African Journal of Urology (2017) **23**, 14–19

African Journal of Urology

Official journal of the Pan African Urological Surgeon's Association
web page of the journal

www.ees.elsevier.com/afju
www.sciencedirect.com

Original article

The role of the percentage free PSA in the diagnosis of prostate cancer in Blacks: Findings in indigenous West African men using TRUS guided biopsy

K.H. Tijani [a,*], C.C. Anunobi [b], A.O. Adeyomoye [c], T.O. Alabi [d], A.O. Lawal [d], N.O. Akanmu [e], R.W. Ojewola [a], O.O. Soriyan [f]

[a] *Section of Urology, Department of Surgery, College of Medicine, University of Lagos, Nigeria*
[b] *Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos, Nigeria*
[c] *Department of Radiodiagnosis, Lagos University Teaching Hospital, Nigeria*
[d] *Department of Surgery, Lagos university Teaching Hospital, Nigeria*
[e] *Department of Anaesthesia, Lagos University Teaching Hospital, Nigeria*
[f] *Department of Clinical Pathology, Lagos University Teaching Hospital, Nigeria*

Received 23 November 2015; received in revised form 13 April 2016; accepted 23 April 2016
Available online 24 December 2016

KEYWORDS
Free PSA;
West African men;
Prostate cancer;
Blacks;
Nigeria;
Lagos

Abstract

Introduction: In Western and Asian literature, the measurement of percentage free prostate specific antigen (%fPSA) has been known to enhance the predictive role of total prostate specific antigen (tPSA) in early prostate cancer (Ca-P) detection. Relationship between the tPSA and Ca-P are known to be influenced by race. To the best of our knowledge, the relationship between %fPSA and Ca-P has not been studied in sub-Saharan Africa using current established biopsy protocol.

Objective: To evaluate the usefulness of %fPSA in indigenous West African men and determine the appropriate cut-off values that may be used as indication for prostate biopsy in men with tPSA of 4–10 ng/ml.

Subjects and methods: A total 169 consecutive patients with tPSA of 4–10 ng/ml with non-suspicious findings on digital rectal examination (DRE) had a transrectal ultrasound (TRUS) guided 10-core prostate biopsy. The technique of PSA analysis was the Access hybritech assay technique using the Beckman's Access autoimmuno analyser. The rates of prostate cancer in different %fPSA ranges were evaluated. Receiver

* Corresponding author at: Senior Lecturer, Section of Urology, Department of Surgery, College of Medicine, University of Lagos.
Tel.: +2348023049739.
E-mail addresses: habeeb_tijani@yahoo.com, ktijani@unilag.edu.ng (K.H. Tijani).
Peer review under responsibility of Pan African Urological Surgeons' Association.

http://dx.doi.org/10.1016/j.afju.2016.04.008

operating characteristic curve (ROC) was used to evaluate the efficiency of %fPSA in the diagnosis of prostate cancer.
Results: A reduction %fPSA was associated with a higher detection rate of Ca-P. There was a 62% prevalence of Ca-P with %fPSA $\leq$ 10% while there was a zero prevalence in patients with fPSA above 20%. At a %fPSA cut off of 20% the sensitivity and specificity were 100% and 45%, respectively. Using the ROC curve, the area under the curve (AUC) was 0.76 while the ROC decision plot showed that a %fPSA cut off 15% was associated with the highest ability to discriminate between benign and malignant diseases.
Conclusion: The %fPSA is an effective discriminating tool in determining the need for prostate biopsy in indigenous West African men with PSA 4–10 ng/ml. A cut off of 15% was associated with the highest performance.

Introduction

The serum prostate specific antigen (PSA) is one of the most useful tumour markers in clinical practice. However, the usefulness of PSA in the diagnosis of prostate cancer is limited by its lack of specificity especially in the so-called grey zone of 4–10 ng/ml in which cancer has been reported to be present in about a quarter of cases [1]. PSA isoforms found in the serum include the free unbound PSA (fPSA) and the complex PSA which is bound to protease inhibitors [2]. Many studies have demonstrated the usefulness of percentage free PSA (%fPSA) to distinguish between malignant and benign prostatic diseases in men with PSA between 4.1 and 10 ng/ml. A lower %fPSA has been associated with a higher likelihood of a diagnosis of prostate cancer (Ca-P) [3–5].

