



## Age-Specific Reference Range for Prostate Specific Antigen: A Retrospective Analysis in North Indian Population

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### ABSTRACT

Studies have attempted to establish age-specific reference range for Serum Prostate Specific Antigen (PSA) levels, to enhance its sensitivity and specificity as a marker for prostate cancer. Biopsy, acknowledged as the gold standard diagnostic tool for prostate cancer, holds the demerits of being invasive procedure. Our study was directed to find a correlation between TPSA with age and to establish its appropriate reference range for evaluation of men at risk for early detection of potentially curable prostate cancer to avoid unnecessary biopsies. Retrospective data of serum PSA levels was analyzed in 1077 men aged between 40-90 years with no diagnostically positive prostate cancer, and whose PSA values were obtained as a part of clinical work up of symptoms related to non-malignant urological conditions, during the period of 2010-11. Serum PSA was estimated by solid-phase, competitive chemiluminescent immunoassay using standard kits. There was a continuous increase in mean and median of PSA, with a significant correlation ( $p < 0.05$ ), with advancing age. It also implies that serum PSA correlates with age, primarily due to increasing prostate volume as age advances.

**Keywords:** Total Prostate Specific Antigen, Prostate Cancer, Reference Range, Chemiluminescence

### INTRODUCTION

Prostate cancer is among the most common cancer in men with the incidence escalating in past two decades in Asian countries. [1] Prostate specific antigen (PSA) is used as a screening tool for prostate cancer. It is a serine protease which is produced by the prostatic epithelium and periurethral glands which is present in large amounts in prostatic secretions. It is an organ specific biomarker and used as a marker of benign epithelial masses. [2] It was initially used as a marker of treatment response and recurrence in men with prostate cancer, its potential for screening was understood in a cohort of 1653 men, using a threshold value of 4 ng/ml. [3] PSA

levels may increase due to number of factors such as hyperplastic growth of prostatic tissues, inflammation, prostatic manipulation, urinary retention, sexual activity, and hypothetically by presence of undetectable clinically insignificant foci of cancer. [4] European randomized study of screening for prostate cancer (ERSPC) indicated 30% positive predictive value of PSA as a screening test [5] and in combination with digital rectal examination (DRE) its positive predictive value increases to 51%. [6] To enhance the clinical significance of the PSA test, it is important to establish the age-specific reference range instead of a single reference range.

## MATERIALS AND METHODS

This was a retrospective data based study of serum PSA levels conducted in the tertiary care centre at Rohtak. 1077 men, mainly representing the Haryana state of Northern India, aged between 40-90 years were selected with no prostate cancer, and whose PSA values were obtained as a part of clinical work up of symptoms related to non-malignant urological conditions, during the period of 2010-11. Men were grouped into six age groups: less than 40 years, 40–49 years, 50-59 years, 60–69 years, 70–79 years and more than 80 years. Group

comparison was done using appropriate statistical test. Serum PSA was estimated by solid-phase, competitive chemiluminescent immunoassay on ADVIA Centaur CP using standard kits provided by Siemens (USA).

## RESULTS

For every age group studied, valid number, mean, standard error, the 95% and +95% confidence range, and the lower and upper range for PSA test values are shown in Table 1 with statistical significance (Table 2).

Age (years)	N	Mean PSA (ng/mL)	Std. Deviation	Std. Error	95% Confidence Interval for Mean PSA	
					Lower Range	Upper Range
<40	60	1.6078	2.05052	.26472	1.0781	2.1375
40-49	76	1.9029	1.87503	.21508	1.4744	2.3314
50-59	202	1.9005	1.88570	.13268	1.6389	2.1621
60-69	410	2.0428	1.89542	.09361	1.8588	2.2268
70-79	293	2.5289	2.16323	.12638	2.2802	2.7776
>80	134	2.7766	2.20523	.19050	2.3998	3.1534
Total	1175	2.1920	2.03069	.05924	2.0757	2.3082

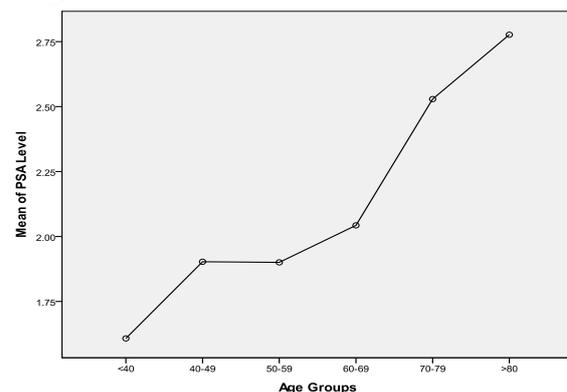
Table-1 presents the frequency of observations for each group. Analysis of mean score indicates that as age advances the PSA level was found to be increasing.

