ORIGINAL ARTICLE

Age-specific Reference Range of Prostate-specific Antigen among Indian Men: A Retrospective Observational Study

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Abstract:

Background: Prostate cancer (CaP) has a varied occurrence across the globe. Serum Prostate Specific Antigen (PSA) level is influenced by various factors which include race and ethnicity, environmental factors, lifestyle, metabolic changes, physiologic changes and advancing age. Data is scarce regarding reference range for Indian population. *Aim and Objectives*: To determine age specific serum PSA level in apparently healthy south Indian men. *Material and Methods*: Reports of 5199 adult males tested for serum total PSA were screened. Persons with PSA >20ng/ml were excluded from the study. A total of 4583 apparently healthy adult men from tertiary care hospital in Mangaluru, India were included as subjects. The median serum PSA levels were calculated in each 10-year age group for Indian males. These were compared with age specific reference range reported in different populations across the country and also among different ethnicities across the globe. The data was analysed using SPSS 16.0, Inc, Chicago, IL. *Results*: The median PSA value was 0.76 ng/ml in subjects younger than 50 years; 0.97 ng/ml in 50-59 years group; 1.38 ng/ml in 60-69 years group; 1.89 ng/ml in 70-79 years group and 2.19 ng/ml in persons older than 80 years. We found a positive correlation between age and serum PSA levels. *Conclusions*: PSA is influenced by various factors which makes depending on a single reference for all age groups a questionable practice. This study highlights the need to establish age specific reference ranges for different populations.

Keywords: Prostate Cancer, Prostate Specific Antigen, Reference range

Introduction:

Incidence of cancer is on a rise due to changes in lifestyle and increased life expectancy. Prostate Cancer (CaP) has a varied occurrence across the globe. It is more commonly diagnosed in the west than in India [1]. Early detection of CaP is possible due to its relatively slow growth, sufficient lead time before becoming incurable and with the help of a simple screening test [2]. Inter-examiner variability and detection of cancer at an advanced stage has led to replacement of Digital Rectal Examination (DRE) by other modalities as screening tools [3]. Presently prostatic biomarkers

including Prostate Specific Antigen (PSA), Acid Phosphatase (ACP) and Prostatic Acid Phosphatase (PAP) are utilized in the screening of CaP [4]. Biopsy is used as a definitive measure for diagnosis of CaP. Serum PSA levels <4 ng/ml are regarded as normal but no PSA level is spared of risk of cancer [5]. PSA corresponds well with clinical stage in patients known to have CaP [6]. Abnormal PSA values can be caused by Benign Prostatic Hyperplasia (BPH), prostatitis, cystitis, ejaculation, perineal trauma, recent use of instruments for testing, surgeries of the urinary tract etc [3]. PSA levels beyond 4 ng/ml associated with abnormal DRE are subjected to biopsy. Since PSA is influenced by ethnicity, environmental factors, lifestyle, metabolic and physiologic changes with advancing age of an individual, acceptance of a western cut-off of 4 ng/ml in our population is open to discussion. Hence, we undertook this study to find the age specific PSA with an objective to establish PSA reference range in Indian men and compare it with males of other ethnic backgrounds.

Material and Methods:

A cross-sectional observational study was conducted on laboratory results for PSA testing during a period of twelve months, after obtaining approval from the institutional research and ethics committee. The data was collected from the biochemistry laboratory database of the central laboratory of a tertiary care hospital, Mangaluru, India.

Sample size calculation was done using the following formula:

$$n = Z_{1-\frac{\alpha}{2}}\sigma^2 / (ME)^2$$

We calculated 464 as the minimum sample size required to estimate PSA reference range with 95% confidence interval. A total of 5199 subjects tested for serum PSA during the period were screened for inclusion by checking their hospital records. The total PSA level was assayed on Cobas e411 hormone analyser by the electrochemi-luminesence immunoassay.

Patients with PSA>20ng/ml were excluded from the study. Similarly, patients who were subjected to prostate biopsy, those diagnosed with prostate disease and on treatment were excluded from the study. A total of 4583 men without prostate disorders were enrolled into the study and divided into five groups based on their age. The decade wise division of study subjects was done as follows: Group 1: <50 years, Group 2: 50-59 years, Group 3:60-69 years, Group 4: 70-79 years and Group 5: >80 years.