Using the classical sextant biopsy, Catalona et al. [3] first reported an increased probability of Ca-P as %fPSA reduced. While studies have reported higher total serum PSA (tPSA) in men of African descent in the US compared with their white counterparts [6], opinion is divided among authors on the racial variation of %fPSA between American whites and blacks and also among Asian populations with many conflicting reports [7–9]. Racial differences in the incidence and biological behaviour of prostate cancer are also well established with Afro-Americans and Afro-Caribbeans most of whom are of West African origin [10] being of higher risk of dying from the disease [2].

The use of %fPSA derived from Western and Asian populations irrespective of race may, however, not be directly applicable to indigenous Black African men. There is a paucity of data on the usefulness of %fPSA in indigenous Black African population. Nigeria, the most populous black nation in the world, and accounting for over 70% of the population of West Africa [11] is an appropriate environment to assess the usefulness of %fPSA and determine the predictive role of various cut-off points in Ca-P detection in black Africans.

The aim of this study was to assess the usefulness of %fPSA for the detection of prostate cancer in indigenous West African men with tPSA value of 4.1–10 ng/ml with normal findings on digital rectal examination and to determine the appropriate cut-off values that may be used as indications for prostate biopsy.

Subjects and methods

Study setting

This prospective observational study was performed at the major urological referral centre in Lagos. It is the only public hospital rendering image guided prostate biopsy in the city. Lagos, the commercial capital of Nigeria, with about 18 million inhabitants, is the most populous and cosmopolitan city in West Africa. Virtually every black race is represented in the city [12].

Ethical approval was obtained from the hospital ethics board. One hundred and eighty-three consecutive patients (who met the inclusion criteria) referred from peripheral health facilities (including different privately organised screening programmes) to the urology unit of the hospital on account of a raised tPSA between 4.1 and 10.0 ng/ml over a period of 24 months (June 2013–May 2015) were included in this study. Patients with findings suggestive of Ca-P on DRE and those on 5-α reductase inhibitors within last 6 months were excluded from the study. Other exclusion criteria included the presence of untreated urinary tract infection, untreated bleeding disorder, history of previous prostate surgery or previous treatment for prostate cancer. Blood samples were collected from these selected patients for repeat tPSA and free PSA (fPSA) thereafter, analyzed within 24 h of sample collection. The analytical procedure used for determination of tPSA and fPSA assay was the Hybritech Paramagnetic Particle Two-Site Immunoenzymatic ("Sandwich") Assay With Chemiluminescent Detection technique using Beckman Access Immunoassay Analyser. The final 169 patients who had their repeat PSA within the range of 4–10 ng/ml had their data analysed. All patients had a minimum of a 10-core TRUS guided biopsy. Additional biopsies were taken in the presence of suspicious lesions detected on transrectal ultrasound scan (TRUS). Haematoxylin and Eosin (H & E) slides were made from the patients' formalin fixed, paraffin embedded blocks. Diagnoses were made and Gleason score was determined for the individual adenocarcinoma cases. Four cases whose diagnoses could not be made based on H & E only were subjected to immunohistochemical studies using antibodies directed against basal cells (p63) and AMACR. Three out of these four were diagnosed as malignant lesions. Data collected and analysed included the demographic characteristics (Table 1), the histology at different %fPSA ranges (Table 2) which was compared with another study (Table 3), while the test of accuracy

Table 1 Demographic and clinical characteristics based on histopathology.

	Bph	Ca-P	*P*-value
Mean age (yrs)	63.0 (±6.5)	65.1 (±7.0)	>0.05
Median PSA (ng/ml)	6.6 (4.2–10)	6.8 (4.1–10)	>0.05
Median free PSA (ng/ml)	1.3 (0.6–3.9)	0.8 (0.3–1.7)	<0.01
Median free total PSA (%)	22.4 (9–46)	11.6% (7–19)	<0.01
Median prostatic vol. (ml)	60.0 (20–213)	55.2 (17–298)	>0.05
Median PSA density	0.11 (0.03–0.32)	0.16 (0.02–0.55)	<0.01

Table 2 PSA range and histological diagnosis.

PSA (ng/ml)	BPH	Ca-P	Total
4.1–5.0	25	3	28
5.1–6.0	7	3	10
6.1–7.0	34	11	45
7.1–8.0	17	6	23
8.1–9.0	34	3	37
9.1–10	15	11	26
Total	132	37	169

Table 3 %fPSA and histological diagnosis.

