PRINT ISSN 1119-8362
Electronic ISSN 1119-8362

Full-text Available Online at
https://www.ajol.info/index.php/jasem
http://ww.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 24 (1) 147-151 January 2020

Pattern of Age-Adjusted Serum Prostate Specific Antigen Reference Intervals among Men in Benin City, Nigeria

[1]EBOREIME, OO; *[2, 3, 4]ATOE, K

[1]Department of Surgery, Igbinedion University, Okada, Edo State, Nigeria.
[2]Department of Chemical Pathology, College of Medical sciences, Edo University Iyamho, Edo State.
[3]Applied Environmental. Biosciences & Public Health Research Group, Department. of Microbiology, University of Benin, Nigeria
[4]Phytomedicine and Drug Discovery Research Group, Dept. of Plant Biology and Biotechnology, University of Benin, Nigeria
** Corresponding Author: Email:* atoe.kenneth@edouniversity.edu.ng

ABSTRACT: Prostate Cancer has assumed an important public health concern in Nigeria. Its incidence is anecdotally on the rise in our community and many prominent Nigerians are dying from it. The current study set out to ascertain the age adjusted prostate specific antigen (PSA) values indigenous to the local community and to confirm the relationship between PSA and age. In this study, enrollees were from a medical outreach carried out by a non-governmental agency in Benin City, Nigeria. The number of volunteers was 443 adult males. Eleven 11(2.48%) of this number were excluded from the study on account of their outlying PSA values. The mean age was 42.4years; the youngest volunteer being 18 years and the oldest, 86 years. The mean PSA value in the ≤40 year, 40-49, 50-59, 60-69, and ≥70year age categories were 1.77 ng/ml, 2.09 ng/ml, 1.99 ng/ml, 2.63 ng/ml, and 2.59 ng/ml respectively. The overall mean PSA was 2.21 ng/ml, whereas the median was 2.09ng/ml. Results showed positive but weak correlation between age and PSA ($R = 0.161$, $P < 0.01$). Nonetheless, significant increases in PSA with age were reported. The current study therefore provides a set of serum PSA values that are indigenous to the local environment, which could be used as cut-off threshold for performing prostatic biopsies.

DOI: https://dx.doi.org/10.4314/jasem.v24i1.21

Dates: Received: 30 November 2019; Revised: 20 December 2019; Accepted: 23 December 2019

Keyword: prostate cancer, prostate specific antigen, glycoprotein, biopsy, Benin City

Prostate cancer is increasingly becoming a public health issue in Nigeria and the most diagnosed internal cancer in male (Clarke et al., 2010; Adedapo et al., 2012). PSA is a glycoprotein in the kallikren-like protease family with reduced chymotrypsin-like enzyme activity. It is produced by all the epithelial cells of the prostate gland. It is organ specific but not specific for carcinoma of the prostate as its levels are elevated in benign prostatic hypertrophy (BPH), urinary retention, acute prostatitis, prostatic ischaemia or infarction, after digital rectal examination, and after sexual activity (Oesterling, 1995; Luboldt et al., 2007). It was not until 1987 that it gained popularity for prostate cancer screening.

The traditional cut-off of serum PSA level of 0-4ng/ml is based on a single study and has appreciable shortcomings; it is based on older (isotopic) technology, non appreciation of the diverse molecular forms of PSA, absence of standardization and lack of knowledge of co-variate of age (Sibly and Sturgeon, 1999). This threshold is insufficient to detect early stage carcinoma of the prostate and as such a great proportion of prostate cancers are missed (Luboldt *et al*., 2007).

The current biopsy guidelines that specifies that a serum PSA level equal or greater than 4ng/ml or PSA velocity greater than 0.75ng/ml per year, as indication for prostatic biopsy, underestimate cancer risk in the 50-59 year old (Moul, 1995). For these reasons, the age –adjusted PSA reference range values were developed by reducing this threshold well below the time honoured value of 4ng/ml for the younger male and raising it in the older male. This allowed for early detection of prostatic cancer, reduction in tumour stage at diagnosis, morbidity and mortality and reduction in the number of unnecessary biopsies in patients with benign prostatic hyperplasia (BPH) without signs and symptoms of prostatic cancer (Luboldt et al., 2007; Heidegger et al., 2015).

