

Need for Age-Specific Prostate-Specific Antigen Reference Intervals in a Nigerian Population

Edwin N. Okafor, Innocent N. Okonkwo, Nkoyo I. Nubila¹, Martin C. Ugonabo²

Departments of Medical Laboratory Sciences, ¹Pharmacology and Therapeutic, University of Nigeria, Enugu Campus, ²Department of Chemical Pathology, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria

Received:
30-Jun-2021;
Revision:
04-Aug-2023;
Accepted:
23-Aug-2023;
Published:
30-Oct-2023

ABSTRACT

Background: In Nigeria, the diagnostic value of prostate-specific antigen (PSA) is a matter of debate. PSA levels are known to vary with population, environmental factors, and advancing age. Studies suggest age-specific reference intervals (ASRIs) of PSA value are more accurate than single cut-off PSA value. For ASRIs to be used effectively, reference intervals (RIs) must be fully evaluated. **Aim:** We determine ASRIs in a Nigerian population. **Materials and Methods:** The study was carried out from January 2016 to January 2019 among 660 adult Nigerian men aged 30–86 years old in Enugu State. Participants completed questionnaire demographics and previous screening. Age group was the indicator. Among them, a total 24 (3.6%) were excluded. Data from 636 (96.4%) men were analyzed for ASRIs. Estimation of PSA was done as per the International Federation of Clinical Chemistry Guideline. Spearman correlation was used to identify correlates *P* values < 0.05 which was considered significant. **Results:** The mean age group was 49.6 ± 10.2 years. ASRIs using 95th percentile, and PSA values in each 10 years groups were 0–1.94 ng/ml (median 0.22), 0–2.52 ng/ml (median 0.42), 0–3.52 ng/ml (median 1.06), 0–4.8 ng/ml (median 2.1), 0–6.95 ng/ml (median 4.1), and 0–5.6 ng/ml (median 2.4), for age groups 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, respectively. There was positive correlation between PSA and age (*r* = 0.9915, *P* < 0.0001). Low income and educational background were more prevalent among the study group. **Conclusion:** Our study provided the ASRIs in our environment but higher than single cut-off value. The data recommended PSA values should be characterized by age and ethnicity.

KEYWORDS: Age, age-specific PSA, healthy men, prostate-specific antigen, reference intervals

INTRODUCTION

The prevalence of prostate cancer (PCa) has increased steadily in the past years, impacting on Nigerian men. PCa has assumed an epidemic proportion around the globe. The pattern both in incidence and mortality has taken an alarming trend in Nigerian men just as is reported in other men of African ancestry.^[1,2] Studies from all regions of Nigeria emphasize late presentation as the pattern.^[3] PCa and its associated complications have a significant impact on patient’s quality of life. The magnitudes of the effects are diverse. A 2000 retrospective study involving 54 adult Nigerian men with urological tumor at Nnamdi Azikwe University Teaching

Hospital (NAUTH), Nnewi Southeast Nigeria, showed that PCa had a sizeable percentage of 77.1%.^[4] Rebbeck *et al.*^[5] reported that African-specific risk profiles may require different screening and treatment method than standard practice in developed countries.


Nigerian men populations are an unscreened group with regard to prostate care. Prostate-specific antigen (PSA) is a glycoprotein in the kallikren-like protease

Address for correspondence: Dr. Edwin N. Okafor, Department of Medical Laboratory Sciences, University of Nigeria, Enugu Campus, Enugu, Nigeria. E-mail: nkemjika.okafor@unn.edu.ng

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Okafor EN, Okonkwo IN, Nubila NI, Ugonabo MC. Need for age-specific prostate-specific antigen reference intervals in a Nigerian population. *Niger J Clin Pract* 2023;26:1430-5.

