maximum patients were in 7<sup>th</sup> decade and minimum in 5<sup>th</sup> decade and in control group were from 7<sup>th</sup> and 8<sup>th</sup> decade age group. Age specific mean serum PSA value for different age group were calculated from the 20 controls who did not have any prostatic complains. The mean value of serum PSA was increased with age and above the 7<sup>th</sup> decade it was more than 4 ng/ml, but none had more than 10 ng/ml although there was no any linear relation found with the age.

Detail of PSA level in Malignant and non malignant case is shown in table 1 and serum PSA level and mean age in control cases and in cases with prostatic lesion is shown in table 2

**Table No.1: Showing relation of serum PSA level with histopathological diagnosis of prostatic lesions.**

Serum PSA level (ng/ml)	Histopathological diagnosis		No. of patients
	Malignant cases	Nonmalignant cases	
< 4	0	17	17
4 to 10	2	49	51
> 10	7	5	12
Total	9	71	80

**Table No.2: Showing mean serum PSA level and mean age in control cases and in cases with prostatic lesions.**

Group	Mean Age (year)	Mean Serum PSA $\pm$ S.D. (ng/ml)
Control cases	60.5 $\pm$ 4.7	3.66 $\pm$ 0.029
Malignant cases	70.3 $\pm$ 5.6	20.33 $\pm$ 0.0106
Nonmalignant cases	68.1 $\pm$ 8.1	6.47 $\pm$ 0.8127

In the patients with prostatic hyperplasia the mean serum PSA value was higher than the mean value of controls in particular age groups, and all serum PSA value were higher than the cut off level 4.0

ng/ml and with carcinoma of prostate the mean serum PSA values were very high as compare to the controls in particular age group. The maximum mean value obtained was 29.3 ng/ml.

In our study we were found that the mean serum PSA values were very high in malignancies followed by in prostatic hyperplasia with PIN III then in prostatic hyperplasia with chronic prostatitis. Although all mean serum PSA values were crossing the cut off level of 4.0 ng/ml in patients with any prostatic lesion as shown in Table-3

**Table No.3: Showing mean serum PSA values in different prostatic lesions and in control group.**

Study Group	n	Mean value S.PSA	
Control group :	20	3.66	
Prostatic lesions :			
Prostatic hyperplasia	16	4.09	
Prostatic hyperplasia with chronic Prostatitis	17	7.80	
Chronic prostatitis	02	5.38	
Prostatic hyperplasia with dysplasia with or without chronic prostatitis	PIN I	20	5.82
	PIN II	12	6.38
	PIN III	04	10.72
Malignancy:welltomoderately differentiated adenocarcinoma	08	18.92	
Malignancy:poorlydifferentiated adenocarcinoma	01	31.60	

Difference in PSA level is highly significant between control cases and nonmalignant cases, ( $p < 0.001$ ) as well as between nonmalignant cases and malignant cases ( $p < 0.001$ ).

**Discussion:** Prostate cancer is the most common form of cancer among men. Although most prostate cancers are relatively slow growing and remain clinically unrecognized, their course is often unpredictable in terms of its spread of progression, perhaps because of the considerable heterogeneity of the histological grade and a multitude of other factors that influence tumor growth.<sup>8</sup> Prostate cancer is very uncommon before the age of 50 years, but its frequency climbs steeply with age to

peak in the 9<sup>th</sup> decade for both incidence and mortality rate.<sup>9</sup>

Two of the reasons for the high mortality are that many patients have incurable disease at the time of diagnosis and patients with potentially curable tumors are rarely symptomatic. Chodak G<sup>10</sup> suggested that to reduce mortality from this disease, screening has frequently been recommended for asymptomatic men in the high risk age group.

