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ORIGINAL ARTICLE

An Evaluation of Usefulness of Prostate Specific Antigen and Digital Rectal Examination in the Diagnosis of Prostate Cancer in an Unscreened Population: Experience in a Nigerian Teaching Hospital

Une évaluation de l'utilité de l'antigène spécifique de la prostate et du toucher rectal dans le diagnostic du cancer de la prostate au sein d'une population sans dépistage- Expérience d'un hôpital universitaire du Nigeria

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ABSTRACT

OBJECTIVE: **To evaluate the usefulness of prostate specific antigen (PSA) and digital rectal examination (DRE) in the diagnosis of cancer of the prostate (CaP) amongst unscreened patients.**

PATIENTS, MATERIALS AND METHODS: **A prospective study168 unscreened men who were referred for evaluation for CaP. They all had a 10-core extended transrectal prostatic needle biopsy using size 16 Tru Cut needle for either an elevated serum total PSA of >4ng/ml or abnormal DRE findings or both. Overall cancer detection rate was determined and detection rates were determined separately for patients with elevated PSA with normal DRE, abnormal DRE with normal PSA and those with both indications. The performances of each indication were determined separately and in combination in terms of their sensitivity, specificity, predictive values and accuracy. The results were compared amongst patients with different indications for biopsy.**

RESULTS: **The overall cancer detection rate was 44.0%. Detection rates in patients with elevated PSA with normal DRE and abnormal DRE with normal PSA were 30.0% and 17.4% respectively. There was statistically significant increased detection of 61.2% amongst patients with both indications. The overall sensitivities of PSA, DRE and combination of both were 94.6%, 75.7% and 70.3% respectively while the specificities were 20.2%, 44.7% and 64.9% respectively. The accuracies of PSA, DRE and combination of both indications were 53%, 58% and 67.3% respectively while the PPVs were 48.3%, 51.9% and 61.2% respectively. Mean Gleason score was 6.82 while the overall complication rate was 23.2%**

CONCLUSION: **Neither PSA nor DRE is sensitive, specific, predictive or accurate enough on its own to be an ideal screening or diagnostic test for CaP. Therefore, optimal evaluation of patients with suspected CaP is best achieved with both even in unscreened populations. WAJM 2013; 32(1): 8–13.**

Keywords: **Prostate cancer, detection rate, sensitivity, specificity, predictive values, accuracy.**

RÉSUMÉ

OBJECTIF: Evaluer l'utilité de l'antigène spécifique de la prostate (ASP) et du toucher rectal dans le diagnostic du cancer de la prostate(CaP) chez des patients sans dépistage.

PATIENTS, MATÉRIELS ET MÉTHODES: Il s'agit d'une étude prospective de 168 hommes n'ayant pas fait l'objet de dépistage, référés pour recherche de CaP. Ils avaient tous subit une biopsie prostatique par voie transrectale prélevant 10 carottes à l'aide d'une aiguille Tru Cut de taille 16 suite à un taux d'ASPe"4ng/ml et/ou une anomalie au TR. Un taux global de détection de cancer a été déterminé puis ce taux a été estimé séparément pour une élévation isolée du taux d'ASP, une anomalie isolée au TR et les 2 anomalies combinées. Les performances de chaque indication ont été évaluées séparément et de façon combinée en terme de sensibilité, de spécificité, de valeur prédictive et d'exactitude. Les résultats ont été comparés parmi des patients avec différentes indications de biopsie.

RÉSULTATS: Le taux global de détection du cancer était de 44,0%. Les taux de détection pour les patients à taux élevé d'ASP avec TR normal et et ceux avec TR anormal et taux d'ASP normal étaient respectivement de 30,0% et 17,4%. Il y'avait une aumentation significative de la détection de l'ordre de 61,2% parmi les patients combinant les 2 indications de biopsie. La sensibilité globale du taux d'ASP, du TR et la combinaison des 2 était de 94,6%, 75,7% et 70,3% respectivement tandis que la spécificité était de 20,2%, 44,7% et 64,9% respectivement. L'exactitude du taux d'ASP, du TR et de la combinaison des 2 indications était de 53%, 58% et 67,3% respectivement tandis que la Valeur Prédictive Positive (VPP) était de 48,3%, 51,9% et 61,2% respectivement. Le score moyen de Gleason était de 6,82 et le taux global de complications était de 23,2%.

