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Original Research Article

Age-specific serum prostate-specific antigen references range among healthy men in Port Harcourt, Nigeria: a retrospective hospital-based study

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ABSTRACT

Background: Total prostate-specific antigen (PSA) levels increase with advancing age. Its age-specific ranges are being advocated to increase its sensitivity and specificity. This study was aimed to examine the relationship between total PSA levels and age, and to determine the age-specific ranges among healthy men without prostatic diseases in our environment.
Methods: In this retrospective hospital-based study, records of men without prostatic diseases who had visited University of Port Harcourt Teaching Hospital for routine screening for prostate cancer using serum total PSA between 1st January 2012 and 31st December 2016 were retrieved and analyzed using descriptive statistics and Spearman's correlation test. A p-value < 0.05 was considered significant.
Results: Records of 476 men aged 38 to 86 years were recruited for the study. The age-specific total PSA reference range using the 95th percentile total PSA concentration values in each 10year groups were 0-1.60, 0-4.93, 0-6.93, 0-7.80, 0-9.65, and 0-13.30 for the age groups 30-39, 40-49, 50-59, 60-69, 70-79 and >80years respectively. There was a positive correlation between serum PSA concentration and age ($r_s = 0.395$; $p<0.001$).
Conclusions: Total PSA increases with advancing age and its age-specific reference range in this study are similar to findings in our environment but higher than the values found in other parts of the world. We suggest serum PSA normal reference values should be characterized by age and race in our environment.

Keywords: Age, Age-specific, Nigeria, Prostate cancer, Reference

INTRODUCTION

Prostate cancer has assumed an epidemic proportion around the globe especially among men of the black race.[1,2] Its rising pattern both in incidence and mortality has taken an alarming trend for the past two decades in Nigeria.[3] Port Harcourt is reported to have the highest incidence rate (37.2%) at the moment in Nigeria with men between 70-79years predominating among other age groups.[4] The disease management has additionally been challenging to Urologists owing to the issue of prostate-specific antigen qualities in the diagnosis of the disease.[5,6] PSA has quite some time been described for not being an ideal tumor biomarker for prostate cancer, however this is currently being addressed contentiously with the idea of derivations of PSA indices (velocity, density and free to total ratio) which are endeavors to enhance its sensitivity and specificity for prostate cancer diagnosis.[6] Its serum levels in men have been observed to vary from one geographical location to another, from ethnicity to ethnicity and from race to race with healthy men of the black race having higher levels than their Caucasian and Asian counterparts and its level also correlates with advancing age and the prostate volume.[7-9] Accordingly,

various authors have questioned the use of the traditional total PSA cut-off value of 0-4ng/ml across all regions and age in the diagnosis of prostate cancer.[10] Thus age-specific total PSA reference values are currently being advocated to increase the PSA sensitivity in the younger age (to enhance detection of early curable prostate cancer) group of men suspected of prostate cancer while increasing the specificity in the older age (to avoid unnecessary management protocols of physiological age-related increase of PSA) group of men.

In Nigeria, the normal reference range still widely accepted remains the total PSA reference range level of 0-4ng/ml. However, a recent community-based study in the South-west of the country has also reported age-adjusted PSA reference values of Nigeria men.[11] The authors had concluded with a suggestion on the need to use their reported age-specific total PSA reference ranges in Nigeria. These authors had determined the age-specific total PSA reference range of Nigerian men in 10-year-age groups (40-49, 50-59 and 60-69), but no reference was reported for men between the age of 70-79years.

Therefore, this study was aimed to examine the relationship between total PSA levels and age, and to determine the age-specific total PSA reference ranges of healthy men without prostatic disease who were visiting University of Port Harcourt Teaching Hospital for prostate cancer screening through the Department of Chemical Pathology and Metabolic Medicine amid a five-year time frame (1st January 2012 to 31st December 2016). Specific objectives of study were to determine the relationship between the serum total PSA levels and age and to determine the age-specific serum total PSA reference range within 10-year-age groups. Also, to compare these groups reference ranges with recent studies in Nigeria and around the globe.