Access this article online	
Quick Response Code: 	Website: www.njcponline.com
	DOI: 10.4103/njcp.njcp_1643_21

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 prostate carcinoma as its levels are increased in benign prostatic hypertrophy, acute prostatitis, urinary retention, and infection, after digital rectal examination and after sexual activity.^[6] The traditional cut-off of serum PSA level (0–4 ng/ml) is based on a single study and has appreciable limitations. It is based on older isotopic technology, non-appreciation of the diverse molecular forms of PSA, the absence of standardization, and lack of knowledge of co-variate of age,^[7] it has been reported that ASRI is better and should be used as an alternative.^[8] Additionally, some studies^[9,10] have documented different ASRIs for Caucasians, Asians, Arabians, and healthy men of African ancestry with higher values. PSA level also correlates with advancing age and prostate volume.^[10,11] Report has questioned the use of traditional total PSA cut-off value of 0–4 ng/ml across all regions and age.^[12]

The Centre for Disease Control and Prevention in Enugu State Nigeria has a screening program for PCa control. 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 early diagnosis. The goal of the study was to determine the ASRIs and compare the value with other studies.

MATERIALS AND METHODS

Study site and design

This was a prospective study in Enugu State. This was a prospective study conducted from January 2016 to January 2019 in Enugu State. Enugu State is one of the states in Southeastern Nigeria. Enugu State had a population of 3,267,837 people at the census held in 2006 (estimated at over 3.8 million in 2012). It is home of the Igbo of southeastern and few Idoma/Igala people in Ete (Igbo-Eze North) of Enugu State, Nigeria.^[13] Primary health cares in each of the three zones of the state were selected as the site of the study. The primary health cares have well-established facilities for screening of chronic diseases. These sites were selected because of the highest number of individuals attending the centers for health checks. Strategic collaboration includes multi-professional teams from department of medicine, chemical pathology, and pharmacology in conjunction with local health department. Before commencement of the study, we engaged in discussion with the participants in disclosing personal information. We set out inclusion criteria to be at least 30 years old with no clinical evidence of any other chronic disease and PCa and verifiable contact address. Approval was obtained

from University of Nigeria Teaching Hospital (UNTH) Enugu. The research has been therefore performed in accordance with the standard laid down in the 1964 declaration of Helsinki.

Participants for enrollment

A total of 660 male participants were invited to complete a questionnaire, of which 636 (96.4%) apparently healthy men met the case definition. Prostate screening involves collection of venous blood followed by digital rectal examination (DRE) which was performed by a surgeon. PSA was determined with microplate reader technique (ELISH Microwells, Monobind incorporated Lake Forest CA, USA), based on enzyme immunoassay method at the department of Chemical Pathology, UNTH, Enugu. The ASRI was performed as per International Federation of Clinical Chemistry (IFCC).^[14] PSA using a single cut-off of 4 ng/ml was considered significant. Referrals were made to the surgeon for follow-up of men with PSA >4 ng/ml and/or abnormal DRE.

Demographics and other questionnaire variables

All 636 participants completed a questionnaire under the guidance of medical staff and were giving opportunity to ask questions. The information included a diversity of measures including demographic data as well as items relevant to PCa risk factors and history of medical screening. Demographics including age in years, the highest level of education, and employment status were completed. Average income earnings were self-reported and recorded in the questionnaire during a face-to-face interview. Average income earnings were reported in Nigerian currency (Naira) but were converted to international currency via Google in December 2019 (₦ 1 = US\$ 0.0061) and categorized into groups; low income group (\$108/month), middle income (\$150/month), upper middle income (\$310–\$644/month), and higher income >\$644/month.

History of previous medical screening/awareness

Participant accessibility to PCa screening/awareness was reported during the face-to-face interview. Participants were asked whether or not they have ever had knowledge of PCa risk factors or screened by a doctor or any other health worker. Responses were recorded in the questionnaire.

Statistical analysis

We calculated the reference intervals in various age groups within 95th percentile. Frequency table for the demographics was determined. All data are presented as mean ± SD for continuous variables as numbers or percentage for categorized variables. Spearman correlation for non-parametric distribution data was used to determine the relationship between serum total PSA

value and age. The SPSS version 16 (SPSS In Chicago) was used for the analysis. $P < 0.05$ was considered as significant.