Prostate specific antigen is the initial screening test and most useful marker for early detection of prostate cancer. Although PSA is invaluable marker for screening, it is prostate specific but not cancer specific, since PSA may also be elevated in prostatic hyperplasia. The discrimination between prostate carcinoma and prostatic hyperplasia is potentially more problematic in patients with serum PSA values between 4.1 to 9.9 ng/ml. Several other methods have been proposed to identify cancer patients with intermediate serum PSA level.<sup>11</sup>

Age specific reference range of serum PSA in control cases in the present study were as follow: < 50 yrs ( $2.0 \pm 0.01$  ng/ml), 50 to 59 yrs ( $2.77 \pm 0.12$  ng/ml vs  $0 - 3.0$  to  $0 - 3.8$  ng/ml), 60 to 69 yrs ( $3.36 \pm 0.02$  ng/ml vs  $0 - 4.0$  to  $0 - 5.4$  ng/ml), 70 to 79 yrs ( $4.08 \pm 0.08$  ng/ml vs  $0 - 5.0$  to  $0 - 6.9$  ng/ml),  $\geq 80$  yrs ( $5.90 \pm 0.8$  ng/ml vs  $0 - 8.8$  ng/ml) in other studies<sup>12,13,14</sup>

Similar findings has been observed by other studies showing increase in serum PSA level with age. The values of serum PSA in the present study are relatively close to the findings of Richardson et al.<sup>12</sup>The higher values in previous studies of may be due to racial difference as they studied cases in white population.<sup>13,14</sup>

In the present study maximum patients with prostatic lesion were in the 7<sup>th</sup> decade of life (46.25 %). The findings of our study is consistent with the findings of Gil et al. (42.9%).<sup>15</sup>

In our study mean serum PSA values in cases of prostatic hyperplasia with or without dysplasia (PIN I to III), prostatitis, well to moderately differentiated adenocarcinoma and poorly

differentiated adenocarcinoma were (6.49 ng/ml vs  $35.95 \pm 4.03$  ng/ml),<sup>16</sup> (5.35 ng/ml vs 8.48 vs 8.03 ng/ml),<sup>17,18</sup> (18.92 ng/ml vs > 100 ng/ml)<sup>[16]</sup> and (31.6 ng/ml vs  $56.22 \pm 4.29$  ng/ml)<sup>16</sup> respectively.

The serum PSA value in cases of prostatitis in the present study is consistent with other studies but the slight lower value was found in the present study because as in other studies, no criteria regarding percentage of inflammatory process were considered in present study.<sup>17,18</sup> Findings of present study are consistent with the study of Emokpae et al but as compare to present study he found high serum PSA values which may be because of racial difference in study group or technical difference of serum PSA analysis as he used electrochemiluminescence assay technique.<sup>16</sup>

In the present study the mean serum PSA values in cases of prostate hyperplasia were higher than values in control cases for particular age groups. Mehmet et al. studied the correlation between PSA and age to analyze serum PSA levels of men proven to have benign prostatic hyperplasia and to document any correlation between PSA and age. They concluded that patients with benign prostatic hyperplasia had mean serum PSA values higher than the control cases. As the age increased the mean serum PSA value in the patients with benign prostatic hyperplasia was increased. The findings of present study were consistent with the findings of Mehmet et al.<sup>14</sup>

In our study malignant cases of prostate the mean age was  $70.3 \pm 5.6$  year and mean PSA was  $20.33 \pm 4.8$  mg/ml whereas in nonmalignant cases the mean age was  $68.1 \pm 8.1$  year and mean serum PSA was  $6.47 \pm 3.5$  ng/ml. Similar findings were observed by other studies.<sup>[15,19]</sup> Gil et al. carried out a Multicentre study on the detection of prostate cancer by digital rectal examination and prostate specific antigen in the men with or without urinary symptoms and found mean serum PSA value 19 ng/ml at mean age  $72.7 \pm 8.5$  year in malignant cases and 6.5 ng/ml at mean age  $69.5 \pm 7.75$  ng/ml in non malignant cases of prostate.<sup>15</sup>