METHODS

Study area and site

This study was carried out in the Department of Chemical Pathology and Metabolic Medicine of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria. The Hospital is a Federal Government-owned tertiary health center located in Port Harcourt, Rivers state, in the heart of Niger Delta area of Nigeria and serves as a referral center for all the primary and secondary health care centers in River State and the neighboring Niger Delta states. Between five to ten men present daily to the Hospital through the Department of Chemical Pathology and Metabolic Medicine for routine cancer screening including prostate cancer using biomarkers.

Study description

A retrospective, descriptive analysis of serum total PSA assay results and determination of age-specific total PSA reference range of 488 men who had presented to the Department of Chemical Pathology and Metabolic Medicine for routine screening for prostate cancer during a five-year period from 1st January 2012 to 31st December 2016 was undertaken.

Inclusion and exclusion criteria

Inclusion Criteria was all men without symptoms or signs suggestive of prostatic diseases (lower urinary tract symptoms and abnormal digital rectal examination findings) presenting to the department for routine screening for prostate cancer using serum total PSA.

Exclusion criteria include all men who presented with symptoms or signs (lower urinary tract symptoms or abnormal digital rectal examination) suggestive of prostatic disease, including men with total PSA level above 20ng/ml and those whose data are incompletely reported in either test or case note records.

Data collection

Data were retrieved from the laboratory record books and case notes of the Department of Chemical pathology and Metabolic Medicine and entered into Statistical Package Social Science (SPSS) version 20. Demographic data (age), clinical diagnosis (routine prostate cancer screening), digital rectal examination findings (Abnormal or normal) and total PSA levels in ng/ml units were all collected.

Specimen collection and laboratory analysis

All specimen collection during the five-year period had been done following strict adherence to the universal basic precautions in the Department of Chemical Pathology and Metabolic Medicine. A random three milliliters (3ml) of venous whole blood was collected via by venipuncture from the antecubital vein of each man. The venous whole blood was transferred immediately into a well-labeled plain specimen tube and allowed to clot for at least 60minutes undisturbed at room temperature.

Following full retraction, samples were centrifuged at 2500g for 15minutes and separated supernatant (serum) transferred using Pasteur's pipettes into another well-labeled plain specimen tubes.

The separated serum was stored frozen at -20^{o}C and temperature validated using external digital freezer thermometer and monitored daily until weekly analysis. Serum total PSA analysis was all carried out by solid-phase enzyme immunoassay methods in the same Department of Chemical Pathology using same reagents brands including three levels of commercial quality control sera sourced from Monoblind Incorporated, California, USA through its distributors in Nigeria (Nums Diagnostics Nigeria LTD).

Statistical analysis

Data were processed utilizing the SPSS version 20 software. The age groups were categorized into six as follows: 30-39, 40-49, 50-59, 60-69, 70-79, >80. Normality was first determined using Shapiro-Wilk test. The 5th, 25th, 50th (Median), 75th and 95th serum total PSA percentiles were determined in each 10-year age group. The observed 95th percentile was then used to determine the upper limit of the reference range for each 10-year group. Spearman's test for nonparametric distributed data was used to determine the relationship between serum total PSA concentrations and age. The p-values were two-tailed and values of <0.05 were considered significant.

RESULTS

During the period of 1st January 2012 to 31st December 2016, 488 men presented for routine screening for prostate cancer using serum total PSA. Data of the 488 were then retrieved and reviewed to determine inclusion and exclusion criteria. 476 (97.5%) men that met the inclusion criteria after review was selected. Twelve men (2.5%) were excluded due to incomplete data (n=3), abnormal digital rectal examinations (n=4) and total PSA above 20ng/ml (n=5).

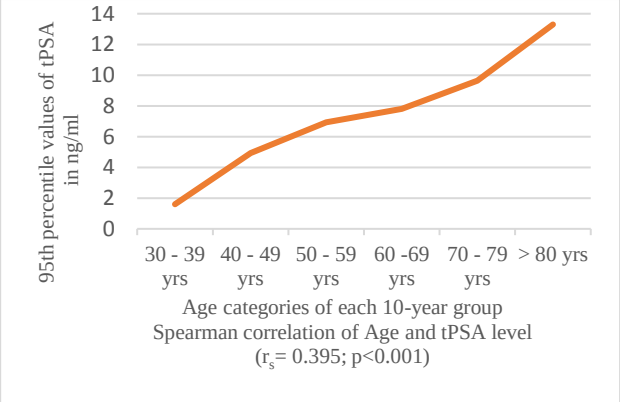
Following normality assessment using Shapiro-Wilk test, non-parametric distribution of data was confirmed (p< 0.001).