RESULTS

The baseline characteristics of all the participants are listed [Table 1]. A total of 636 male participants aged 30–86 years were enrolled according to the study criteria representing 96.4%, while 3.6% were excluded on account of their outlier PSA values. The mean age of the study population was 49.5 ± 10.2 years. The most reported age groups were 30–39 years (28.6%),

40–49 years (22.8%), while other age groups were 50–59 years (25.6%), 60–69 years (13.0%), and 70–79 years (8.5%). Additionally, 235 (36.9%) of the participants reside in urban areas, while 401 (63.1%) reside in rural areas. The result shows that 23.6% reported no formal education, 15.7% less than primary education, 31.5% had primary education, 23.6% reported secondary education, while 5.7% reported university. Their job varied with unskilled workers (64%) and skilled workers (31%) while unemployed (4%). Average daily income varied low income (61.3%), low middle income (23.6%), upper middle income (7.9%), and higher income (2.5%) while unknown (4.7%). Mean of average income is $\$8 \pm 4.9$. The participants were not aware of the risk factors of PCa; however, they recorded family history (12.6%), lifestyle (7.9%), environmental factors (15.7%), eating habit (1.6%), and obesity (0.8%).

Table 1: Socio-demographic information and its average mean (among participants (n=636)

Characteristics	Values	
Gender		
Male	636	(96.4%)
Age	49.6±10.2 years	
Age group years		
30–39	182	(28.6%)
40–49	145	(22.8%)
50–59	163	(25.6%)
60–69	83	(13.0%)
70–79	54	(8.5%)
≥80	9	(1.4%)
Geographical location		
Urban	235	(36.9)
Rural	401	(63.1%)
Education completed		
No formal school	100	(23.7%)
Less than Primary school	150	(23.6%)
Primary school	200	(31.4%)
Secondary School	150	(23.6%)
University	36	(5.7%)
Occupation		
Unskilled	410	(64%)
Skilled	136	(21.4%)
Unemployed	100	(15.7%)
Average daily income (US \$)		
Low income	390	(61.3%)
Low middle income	150	(23.6%)
Upper middle income	50	(7.9%)
High income	16	(2.5%)
Unknown	30	(4.7%)
Mean average daily income	$\$8 \pm 4.9$	
Previous screening of risk factors		
Family history/shared	80	12.6%
Lifestyle factor	50	7.9%
Environmental factors	100	15.7%
Eating habit	10	1.6%
Race	-	-
Genetic changes	-	-
Obesity	5	0.8

Note: Values represent mean±standard deviation and numbers (%)

Table 2: This shows the mean, median of serum PSA values in six categorized age groups. The 95th percentile PSA value in the 30–39 age group was the least at 1.94 ng/ml, while the highest value of 6.95 ng/ml occurs in the 70–79 age group. However, contrary to our expectation, the 95th percentile serum PSA value for the ≥80 age group was lower (5.6 ng/ml), than that of 70–79 age group. The overall serum PSA level in the study was (0–6.95 ng/ml). 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 0 ng/ml.

The correlation between serum PSA and age categories has been presented in [Figure 1]. This shows a progressive increase in PSA values with advancing age in each 10 year age group except age group ≥80. Using Spearman correlation test for non-parametric distributed data, the serum PSA correlated positively and significantly with age ($r = 0.9915, P < 0.0001$). As age

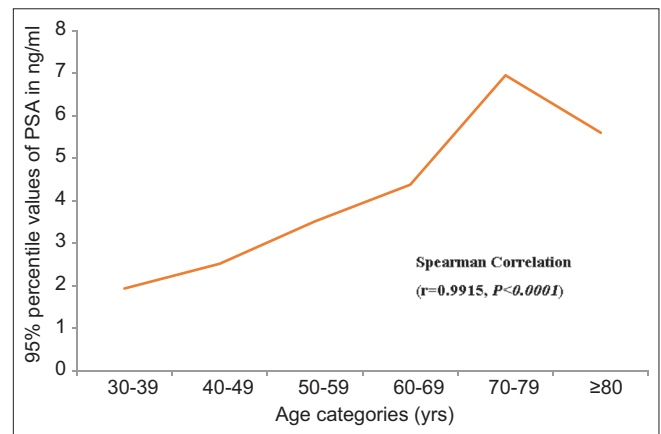


Figure 1: Correlation between 95th percentile values of PSA and age group categories. tPSA = total prostate-specific antigen, ng/ml = nanogram per milliliter