%fPSA	Bph	Ca-P	Total	% Ca-P
≤10	10	16	26	62
10.1–15	22	12	34	35
15.1–20	41	9	50	19
20.1–25	23	0	23	0
25.1–30	14	0	14	0
30.1–35	11	0	11	0
35.1–40	4	0	4	0
40.1–45	7	0	7	0
Total	132	37	169	22

of %fPSA was also analysed (Table 4). The relationship between %fPSA the number of positive cores and Gleason scores were also analysed.

Results were expressed using tables and charts. The paired *t*-test, the ANOVA test or the Mood's median test were used to compare the means or medians as appropriate, and a *P*-value of less than 0.05 was regarded as significant. Receiver Operating Characteristics (ROC) curves were generated for %fPSA by plotting sensitivity versus 100-specificity (Figs. 1 and 2). The software programme SPSS version 21 was used for statistical analysis.

Table 4 Prevalence of prostate cancer based on different %fPSA cut off comparison with Catalona et al.

%fPSA	Catalona	Tijani
0–10	56%	62%
10.1–15	28%	35%
15.1–20	20%	18%
20.1–25	16%	0%
>25	8%	0%

Results

The overall mean age was 63.4 years (range 45–81). About 93% of the subjects were Nigerians while 7% were citizens of 4 other West African countries who were residing in Lagos. The median fPSA was 1.4 ng/ml with prostate cancer detected in 37 (22%) patients while the median number cores taken was 12 (10–16). The median free PSA and %fPSA were significantly less in patients with Ca-P compared with the BPH group ($P < 0.01$), while the median prostatic volume was less in the Ca-P group but this was not statistically significant. The mean age and the median PSA were higher in the Ca-P group but these differences were not statistically significant while the median PSA density was significantly higher in the Ca-P group (Table 1). The peak incidence of Ca-P of 11 cases was found in men in the PSA ranges of 6.1–7.0 and 9.1–10.0 ng/ml, while the peak incidence of BPH (34) was found in the 6.1–7.0 and 8.1–9.0 ng/ml groups (Table 2). There was a gradual reduction in the prevalence of Ca-P as the %fPSA increased. The highest prevalence of Ca-P (62%) was found in patients with %fPSA ≤ 10, while %fPSA above 20% was associated with a zero prevalence (Tables 3 and 4). Among the groups that were positive for cancer, the number of positive cores ranged from 1–7 (mean 2.5 ± 1.3). The highest mean number of positive cores of 3(SD ± 1.4) was associated with %fPSA ≤ 10, while the lowest mean of 2.5(±1.2) was found in men with %fPSA in the 10.1–15 range but there was no statistically significant relationship between %fPSA and the number of positive cores. The Gleason score ranged from 4–9, with an overall median of 6 with the highest of 6.5 found in men in the 10.1–15 range. Using different cut-offs, the sensitivity and the negative predictive value (NPV) of %fPSA for Ca-P increased as the %fPSA increased both reaching 100% at %fPSA of 20% while the specificity and the positive predictive value reduced with increasing %fPSA. The highest specificity and PPV were 92% and 62%, respectively at %fPSA of 10% (Table 5). The area under the curve (AUC) in the ROC curve was 0.76 (Fig. 1) while the decision plot of sensitivity against specificity revealed that a %fPSA cut-off 15% was associated with the highest ability to discriminate between benign and malignant diseases (Fig. 2).

Table 5 Test of accuracy for %fPSA at different cut off levels sensitivity, specificity and positive predictive values for prostate cancer at different %fPSA cut-offs.

%fPSA	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≤10	43.2	92	62	85
≤15	76	76	47	92
≤20	100	45	34	100
≤25	100	27	28	100
≤30	100	16	25	100
>30	100	9	23	100

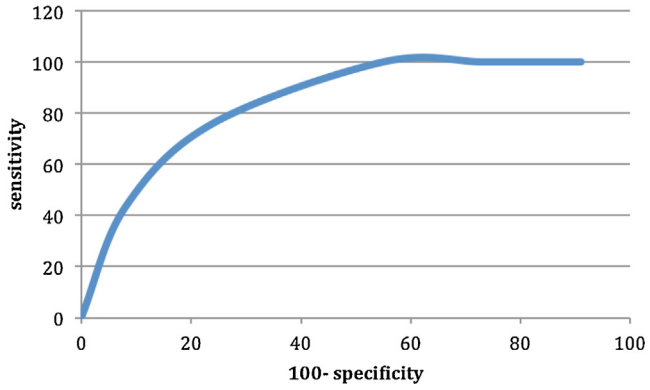

Figure 1 The receiver operating characteristic (ROC) curve. The ROC curve – plotting sensitivity against 100-specificity. The area under the curve (AUC) – 0.76.