Table 1: Analysis of total serum prostate-specific antigen level (ng/ml) based on all six age groups distributions (total n = 476).

Age (years)	N	Mean	Median	Minimum	Maximum	5th	25th	50th	75th	95th
30-39	6	1.23	1.15	0.50	1.60	0.90	0.97	1.15	1.52	1.60
40-49	106	2.00	1.50	0.70	6.30	1.00	1.30	1.50	2.10	4.93
50-59	167	2.85	1.95	0.80	10.00	1.00	1.20	1.95	4.30	6.93
60-69	134	3.09	2.40	0.90	11.10	1.76	1.90	2.40	3.40	7.80
70-79	46	3.82	3.10	1.20	12.10	1.24	2.10	3.10	5.10	9.65
>80	17	5.71	5.00	2.90	13.3	2.90	3.75	5.00	7.15	13.30

ng/ml = Nanograms per milliliter

As shown in Table 1, the age range varied from 38-86years (mean=57.5years) with age group 50-59years (35.1%) more preponderant among all six groups. The descriptive statistics parameters inclusive mean and the median total PSA levels increases as the age also advance across each of the age group as shown in Table 1. The observed 95th percentile of serum total PSA for each 10year group are as 1.6, 4.93, 6.93, 7.80, 9.65 and 13.30 for age groups 30-39, 40-49, 50-59, 60-69 and >80years respectively. The overall serum PSA mean of the study was 2.90 (0.6-13.3). The calculated 95th percentile serum total PSA value for each age group is designated in this study as the upper limit of the reference range while the lower limit is designated as 0ng/ml.



tPSA=Total Prostate-specific Antigen; ng/ml = Nanogram per milliliter

Figure 1: Graph showing the relationship between the 95th percentile values in each 10-year age-group.

In Figure 1, where the 95th percentile total PSA values was plotted against each of the six age groups, revealed an upward trend of the total PSA values as the age increases in each 10-year age group. Using the spearman correlation test for non-parametric distributed data, the serum total PSA correlated positively and significantly with age (rs = 0.395; p<0.001).

In Table 2, the 95th percentile total PSA values in each 10-year group for this study were found to be almost similar to the values obtained in the recent Nigeria study for the age groups 40-49, 50-59 and 60-69 but higher across all age groups of the Caucasian, the Chinese and Japanese studies. There were also similarities of the two reported Japanese studies as shown in Table 2 also.

DISCUSSION

The utilization of serum PSA to screen and diagnose prostate cancer had come with a single cut-off value of 0-4ng/ml for more than two decades. However, since the first epidemiologic evidence of variation of total PSA with age and race, there have been numerous studies suggesting the use of age-specific and race-specific reference ranges from the United States Europe, Asia including the Middle-east.[12-15] In each of these studies, there was mounting epidemiologic evidence that supports adjusting the PSA reference ranges based on age and race.[12-15]

This same pattern was observed in the index study were we found that the descriptive statistics parameters of PSA

concentration values tend to increase with advancing age across each of the categorized six age groups as shown in Table 1 of this study. Though we could not draw any significant conclusion from the groups of 30-39 (n=6) and >80 (n=17) due to the very low number of patients in those two groups. Supporting this observation in this study also is the positive correlation of total PSA concentration levels and patients age (rs=<0.395; p= <0.001) as shown in Figure 1 which is in consonance with the findings from the recent Nigeria study where they reported correlation between serum total PSA levels and age also (r=0.097; p <0.001).[11] Prostate volume has been observed to increase as men age and with this increase in volume of the gland results in more total PSA to be released into the systemic circulation.[9] This expansion in prostate volume has been more pronounced in blacks than the Caucasian, therefore, contributing to the reason why black men seem to have higher total PSA concentrations than their Caucasian, Chinese and Japanese counterparts.[16]

Table 2: Comparison of age-specific reference ranges of previous studies determined using the 95th percentile values of total PSA values (ng/ml).