Downloaded from http://journals.lww.com/njcp by BhdMf5eP-HKav1zEoum1tQIN4a+kLlHEZ9bstH04XMI0hCjwCXC1AW nYOp/llQHd3i3D00ORy7Tvsf14C33VC1y0abggQZxdwIKZBYtws= on 01/03/2025

Table 2: Analysis of total serum prostate-specific antigen level (ng/ml) based on all six age groups distributions (total n=636)

Age (years)	N	Mean	Median	Minimum	Maximum	5 th	25 th	50 th	75 th	95 th
30–39	182	0.46	0.22	0.00	3.21	0.00	0.01	0.22	0.69	1.94
40–49	145	0.86	0.42	0.00	3.52	0.00	0.15	0.42	1.41	2.52
50–59	163	1.39	1.06	0.00	4.7	0.00	0.39	1.06	2.30	3.52
60–69	83	2.0	2.1	0.01	4.51	0.03	0.80	2.1	2.97	4.38
70–79	54	3.90	4.15	0.27	7.0	0.27	2.20	4.15	4.83	6.95
80 and above	9	2.43	2.4	0.24	5.6	0.24	1.60	2.4	2.6	5.6

tPSA=total prostate-specific antigen, ng/ml=nanogram per milliliter

Table 3: Comparison of age-specific reference intervals of present study with previous studies using the 95th percentile values of total PSA

Present study with previous studies	N	Age groups					
		30–39	40–49	50–59	60–69	70–79	≥80
Enugu (community-based), Nigerian population (present study)	636	0–1.94	0–2.52	0–3.52	0–4.51	0–6.95	0–5.6
Hospital-based study, Port Harcourt, Nigeria ^[15]	476	0–1.60	0–4.93	0–6.93	0–7.80	0–9.69	0–13.30
African–American White men ^[16]	471	-	0–2.5	0–3.5	0–4.5	0–6.5	-
European White men ^[17]	1,160	0–1.78	0–1.75	0–2.27	0–3.48	0–4.26	0–2.64
Asian Chinese men ^[18]	1,096	-	0–2.15	0–3.20	0–4.10	0–5.37	-
Indigenous Japanese men ^[19]	345	-	0–2.0	0–3.0	0–4.0	0–5.0	-
South Indian men ^[20]	583	0.9	1.3	1.48	1.6	2.0	2.47
Healthy Indian men ^[21]	1,253	0.71	0.85	1.13	1.45	1.84	2.35

n=number of participants, tPSA=total prostate-specific antigen, ng/ml=nanograms per milliliter

increases, there is a tendency for the serum PSA to also increase.

Table 3: The present community-based study in Enugu had a higher number of male participants than the hospital-based study in Port Harcourt, Nigeria. However, the ASRIs were lower than hospital-based study in Port Harcourt, Nigeria, for all the age group categories expect in age group 30–39 years, but higher across all age groups in Caucasian, European White, Chinese and Asians, Indigenous Japanese, and Indians studies.

DISCUSSION

This study was carried out to determine age-adjusted serum PSA reference intervals in a community-based study conducted in Enugu, Nigeria, and also to confirm the relationship between age and serum PSA in our locality. The results show that the 95th percentile of the serum PSA values for each age category increased with age. Though we could not draw any conclusion from age group ≥80 years because of sample size, supporting this observation is a positive and significant correlation between PSA values and subjects age as shown in Figure 1 ($r = 0.9915$, $P < 0.0001$). This agrees with hospital-based study in Port Harcourt, Nigeria.^[15] The result of the present study showed that a single serum PSA cut-off threshold cannot be used for all age groups. Serum PSA is influenced by age, race, diet,

and environment.^[22,23] It also has an association with age-related volume changes due to hyperplasia of the prostate tissue.^[6] Report shows that age is a risk factor as susceptibility toward the disease increase with age. In a research conducted by Oesterling *et al.*,^[17] it was found that PSA values increased approximately by 3.2% per year in a 60-year-old man. In the present study, as age of the subject differs, it indicates that PSA values were explained by age factors since it was stratified by age. PSA values showed upward trend from the lowest age group of 30–39 years and peaked at 70–79 years age group. Therefore, ASRI is better in their age-specific medium for young men and older age groups. Nevertheless, serum PSA cut-off of 0–4 ng/ml was used as the basis for conducting prostatic biopsy regardless of age. This proposition was based on a single study which had an appreciable limitations, on older technology which ignored the diverse molecular forms of PSA, and is hardly a standard test which also does not take into consideration the co-variate of age.^[7] Additionally, this threshold of 0–4 ng/ml is insufficient to detect early stage of prostate carcinoma and as such a greater significant proportion of PCa.^[24] In the present study, the 95th percentile cut-off of serum PSA value increases steadily from 1.94 g/ml in the 30–39 years category to 6.95 ng/ml in the 70–79 years category [see Table 2 and Figure 1]. This trend was also replicated in other Nigerian studies.^[15,25] However, the serum PSA values obtained in this study were about two times