CONCLUSION: Ni le taux d'ASP ni le TR ne sont isolément assez sensitifs, spécifiques, prédictifs ou exacts pour être un test idéal pour le dépistage et le diagnostic du CaP. Une évaluation optimale des patients suspects de CaP est meilleure avec la combinaison des 2 indications même dans une population sans dépistage. **WAJM 2013; 32(1): 8–13.**

Mots Clés: Cancer de la prostate, taux de détection, sensitivité, spécificité, valeurs prédictives, exactitude

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Abbreviations: BPH, Benign prostatic hyperplasia; **Cap,** Cancer of the prostate; **DRE,** Digital rectal examination; **NSAIDs,** Non-steroidal anti-inflammatory drugs**PSA,** Prostate specific antigen; **TRUS,** Transrectal ultrasound

INTRODUCTION

Prostate cancer (CaP) is the most common non-cutaneous cancer among males[1]. Globally, it is the fourth most common cause of cancer in males.[2] Studies have shown a high incidence of CaP in Nigerian men and indeed, it is the commonest cancer amongst males.[3,4] Unfortunately, the screening programmes for CaP are not yet developed in Nigeria and most sub-Saharan African countries making the mortality from the disease to be very high.[5–9]

Three technological advances have greatly contributed to the startling increase in the diagnosis of CaP worldwide.[10] These are refinement in ultrasound technology, development of spring-loaded automated biopsy devices and the measurement of prostate-specific antigen (PSA). Of all these advances, however, improvements in the measurement of PSA have had the most significant effect. This has led to a dramatic increase in the number of prostate biopsy being performed in our urologic practice worldwide.[10]

The main indications for prostate biopsy in urological practice are elevated PSA, abnormal DRE findings and abnormal findings on imaging studies.[10] Ultrasound especially transrectal ultrasound (TRUS) of the prostate has been suggested as a screening and diagnostic tool for CaP butowing to its expense and limited sensitivity and specificity, enthusiasm for its use has dissipated.[11] However, it has become indispensable for guiding the taking of prostatic biopsies because it can accurately guide biopsy needle to targeted zones and suspicious areas of the prostate.

Of these tools, elevated PSA value and abnormalities on DRE are the most universally accepted indications for prostate biopsy.[12] Many studies have been done to assess the performances of these tools with conflicting results but were conducted mostly amongst screening or asymptomatic populations.[13–15] This study therefore aims at evaluating the usefulness of PSA and DRE in the diagnosis of CaP amongst patients seen in our urological practice where there are no organized screening programmes for CaP.

SUBJECTS, MATERIALS AND METHODS

The study was prospectively conducted in the urology unit of our hospital between January and December 2010. All male patients who were referred to urology clinic for evaluation for prostatic disease(s) had a serum total PSA measurement and a DRE performed on them. Inclusion criteria were presence of elevated PSA (>4ng/ml) or abnormal DRE finding(s) or both. One hundred and sixty-eight patients who met the inclusion criteria had a 10-core extended prostate biopsy (including the traditional sextant biopsies and additional four lateral biopsies) using size 16 Tru Cut needle after 2% xylocaine gel rectal lubrication and intravenous (i.v) Pentazocin 30mg stat. Biopsy was done after the unit protocol of preparation viz; stoppage of non-steroidal anti-inflammatory drugs (NSAIDs), rectal washout and i.v Ciprofloxacin 200mg stat. All tissue samples were sent for histopathological examination.

Relevant information including the demographic data, examination findings, indication(s) for biopsy and results of histopathology were obtained using a pro forma. The data were analyzed with Epi Info computer statistical soft-ware (version 3.5.1) and results were displayed in tables and charts. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)and accuracy of each diagnostic tool were determined separately and in combination and these results were compared.

RESULTS

A total of 168 patients were enrolled in the study. Ages of the patients ranged from 48–92 years with a mean age of 67.9±7.5years. One hundred and twenty three (73.2%) were above 60 years of age. The peak age range was 61–70 years and accounted for 70 (41.7%) of the entire study population. Mean age for patients with benign prostatic hyperplasia (BPH) and CaP were 66.5 and 68.3years respectively with no significant difference between them.

The commonest indication(s) for biopsy was combination of elevated PSA and abnormal DRE in 85 cases (50.6%) while abnormal DRE only constitutes the least indication in 23 (13.7%) cases. In all, 145 patients (86.3%) had elevated PSA either alone or in addition to abnormal DRE findings while 108 patients (64.3%) had abnormal DRE findings either alone or in addition to elevated PSA (Figure 1).