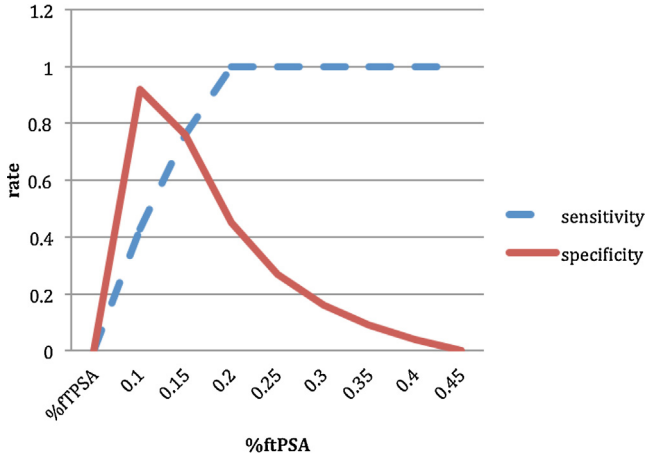

Figure 2 The ROC decision plot. A decision plot shows the sensitivity (true-positive rate) and specificity (true-negative rate) curves of %fPSA levels. The point where the lines cross (0.15) is the optimum threshold level of accuracy.

Discussion

The purpose of this study was not only to determine the appropriate cut-off value for %fPSA but also to evaluate the popular %fPSA cut-off points such as the ones defined by Catalona [3] and also our previous study [13] using a different biopsy protocol. In this study, we used a minimum of 10-core biopsies under TRUS guidance.

The overall cancer detection rate of 22% was consistent with other studies that have reported a prevalence of 2–53%% in Western and Eastern populations [1,3,7,8,14]. A previous study in our environment had reported a prevalence of 13% of Ca-P in patients with PSA in the intermediate zone [13]. However, in that study, the biopsy was not image guided thereby reducing its accuracy and reliability [2,13].

Even though the average prostatic volume was less in patients with Ca-P compared with those with BPH, it was not statistically significant (Table 1). This is consistent with results of others which have documented a higher Ca-P detection rate in patients with low prostatic volume with PSA in the intermediate range [3,8,13]. Comparing the tPSA range and the histological diagnosis, both BPH and Ca-P had 2 peaks each; with the highest incidence of Ca-P at the tPSA 9.1–10 ng/ml range and that of BPH at 8.1–9.0 ng/ml while both also shared a similar peak at 6.1–7.0 ng/ml (Table 2). However, the average PSA density was significantly higher in the Ca-P group which was consistent with the reports of others [15,16].

While the median %fPSA was significantly lower in the Ca-P group, there was no significant difference in the medians of the tPSA in the 2 groups again highlighting the poor discriminating ability of tPSA in the 4–10 ng range.

The cancer detection rate was highest in patients with %fPSA < 10% and reduces dramatically to 0% in patients with %fPSA above 20% (Table 3). Other studies have reported a similar reduction in the cancer detection rates as the %fPSA reduces. Our findings of a 0% prevalence of cancer in patients with %fPSA above 20% differs from others who had found a cancer prevalence of 16–29% in patients with %fPSA of 20% and above [3,17] (Table 4). Reasons for these differences are unclear. Environment and genetic factors as well as the study design and techniques of PSA assay may play a role. Some of these studies had included men with abnormal findings on DRE thereby increasing the likelihood of Ca-P. In a systematic review of studies comparing different PSA assay techniques [18], the Access hybritech assay technique which was used in this study was more commonly associated with a relatively higher total PSA and relatively lower free PSA with the consequent possibility of lowering the %fPSA. Also, while the %fPSA has been shown to have a high specificity and sensitivity for prostate cancer in the 4–10 ng/ml PSA range, opinion is divided amongst authors on the effect of race on the predictive role of a %fPSA cut-off points in Ca-P detection. While Catalona [7] et al. found no significant differences in %fPSA in Caucasians and African-Americans, Fowler [8] found racial differences in the relationship between %fPSA and cancer detection and thus suggested a higher cut-off value of %fPSA of 32% for blacks as against the 25% for Caucasians. Our findings appear to be different. A cut-off of 10% %fPSA was associated with specificity of 94% and a sensitivity of 43.2% while a cut-off of 25% was associated with a sensitivity of 100% and a specificity of 27% (Table 5). In assessing the overall predictive value of %fPSA, many studies have used the area under the curve (AUC) in a ROC analysis with values ranging from 0.5–0.99 [10,11,19,20]. The AUC of 0.76 in this study was consistent with this, thereby indicating a high discriminating ability of %fPSA in the diagnosis of Ca-P (Fig. 1). Even though, by using the ROC curve decision plot, the threshold that optimally discriminated between patients who had prostate cancer and those who did not was 15% (Fig. 2) by using a cut-off of 20% %fPSA for prostate biopsy, 100% of all cancers would be picked up, while 45% of all unnecessary biopsies would have been avoided.