Increasing incidence of prostate cancer and their late presentation has been observed by the authors during practice. This prompted the need to ascertain the actual serum PSA cut-off threshold for the different age groups in our locality with the view to help in the early

** Corresponding Author: Email:* atoe.kenneth@edouniversity.edu.ng

detection and treatment of prostate cancer. The objective of this study therefore was to determine the age-adjusted PSA reference ranges indigenous to our environment.

PARTICIPANTS AND METHODS

Four hundred and forty three male volunteers between the ages of 18 to 86 years were recruited into the study. They were randomly drawn up from the resident male population in Oredo Local Government area, Edo State Nigeria. Those with symptoms of lower urinary tract symptoms (LUTS), prostate disease, bladder outlet obstruction (BOO) and PSA outlier levels were excluded from the study.

Detailed demography, history and physical examination including direct digital examination (DRE) were carried out and blood samples were collected before DRE from each volunteer for PSA estimation. Volunteers were educated and counselled on the study and informed consent was taken from each of them. Ethical Committee approval for the study was issued by the Edo State Ministry of Health, the appropriate authority.

Prostate specific antigen (PSA) Analysis in Serum: PSA analysis was carried out using the enzyme-linked Immunosorbent Assay (ELISA) method described by Chretien *et al. (*1989). The PSA ELISA test was based on the principle of a solid phase enzyme-linked immunosorbent assay. The monoclonal anti-PSA-horseradish peroxidase conjugate was then reacted with the immobilized antigen for 60 minutes at room temperature resulting in the PSA molecules being sandwiched between the solid phase and enzyme-linked antibodies. The horseradish peroxidase activity bound in the wells was then assayed by a colorimetric reaction.

Statistical Analysis: The data was processed using SPSS version 22. The age groups were categorized into < 40years, 40-59 years, 60-69 years, 70-79years and >80years. The PSA values were analysed for age-adjusted PSA using 75th, 80th, 85th, 90th and 95th percentiles but 95th percentile was used as upper limit for each category. The relationship between PSA and age was determined using the Person's correlation (2 tailed) coefficient.

RESULTS AND DISCUSSION

The number of volunteers who registered for screening was 443 adult males. Eleven participants (2.48%) of this number were excluded from the study on account of their outlier PSA values. The highest number of volunteers, 118(27.3%) fell into the 60-69 age category while the least number occurred in 70 years and above age category. The mean age was 42.4years.

Table 1: Mean values of serum PSA in the age categories

Age (years)	n(%)	PSA (ng/ml) Mean ± SD	95% CI (Lower)	95% CI (Upper)	p-value	50th Percentile	95th Percentile
<40	80 (18.5)	1.77 ± 0.63	1.63	1.91	<0.001	1.9	2.89
40-49	69 (16.0)	2.09 ± 0.86	1.89	2.29		2.0	3.60
50-59	113 (26.2)	1.99 ± 1.09	1.78	2.19		1.9	4.30
60-69	118 (26.2)	2.63 ± 1.68	2.32	2.94		2.2	5.21
≥70	52 (27.3)	2.59 ± 1.94	2.05	3.13		1.7	7.01
Total	432	-	-	-	-	-	-

Table 1 shows the mean, median and standard deviation of serum PSA values in five categorised age groups. The mean PSA value in the ≤40 year age category was the least at 1.77ng/ml. while the highest value of 2.59ng/ml occurred in the ≥70years age group. However contrary to our expectations, the mean serum PSA value for the 40-49years age category stood at 2.09ng/ml, a higher value than the older age category (50-59 year) which stood at 1.99ng/ml. Again the mean serum PSA for the 60-69 years age group stood at 2.63ng/ml, a higher value than that of the ≥70years category (2.59ng/ml). The overall mean was 2.21ng/ml. The correlation between PSA and age has been presented (Figure 1). There is a positive relationship between age and PSA. As age increases there is a tendency for the serum PSA to also increase. The correlation between both parameters is however a weak correlation ($R = 0.161$, $P < 0.01$). This Figure 2 shows graphs of 75th, 80th, 85th, 90th and 95th percentiles of the serum PSA values plotted against the age categories. The PSA values increased uniformly with age in the 90th and 95th percentiles unlike in the 75th, 80th and percentiles. The overall mean of the 95th percentiles was 4.6ng/ml.