Muhittin et al. carried out diagnostic approach to prostate cancer using total prostate specific antigen-based parameter together. He found mean

serum PSA value  $21.5 \pm 4.21$  ng/ml at mean age  $66.9 \pm 7.9$  years in malignant cases and  $9.61 \pm 0.74$  ng/ml at mean age  $63.6 \pm 5.9$  years in non malignant cases.<sup>11</sup>

In the present study detection rate of prostatic malignancy was 3.92% (2 out of 51 case) when serum PSA values were between 4.0 ng/ml to 10 ng/ml whereas detection rate was 58.33% (7 out of 12 cases) when serum PSA values were above 10 ng/ml. Cooner et al. found the prostatic malignancy detection rate 38.1% and 65.6% when serum PSA values between 4 to 10 ng/ml and above 10 ng/ml respectively in cases suspicious for malignancy by digital rectal examination, while the rate was 5.5% and 31.3% when serum PSA values between 4 to 10 ng/ml and above 10 ng/ml respectively in cases not suspicious for malignancy on digital rectal examination.<sup>19</sup>

Braver et al. found the prostatic malignancy detection rate 22% and 67% when serum PSA values between 4 to 10 ng/ml and above 10 ng/ml respectively in cases suspicious either by digital rectal examination or ultrasonography or both.<sup>20</sup>

The findings of present study are consistent with other studies when using serum PSA cut off level 10 ng/ml. But the detection rate of other studies is higher when using serum PSA cut off level 4 ng/ml especially in those selected cases suspicious for malignancy on digital rectal examination or ultrasonography or both. This is because of in present study all cases were selected whether suspicious for malignancy by other parameter or not.<sup>19,20</sup>

In this study using cut off value of serum PSA 4 ng/ml the sensitivity, specificity and positive predictive value were (100% vs 86.7% to 93.58%, 23.94% vs 21.05% to 37% and 14.28% vs 43.4% to 60.53%) respectively while using 10 ng/ml the findings were (77.77% vs 44.90% to 63.9%, 92.95% vs 68.42% to 73.1% and 58.33% vs 60.2% to 64.71%) respectively.<sup>21,17,22</sup>

We have calculated at different cut off values because the results obtained at serum PSA level between 4.0 to 10 ng/ml were not diagnostic of malignancy. The findings of the present study were

consistent with other studies<sup>19,20</sup> shows that as the cut off value of serum PSA is raised the sensitivity of the test is decreased but the specificity and positive predictive value increased. This suggests that increasing cut off level increases the cancer detection rate.

Prostate malignancy is most common form of cancer with increasing age of men. Its early detection reduces mortality and morbidity. Serum PSA measurement help much for screening for prostate malignancy but serum PSA level increases with age as well as many other factors and prostatic lesions affect serum PSA level. So its specificity can be increased with increasing cut off level or using age specific reference range. However serum PSA as a single most screening parameter is not sufficient to screen for prostatic malignancy.

**Conclusion:** Serum PSA increases with age in cases not having any prostate related complains. In cases of prostatic hyperplasia and chronic prostatitis serum PSA value increases significantly ( $P < 0.001$ ) above the standard (0 to 4 ng/ml) and also above the age specific reference ranges but in majority of cases the values are below 10 ng/ml. In cases of prostatic malignancy, serum PSA value increases significantly ( $P < 0.001$ ) as compare to control and nonmalignant group. In majority of cases it is above 10 ng/ml. For detection of prostatic malignancy by serum PSA, the specificity and positive predictive value increases with raising the cut off level from 4 ng/ml to 10 ng/ml. Statistically there is significant difference in serum PSA values between control cases and non malignant cases as well between nonmalignant cases and malignant cases of prostate, but when serum PSA values are between 4.0 to 10.0 ng/ml it makes interpretation difficult as serum PSA values of some nonmalignant cases and malignant cases are overlapping here. Serum PSA estimation is invaluable test for detection of prostatic malignancy but as it is affected by many factors and also increases in prostatic non malignant lesions, limiting its diagnostic accuracy especially when the values obtained between 4.0 to 10.0 ng/ml. In such cases it requires help of other parameters also to consist or rule out the diagnosis.

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