In a recent study, Judenary et al. [21] compared the sensitivity and specificity of both the manual and the automated assay of %fPSA in Caucasians and African-Americans. For the automated assay, they used the Beckman's auto analyser as was used in our study. They reported a statistically significant difference in the sensitivity of the two techniques in whites, but not in blacks. Even though the authors only used a cut off of 25% to assess the predictive values of %fPSA for prostate cancer, they also found a 100% sensitivity in Afro-Americans and only 75% sensitivity in whites, thereby implying that no Afro-Americans with %fPSA greater 25% had prostate cancer. Even though they did not assess the predictive value for %fPSA at 20%, their findings appear consistent with ours with a 100% sensitivity of %fPSA at 20% and 25%, indicating that rather

than increasing the cut-off value for blacks as had been suggested by Fowler [8] it appears that the cut-off should be reduced when the Beckman automatic assay techniques is used. Reports from other studies [22] have suggested an inverse but statistically significant relationship between tumour volume and the %fPSA. In this study, even though the highest mean number of positive cores was associated with men with %fPSA less than 10%, there was no statistically significant relationship between the number of positive cores and the %fPSA. Our sample size of only 37 (cases of Ca-P) may however be a contributory factor to the inability of the present study to demonstrate a statistically significance difference. The reports on the relationship between Gleason score and %fPSA have also been conflicting with some [23] reporting a statically significant inverse relationship while others [24] found no relationship at all. In this study, the %fPSA did not have a statistically relationship with the Gleason score. To the best of our knowledge this is the first study in Sub-Saharan Africa that has tried to assess the usefulness of %fPSA in the detection of Ca-P using image guided biopsy and one of the largest series involving Blacks with normal DRE findings.

The limitations of this study need to be highlighted. Even though TRUS guided biopsy still appears to be the standard of care for routine prostate biopsy its diagnostic accuracy has been a subject of concern as up to 39% of malignant lesions in the prostate are isoechogenic and only 17–57% of hypoechoic [25] lesions are malignant. While some studies have also reported improved tumour yields with higher number of (minimum) cores, the minimum number of cores in this study was 10, so as to limit the morbidity. The limitations of PSA in the screening for Ca-P have also been well documented. All these factors increase the likelihood of missing some cases of Ca-P.

In conclusion, the %fPSA is an effective discriminating tool in determining the need for prostate biopsy in indigenous West African men with PSA 4–10 ng/ml. The cut off of 15% was associated with the highest performance in our study.

Authors' contributions

Dr K.H. Tijani - habeeb_tijani@yahoo.com, khtijani@cmul.edu.ng.

Concept, design, data collection, analysis of data, writing of manuscript.

Dr. C.C. Anunobi - dozieanunobi@yahoo.com.

Design, data collection (Did all the histopathology), writing of manuscript.

Dr A.O. Adeyomoye - kunleadeyomoye@yahoo.com.

Design, data collection (supervised all imaging) and manuscript writing.

Dr T.O. Alabi - taiwo_allaby@yahoo.com.

Data collection, analysis and manuscript.

Dr A.O. Lawal - razzaklawal@yahoo.com.

Analysis (especially the statistical and manuscript writing.

Dr N.O. Akanmu - lanre.akanmu@yahoo.com.

Design, data collection, manuscript writing.

Dr R.W. Ojewola - rwaleojewola@yahoo.com.

Design, data collection and critical review manuscript.

Dr O.O. Soriyan - tunjisoriyan@gmail.com.

Data collection (chemical pathology) and manuscript.

Ethical committee approval

Ethical approval was obtained from the Lagos University Teaching Hospital Health Research and Ethics Board.

Conflict of interest

The authors declare that there are no conflicts of interest.

Funding

The study was funded by a research grant from the Central Research Committee of the University of Lagos, Nigeria (Ref-CRC. NO. 2013/01).

Acknowledgements

There was logistic support from the Lagos University Teaching Hospital with special thanks to the head of Radio-diagnosis department.

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