Figure 3 shows the box and whiskers plots for 95th percentile PSA values and age categories. There is a direct relation between age and serum PSA values. This figure also displays the spread of the 95th serum PSA values and the outliers. PSA values for 2.48% of the study participants made up the outliers. The median value for all the ages cattery ranged from 2.81 – 3.22 ng/ml

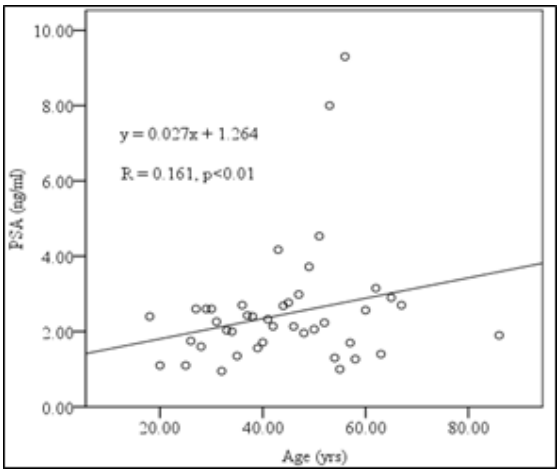

Fig 1: Scattergram showing the correlation between age and serum PSA levels

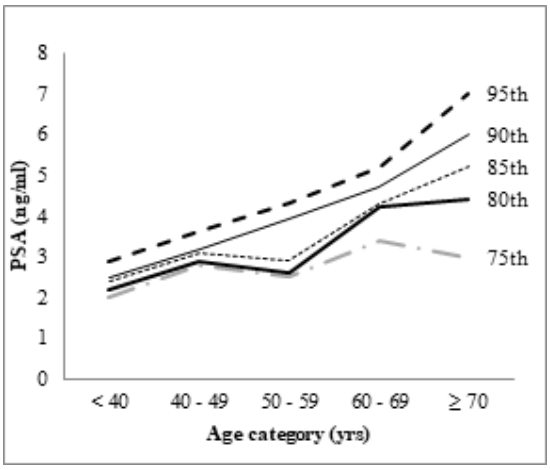

Fig 2: Percentiles of serum PSA and age categories

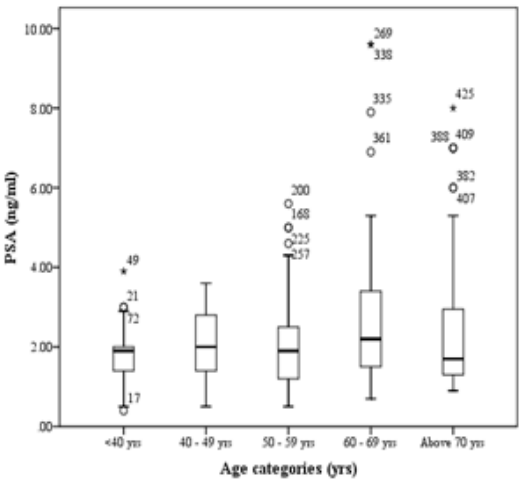

Fig 3: Box and whiskers plots for mean age-patterned PSA values

This study was conducted to determine the age-adjusted serum PSA ranges in a medical outreach cohort study carried out in Benin City, Nigeria and also to confirm the relationship between age and serum PSA in the Benin City environment. The results show that there was a positive correlation between PSA values and age (R = < 0.161; p=0.01, 2-tailed). The 95th percentiles of the serum PSA values for each age category also increased with age (see Figures 1 and 2); and this agreed with the findings in other studies (Amadi and Odum, 2018) .Results of the present study indicated that a single serum PSA cut-off threshold cannot be used for all age groups. Serum PSA is influenced by age, race, geography, diet, androgens and environment (Read *et al*., 2007; Ikuerowo *et al*., 2016; Al-Abdin andAl-Beeshi, 2018). It also has a direct relationship with age-related volume changes resulting from hyperplasia of the prostate tissue. In old age, the prostate gland cells become more porous and leaks more PSA into the serum (Scattoni *et al*., 1999; Sibly and Sturgeon, 1999; Clarke et al., 2010; Luboldt et al., 2007). Hitherto, serum PSA cut-off of 0 – 4 ng/ml was used as the basis for carrying out prostatic biopsy regardless of age. This concept was premised on a single study which had appreciable shortcomings; an older (isotopic) technology which ignored the diverse molecular forms of PSA, and is hardly a standardized test which also does not take into consideration the co-variate of age (Sibly and Sturgeon, 1999). Similarly, this threshold of 0 - 4mg/ml is insufficient to detect early stage carcinoma of the prostate and as such a great proportion of prostate cancers are missed when applied (Luboldt *et al*., 2007). In this study, the 95th percentile cuff-off serum PSA value increased steadily from 2.89 ng/ml in the <40 years category to7.0 ng/ml in the ≥70years category (see Figure 2). This trend was also replicated in other Nigerian studies (Amadi and Odum, 2018; Al-Abdin andAl-Beeshi, 2018). However, the mean PSA