Statistical Analysis:

All the data of cases were analysed using SPSS 16.0, Inc, Chicago, IL. Descriptive statistics, including the median, 25th and 75th percentiles of serum PSA levels distribution, were calculated in each 10-year age group. The relationship between serum total PSA level and age was assessed using Spearmann's correlation. All the p-values were two-tailed, and those <0.05 (95% Confidence Interval) was considered as statistically significant. Kruskal Wallis test was used to determine difference between median serum PSA in various age groups in our study and to compare across other stated studies.

Results:

The results of serum PSA concentrations in serum of 4583 apparently healthy males were analysed. The subjects ranged from 19 years to 96 years of age. Majority of the patients were in the age group 60-79 years. The median PSA value of the entire study population was 1.28 ng/ml. PSA was more than 4 ng/ml in 948 men, accounting to 20.3% of the study participants. Spearmann's correlation coefficient between PSA and age was found to be 0.266 ($p < 0.01$) for the overall sample size. The results of decade wise sub grouping of healthy men are presented in Table 1. The median PSA value is seen to be increasing with age; the PSA value in men younger than 50 years was 0.763ng/ml where as men older than 80 years had median PSA value of 2.195ng/ml. Progressive increase in median PSA concentration with advancement in age was witnessed. Kruskal Wallis test was used to determine difference between serum PSA in various age groups, it was not found to be statistically significant. Comparison of serum PSA levels among various populations shows, the median level of serum PSA in the Indian males were different from populations across the globe (Table 2).

Table 1: Distribution of Median Serum PSA Levels and their Interquartile Range among the Study Population Divided into Subgroups Based on Age

Age (Years)	Mean Age (Years)	Patients [n]	Prevalence of PSA (n)			Median PSA ng/ml	Percentile (25,75) ng/ml
			< 4 ng/ml n(%)	4-10 ng/ml n(%)	10-20 ng/ml n(%)		
<50	44	462				0.763	(0.495 , 1.33)
50-59	55.2	1244	1100 (88.5)	120 (9.6)	24 (1.9)	0.971	(0.555 , 1.94)
60-69	64.3	1499	1199 (80)	228 (15.2)	72 (4.8)	1.385	(0.713 , 3.125)
70-79	73.6	1049	777 (74)	196 (18.8)	76 (7.2)	1.89	(0.803 , 4.29)
>80		329	214 (65)	74 (22.5)	41 (12.5)	2.195	(0.869 , 6.15)

Table 2: Distribution of Median Serum PSA Levels (ng/ml) and the Interquartile Range (25^{th}, 75^{th} percentile) among Different Races and Studies according to Age Intervals

Age (years)	White [8]	Japanese [9]	Chinese [10]	Saudi [11]	Indian (our study)
40-49	0.7 (0.5, 1.1)	0.6 (0.4, 0.8)	0.87 (0.61, 1.24)	0.78	0.75 (0.48 , 1.41)
50-59	1.0 (0.6, 1.4)	0.7 (0.5, 1.2)	0.92 (0.63, 1.34)	0.87	0.97 (0.55 , 1.94)
60-69	1.4 (0.9, 3.0)	0.9 (0.5, 1.5)	1.15 (0.73, 1.95)	1.07	1.38 (0.71 , 3.12)
70-79	2.0 (0.9, 3.2)	1.4 (0.7, 2.1)	1.39 (0.80, 2.80)	1.26	1.89 (0.80 , 4.29)

Table 3: Decade wise Comparison of Median PSA among Indian Males

Age (Years)	Our Study (n=4667)	Karpaghavalli *et al.* [7] (n=461)	Gupta *et al.* [14] (n=1253)
40-49	0.75	0.7	0.65
50-59	0.97	0.8	0.79
60-69	1.38	1.1	0.88
70-79	1.89	1.04	1.25
>80	2.19	-	1.45

Table 4: Decade wise Comparison of Mean PSA among Indian Males

Age (Years)	Our Study (n=4667)	Agarwal *et al.* [13] (n=1772)
40-49	1.33	1.22
50-59	1.84	1.97
60-69	2.74	2.08
70-79	3.28	-
>80	4.16	-

The data among various studies done in the Indian Subcontinent have been compared with PSA levels obtained in our study subjects and presented in Table 3 (studies reporting median values) and Table 4 (Studies reporting mean values).