PSA Level					
	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	132.166	5	26.433	6.562	.000
Within Groups	4709.078	1169	4.028		
Total	4841.244	1174			

One way Analysis was used to ascertain whether there are any significant differences among the mean scores of six groups. Results of F-statistics (given in Table-2) of 6.56 ( $p < 0.05$ ) indicate that at least one of the group differs from the rest in its mean score.

There was a continuous increase in mean and median of PSA, with a significant correlation ( $p < 0.05$ ), with advancing age. The recommended age-specific reference range of PSA values were as follows: for the age group less than 40 years, 0-2.14 ng/ml; for the age group 40-49 years, 0-2.33ng/ml; for the age group 50-59 years, 0-2.16 ng/ml; for the age group 60-69 years, 0-2.27 ng/ml;

for the age group 70-79 years, 0-2.78 ng/ml and for the age group more than 80 years, 0-3.15ng/ml There was statistically significant correlation between PSA and age, higher levels were found with increasing age (Graph 1, Table 3 and Table 4).



Graph 1

For the detailed analysis, Post hoc analysis (Tukey HSD method) was applied. T-statistics values (given in Table-3) indicate that PSA level of age group of 70-79 differ significantly in its mean PSA score from the age groups of <40 (t-value 3.24  $p < 0.05$ ), 50-59 (t-value 3.42  $p < 0.05$ ) and 60-69 (t-value 3.17  $p < 0.05$ ).

Table-3 Multiple Comparisons						
Dependent Variable: PSA Level						
Post hoc Method: Tukey HSD						
Category: 70-79						
(J) Age Groups		Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
dimension3	<40	.92107*	.28441	.016	.1093	1.7329
	40-49	.62601	.25836	.149	-.1115	1.3635
	50-59	.62841*	.18355	.008	.1045	1.1523
	60-69	.48610*	.15354	.020	.0478	.9244
	>80	-.24766	.20931	.845	-.8451	.3498

\*. The mean difference is significant at the 0.05 level.

Similarly, PSA level of age group of >80 differ significantly in its mean PSA score from the age groups of <40 (t-value 3.75 p<0.01), 50-59 (t-value 3.92 p<0.01) and 60-69 (t-value 3.67 p<0.01).

Table-4 Multiple Comparisons						
Dependent Variable: PSA Level						
Post hoc Method: Tukey HSD						
Category: >80						
(J) Age Groups		Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
dimension3	<40	1.16873*	.31177	.003	.2788	2.0587
	40-49	.87367*	.28821	.030	.0510	1.6964
	50-59	.87607*	.22362	.001	.2378	1.5144
	60-69	.73376*	.19972	.003	.1637	1.3038
	70-79	.24766	.20931	.845	-.3498	.8451

\*. The mean difference is significant at the 0.05 level.

## DISCUSSION

Single cut off value of 4ng/mL is not apt for all age groups. The standard reference range of < 4.0 ng/ml for PSA does not compensate for age-related volume changes in the prostate primarily due to hyperplastic growth of prostatic tissue. Our results of increasing PSA level with advancing age are similar to study by Agarwal et al. They found a statistically significant correlation between PSA and age, higher levels were found with increasing age (rs = 0.70, p<0.001). [7] Similar results are seen in studies of Gupta et al and Berger et al. [8-9] Young patients with smaller prostates may be at risk below this value. In older patients slightly higher values may not be alarming when compared with peer group. Some countries are using less than 2ng/mL for early detection of malignancy in young population. [10-12] It has been suggested that serum PSA levels varies among different races. An Indian study by Agarwal et al in a hospital-based population describes the PSA and PSA density values. The values tend to be higher than those reported in the western literature.

[7] Richardson et al have compared age specific PSA reference ranges in Japanese men with caucasians. Japanese men have lower age- specific PSA and higher PSAD values when compared with western literature. [10] Gupta et al also noted that Japanese men with lower urinary tract symptoms (LUTS) and clinical benign prostatic hyperplasia (BPH) release more PSA per unit volume than western men. The apparent difference was attributed to difference in composition of the prostates. [8]

## CONCLUSION

The study emphasizes PSA level as a function of age, primarily due to increasing prostate volume as the age advances. The concept of age specific reference range of PSA value might address various shortcomings of PSA test. First, it could improve the sensitivity of PSA by detecting curable, organ confined tumors in younger men when the widely accepted threshold of 4ng/mL is lowered. Secondly, age specific reference range would modulate PSA interpretation in older men, taking into

account the increasing prevalence of both benign prostatic growth and incidental, non-life threatening encapsulated cancers in the older cohort of men. Further it can help to reduce unnecessary prostate biopsies. However, the association between PSA value and age is not entirely clear and reference range for the respective population needs to be established on a much larger cohort of men to come to a definitive conclusion.

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