values obtained in this study were about two to two and half times higher than values reported by some researchers in the western world (Luboldt et al., 2007; Heidegger et al., 2015). Nonetheless, this was lower than other studies from Nigeria (Al-Abdin andAl-Beeshi, 2018) probably due the different population sizes, the types of the cohort, inter-assay variabity, inconsistent calculation of age specific reference ranges and verification bias (Luboldt *et al*., 2007).

Some authorities (Ganpule and Dessai , 2007; Amadi and Odum, 2018; Al-Abdin andAl-Beeshi, 2018) suggested that a PSA threshold of 2.0 to 2.5ng/ml should be used for 40-49 years in African – American (NCBI, 2009) compared to 0 - 3.6mg/ml in the present study. Other studies have revealed that serum PSA is higher in blacks than in whites, Chinese, Indians and

Japanese (Ganpule and Dessai, 2007; Al-Abdin andAl-Beeshi, 2018). Al-Abdin and Al-Beeshi (2018) claimed that in blacks the prostate volume is larger than in Caucasians age for age. In the current study, the mean serum PSA values in the 40-49 years (2.09ng/ml) and 60-69years (2.63ng/ml) age categories were higher than that of the 50-60 years (1.99ng/ml) and ≥70years (2.59ng/ml) categories respectively against expectations based on the findings of similar studies (Ganpule and Dessai, 2007; Ikuerowo *et al.,* 2016; Amadi and Odum, 2018; Al-Abdin andAl-Beeshi, 2018).

It is believed that using these threshold values which are lower and higher than 0-4ng/ml in the younger age and older age group respectively, localised prostatic cancers would be detected early leading to appropriate interventions, reduced morbidity and mortality and a reduction in unnecessary biopsies in patients with benign prostatic hyperplasia without missing the presence of prostatic carcinoma (Heidegger et al., 2015). It has been suggested that using the age-adjusted serum PSA ranges, sensitivity and specificity for prostatic cancer detection is enhanced in the younger male and older male respectively (Luboldt et al., 2007). It is recommended that a future a mega multicentre community based study be carried out for validation of these results.

Conclusion: The present study confirms that serum PSA values increased with age and this cut across all races although the degree of increase differed from race to race when compared with literature evidence. It also provides a set serum PSA values indigenous to the local environment; this could be used as cut-off threshold for performing prostatic biopsies.

Acknowledgement: The authors are grateful to the health workers that volunteered their services during the outreach programme. The study was privately funded.

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