Discussion:

PSA, a marker for prostatic carcinoma, is a serine protease, 33-kDa protein, produced by prostatic ductal and acinar epithelium[7]. Serum PSA is a valuable diagnostic tool for detecting early CaP and monitoring its response to treatment. In order to help detect malignancy of prostate in younger males, it is favourable for laboratories to have age specific reference for PSA. A reference value of PSA <4 ng/ml is considered as a normal in our laboratory. This reference limit cannot be universal as it is influenced by the several endogenous factors such as genetics, hormonal profile, and immunological status of the individual [1]. This study was undertaken with an objective to establish PSA reference range in Indian men and compare it with males of other ethnic backgrounds.

This cross-sectional observational study included 4583 men without clinically evident prostate

disease. Median serum PSA levels were estimated in the various age groups. A positive correlation between PSA and age is noted which is strongly supported by previous reports in men of different races [10]. Indian men reported median PSA levels dissimilar in comparison with men from other ethnic background (Table 2).

Prostate being an important source of PSA can contribute to its elevated levels. This increase in serum PSA may be due to physiological or pathological variations in size of the prostate gland. PSA is elevated in many benign conditions like benign prostatic hyperplasia and prostatitis which are reported to be having higher occurrence after the 5^{th} decade in life. Elevation of PSA parallel with age can be attributed to the enlarging size of the prostate gland leading to increase in its volume. The anatomical transition zone is rapidly growing region of prostate in the middle-aged men contributes to the increasing PSA [12].

PSA <4 ng/ml is accepted as the normal range for all age groups. This cut-off was drawn based on the western population [5, 7, 10] without taking the age of the patient into contemplation. On exploring literature of various races it is evident that the median PSA is dissimilar across the globe for a particular age group. The African men are reported to have elevated levels of PSA when compared with age matched Asian men. PSA is widely influenced by a variety of factors like age, ethnicity, benign prostate disorders and presence of positive family history which amounts to a first degree relative having cancer of the prostate gland [12].

Wide spread usage of PSA screening has revealed greater incidence of prostate cancer in the western population than the Asian men. Earlier works have shown that the Asians have lower median PSA as compared to their western counterparts [15]. This could be justified by the lower incidence of prostate cancer in the Asian men [1]. The African men have been proposed to have higher predisposition to develop prostate cancer owing to elevated levels of the androgens like testosterone in the blood [16]. Testosterone causes proliferation of prostate gland leading to higher serum PSA levels [17]. The Caucasians are shown to have lower baseline testosterone [16]. A previous study conducted in 11,101 men who underwent prostatectomy showed that racial differences in the prostate size was a negligent contributor to variation of PSA in the different races [18]. Hormones such as estrogen, insulin and insulin like growth factor regulate the size of the prostate gland, consequently influencing the levels of PSA. Genetic polymorphism is another proposed theory for racial differences in the PSA levels. Shorter CAG trinucleotide repeats in the gene for androgen receptor are found to be present in the African American men. The lower activity of CYP3A4 gene responsible for testosterone deactivation is another genetic variation leading to higher PSA among few races [19-20].

On comparing our findings with previous studies (Table 3), we found an increased median PSA value as compared to the previous studies in the south Indian men. Table 4 shows the mean PSA being compared with an Indian study [13]. There is a paucity of data in this arena, which needs to be addressed. The Asian countries also are reflecting an increase in the incidence of CaP in the past decades probably under the influence of changing diet and lifestyle [21]. Increase in age is associated with higher incidence of CaP [22]. Etiopatho-genesis of prostate cancer has not been clearly understood. It is thought to be a multi stage process, in which race, positive family history,

lack of physical activity and other environmental factors have significant influence [23]. Present universal cut-off of PSA >4 ng/ml, needs to be viewed in new light. Prostate cancer is a treatable condition if detected early in the course of the disease. This emphasizes the need to reconsider serum PSA cut-off to suit the age and race of an individual. Considering reference interval for PSA which is age and race specific will make it a more potent biomarker to make a distinction of individuals with early focus of malignancy.

Our study being hospital based might have included subjects with benign conditions of prostate which are clinically asymptomatic leading to slightly higher values of PSA. The main strength of this study lies in its large study population. Thus, the results may be extended to the general population of this region.

Conclusion:

The results for serum PSA were found to be lower in Indians compared to western population. Ethnicity has an influence on serum PSA levels. Establishment of age specific reference ranges for different populations helps in diagnosing CaP in younger males and avoiding unnecessary biopsy in older males. Formulation of reference range can help clinicians to detect CaP at an early stage, while taking all factors into consideration. One cannot rely on a single reference for all age groups and hence further multicentre studies are warranted in this direction.

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