higher than values obtained by scientists in the Western world.^[17,19] Nevertheless, this was lower than hospital-based study in Port Harcourt, Nigeria, probably due to population sizes, types of study, inter-assay variation, inconsistent calculation of age-specific reference intervals, and verification bias.^[24] Some authors^[20,21] suggested that a PSA threshold of 2.0–2.5 ng/ml should be used for 40–49 years in African–American^[26] compared to 0–2.52 ng/ml in the present study. Other studies have shown that serum PSA is higher in blacks than in Whites, Chinese, Indian, and Japanese.^[19-21] The similarities of high PSA values in both Nigerian studies compared with traditional accepted cut-off values give credence to the influence of race on PSA value with men of the same race having similar values, while variation exists between race groups. Therefore, we suggest that ASRIs should be applicable to Nigerian indigenous population.

It is believed that using this threshold values which are lower and higher than 0–4 ng/ml in the younger and older age group, respectively, localized PCa will be detected early leading to necessary interventions, reduce morbidity and mortality and a reduction in an unnecessary biopsy in patients with benign prostatic hyperplasia without missing the presence of prostatic carcinoma. It has been proposed that using the age-adjusted serum PSA intervals, sensitivity, and specificity of PCa detection is enhanced in younger male and older male, respectively. It is recommended that a future multi-center community-based study be carried out to validate this result. Awareness, education, and screening are quiet low for PCa prevention in Nigerian men; hence, there is need for organized screening. Low income and educational background were more prevalent among the study group.

Limitation of the study

Trans-Rectal Ultrasound Scan (TRUS) of the prostate gland and prostate biopsy using the traditional cut-off of 0–4 ng/ml were not done on any of these participants. However, all the subjects screened for PSA were without complaints of any symptoms suggestive of prostatic disease.