Age groups (years)	Index study of black men	Nigerian black men[11]	African-american white men[16]	European white men[13]	Asian chinese men[14]	Indigenous japanese men[18]	Indigenous japanese men[19-20]
n	476	4,032	471	1,160	1,096	345	3522
20 - 29	-	-	-	0-1.16	-	-	-
30 - 39	0-1.60	-	-	0-1.78	-	-	-
40 - 49	0-4.93	0-4.78	0-2.5	0-1.75	0-2.15	0-2.0	0-2.1
50 - 59	0-6.93	0-5.47	0-3.5	0-2.27	0-3.20	0-3.0	0-2.9
60 - 69	0-7.80	0-8.83	0-4.5	0-3.48	0-4.10	0-4.0	0-4.0
70 - 79	0-9.69	-	0-6.5	0-4.26	0-5.37	0-5.0	0-5.2
>80	0-13.30	-	-	0-2.64	-	-	-

tPSA = Total Prostate-Specific Antigen; ng/ml = nanograms per milliliter.

Using the 95th percentile total serum PSA values in ng/ml as our upper limit of the reference range and the lowest as 0 ng/ml in this study, the age-specific ranges for our cohort were 0-4.93, 0-6.93, 0-7.80 and 0-9.65 for the age groups 40-49, 50-59, 60-69 and 70-78 respectively which were higher than the values first reported by Oesterling among US white males in I993 including similar studies from Europe and Asia as shown in Table 2 with emphasis on the same 10-year age groups 40-49, 50-59, 60 -69 and 70-79.[13,14,16] Though our age-specific range for the 30-39year group was lower than the comparative European study, this could be because of the limited number (n=6 on Table 1) of men in that group.[13] These various studies had all used same 95th percentile total PSA values to derive their respective age-specific reference ranges as in this study.

The total PSA age-specific reference range trend in age groups 40-49 (0-4.93ng/ml), 50-59 (0-6.93ng/ml) and 60-67(0-7.80ng/ml) in this study is almost in agreement with the findings from a recent community-based study in Nigeria11 that reported their age-specific total PSA reference ranges as 0-4.78, 0-5.47 and 0-8.93 for the age groups 40-49, 50-59 and 60-69 respectively. However, this recent community-based study did not report the age-specific reference range for the age group 70-79 years.[11] This age group (70-79) has the highest incidence of prostate cancer in our environment and we found the groups age-specific reference range to be 0-9.69ng/ml which is higher than those found in African-American white men as reported by Oesterling and in the Europeans and Asian Chinese men as shown in table 3.[4,17]

We noted same race similarity of the 95th percentile total PSA levels (4.93 versus 4.7.8), (6.93 versus 5.47) and (7.80 versus 8.93) for age groups 40-49, 50-59 and 60-69 between this study and that of the recent community-based study in Nigeria but significant variation with other race groups as shown in Table 3.[11,13,14,16] The little insignificant variation observed between our study and the recent Nigeria study could be due to serum PSA assay methodological differences. This similarity gives credence to the influence of race on PSA values, with men of the same race having similar values while variation existing between race groups.[12]

Similarities of PSA age-specific reference ranges have also been noted within same race groups in Japan.[18-20] Oesterling et al and Imai et al had also reported similarity of age-specific PSA reference ranges for age groups 40-49, 50-59, 60-69 and 70-79 among native Japanese men in 1995 as (2.2 versus 2.1), (3.0 versus 2.90), (4.0 versus 4.0) and (5.0 versus 5.20) as shown in Table 2.[18-20]

Similarities of PSA reference ranges within race groups have been adduced to genetics, environmental, dietary and hormonal factors inherent in those specific race groups.[12] Among the hormonal elements is the influence of testosterone that has been linked to the high PSA levels in black men than their comparable Caucasian counterparts.[12] PSA is an androgen-dependent protease and Etawo et al had attributed testosterone effect on higher serum PSA concentrations of men in our environment.[17]

The study had some limitation that warrants mentioning. Firstly, is the fact that the study is a retrospective study from one health center in the South-south zone of Nigeria which might not be representative of the general population. Secondly, Trans-rectal ultrasound scan (TRUS) of the prostate gland and Prostate biopsy using the traditional cutoff of 4ng/ml were not done on any of these patients. However, all the patients had presented for routine screening without complaints of any symptoms suggestive of prostatic disease.

CONCLUSION

In conclusion, this study confirms serum PSA increases with advancing age with race-dependent disparities. We suggest that PSA levels in men should be defined by considering the impact of age and race on its concentration in screening and diagnosis of prostate cancer in our environment.

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