CONCLUSION

The study confirms that serum PSA values increased with age and this cut across all ethnicities, although the degree of increase differs from ethnicity to ethnicity when compared to literature evidence. It also gives a set and serum PSA values indigenous to the local environment. We suggest that this could be used as cut-off threshold for performing PSA biopsies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Delongchamps NB, Singh A, Haas GP. Epidemiology of prostate cancer in Africa: Another step in the understanding of the disease? *Curr Probl Cancer* 2007;31:226-36.
2. Obiorah CC, Nwosu SO. A histopathological study of carcinoma of the prostate in Port Harcourt, Nigeria. *Niger J Clin Pract* 2011;14:363-7.
3. Dawam D, Rafindadi AH, Kalayi GD. Benign prostatic hyperplasia and prostate carcinoma in native Africans. *BJU Int* 2000;85:1074-7.
4. Nwofor AM, Oranusi CK. Cancer of the prostate: Experience at Nnewi, Southeast, Nigeria. *Niger J Clin Pract* 2004;7:65-8.
5. Rebbeck TR, Devesa SS, Chang BL, Bunker CH, Cheng I, Cooney K, *et al.* Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. *Prostate Cancer* 2013;2013:560857. doi: 10.1155/2013/560857.
6. Heyns CF, Mathee S, Isaacs A, Kharwa A, De Beer PM, Pretorius MA. Problems with prostate specific antigen screening for prostate cancer in the primary healthcare setting in South Africa. *BJU Int* 2003;91:785-8.
7. Loeb S, Nadler RB, Roehl KA, Antenor JA, Catalona WJ. Risk of prostate cancer for young men with a prostate specific antigen less than their age specific median. *J Urol* 2007;177:1745-8.
8. Senior K. Age-specific PSA screening better. *Lancet Oncol* 2007;8:378.
9. Collins GN, Lee RJ, McKelvie GB, Rogers AC, Hehir M. Relationship between prostate specific antigen, prostate volume and age in the benign prostate. *Br J Urol* 1993;71:445-50.
10. Gray MA, Delahunt B, Fowles JR, Weinstein P, Cookes RR, Nacey JN. Demographic and clinical factors as determinants of serum levels of prostate specific antigen and its derivatives. *Anticancer Res* 2004;24:2069-72.
11. Etawo US, Ekeke ON, Miaba AB. Prospective study of sex hormone levels among prostate cancer patients attending the University of Port Harcourt Teaching Hospital. *Niger Health J* 2012;12:29-42.
12. Oesterling JE. Using prostate-specific antigen to eliminate unnecessary diagnostic tests: Significant worldwide economic implications. *Urology* 1995;46(3 Suppl A):26-33.
13. "Population by State and Sex" (PDF). population.gov.ng. Archived from the original (PDF) on 19 May 2011.
14. Solberg HE. International Federation of Clinical Chemistry (IFCC), Scientific Committee, Clinical Section, Expert Panel on Theory of Reference Values, and International Committee for Standardization in Haematology (ICSH), Standing Committee on Reference Values. Approved Recommendation (1986) on the theory of reference values. Part 1. The concept of reference values. *J Clin Chem Clin Biochem* 1987;25:337-42.
15. Amadi C, Odum EP. Age specific serum prostate-specific antigen references range among healthy men in Port Harcourt, Nigeria: A retrospective hospital-based study. *Int J Res Med Sci* 2019;6:417-21.
16. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, *et al.* Prostate cancer disparities in Black men of African descent: A comparative literature review of prostate cancer burden among Black men in the United States, Caribbean,

- United Kingdom, and West Africa. *Infect Agent Cancer* 2009;4 Suppl 1(Suppl 1):S2. doi: 10.1186/1750-9378-4-S1-S2.
17. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, *et al.* Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860-4.
 18. Lim J, Bhoo-Pathy N, Sothilingam S, Malek R, Sundram M, Hisham Bahadzor B, *et al.* Ethnicity is an independent determinant of age-specific PSA level: Findings from a multiethnic Asian setting. *PLoS One* 2014;9:e104917. doi: 10.1371/journal.pone.0104917.
 19. Oesterling JE, Kumamoto Y, Tsukamoto T, Girman CJ, Guess HA, Masumori N, *et al.* Serum prostate-specific antigen in a community-based population of healthy Japanese men: Lower values than for similarly aged white men. *Br J Urol* 1995;75:347-53.
 20. Malati T, Kumari GR. Racial and ethnic variation of PSA in global population: Age specific reference intervals for serum prostate specific antigen in healthy South Indian males. *Indian J Clin Biochem* 2004;19:132-7.
 21. Gupta A, Gupta D, Raizada A, Gupta NP, Yadav R, Vinayak K, *et al.* A hospital based study on reference range of serum prostate specific antigen levels. *Indian J Med Res* 2014;140:507-12.
 22. Reed A, Ankerst DP, Pollock BH, Thompson IM, Parekh DJ. Current age and race adjusted prostate specific antigen threshold values delay diagnosis of high grade prostate cancer. *J Urol* 2007;178:1929-32.
 23. Ikuerowo SO, Omisanjo OA, Bioku MJ, Ajala MO, Mordi VP, Esho JO. Prevalence and characteristics of prostate cancer among participants of a community-based screening in Nigeria using serum prostate specific antigen and digital rectal examination. *Pan Afr Med J* 2013;15:129. doi: 10.11604/pamj.2013.15.129.2489.
 24. Luboldt HJ, Schindler JF, R b ben H. Age specific reference ranges for prostate- specific antigen as a marker for prostate cancer. *EA-EBU Update Series* 2007;5:38-48.
 25. Adedaapo KS, Kareem IO, Mary A, Akinloye O. Pattern of prostate specific antigen request in a Nigeria tertiary health care: A Decade Review. *Andrology* 2012;1:104.
 26. PSA: Prostate-specific antigen, persisting scientific ambiguities. *Harv Mens Health Watch* 2009;13:1-6.