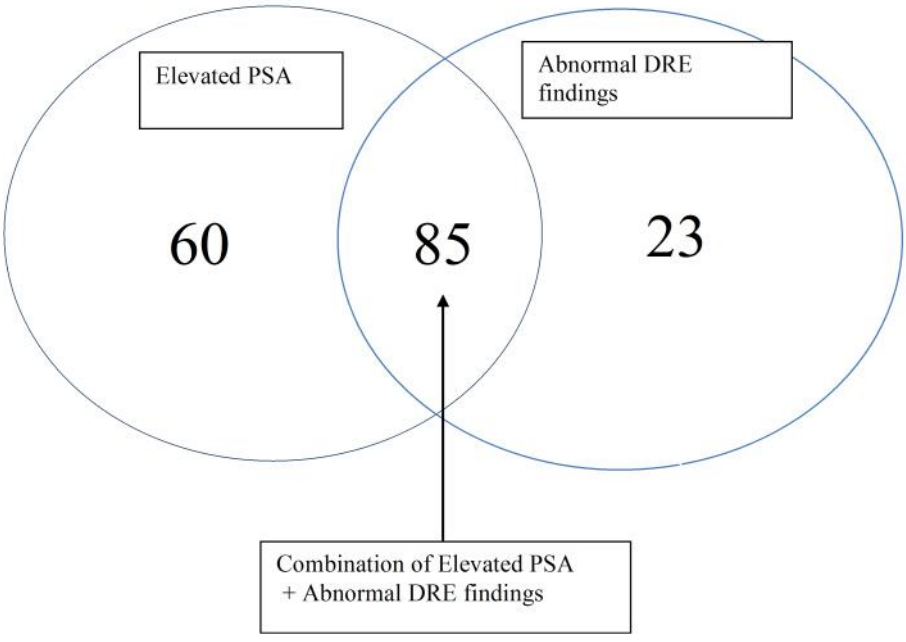

Figure 1: Indications for Prostate Biopsy.

Seventy-four of the 168 patients had malignant histology with the overall cancer detection rate of 44.0% (74/168) while 94 (56%) had benign lesions. Benign histopathology results include BPH in 46.4% (78/168), BPH with prostatitis in 7.7 % (13/168) and low grade PIN in 1.8% (3/168) of all biopsied patients. High grade PIN was found in co-existence with *CaP* in two (2) patients. All malignant biopsies were adeno-carcinomas.

The PSA range was 0.6 to 157 with a mean of 26.5 ± 14.6 ng/ml and median of 28.6ng/ml. Among patients with malignant and benign histopathology results, ranges of serum total PSA were 2.7 to 157ng/ml and 0.6 to 54.6ng/ml while the mean PSA were 33.6 and 10.3ng/ml respectively.

The cancer detection rate amongst patients of different indications is depicted in Figure 2. PPV of PSA alone (when DRE is normal), DRE alone (when PSA is normal) and PSA+DRE were 30% (18/60), 17.4% (4/23) and 61.2% (18/60) respectively. There was a very strong positive correlation between CaP and presence of both elevated PSA and abnormal DRE findings in patients (0.000041).

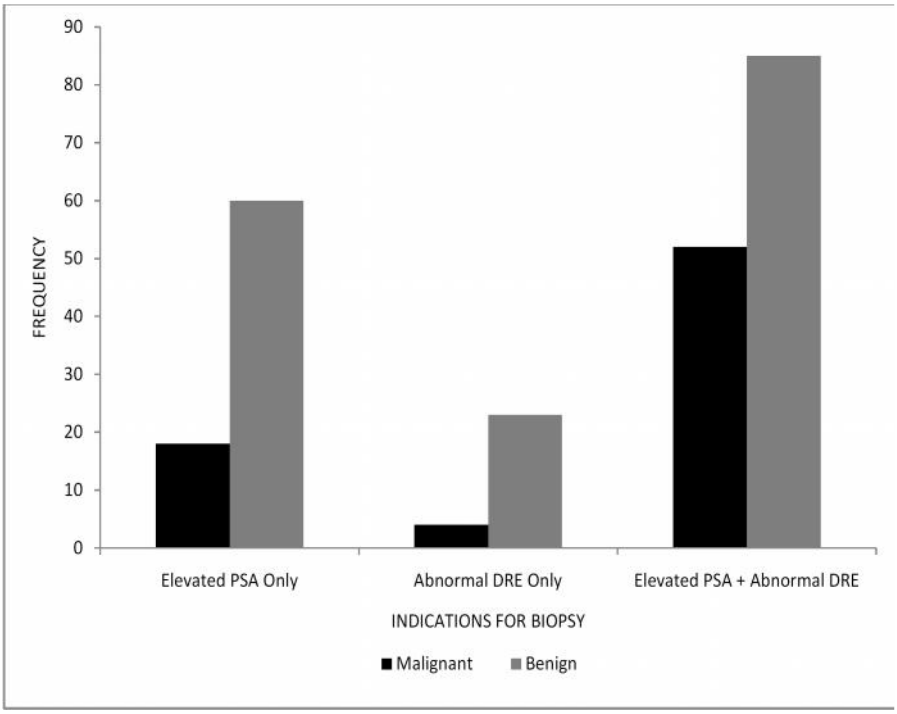

Figure 2: Histopathology Results in Patients with Different Indications for Biopsy

Table 1: Sensitivity, specificity, predictive values and accuracy of PSA and DRE

Indication(s) ì	Elevated PSA Irrespective of DRE findings	Abnormal DRE Irrespective of PSA level	Elevated PSA + Abnormal DRE
No of patients	145	108	85
No of malignant histology	70	56	52
No of benign histology	75	52	33
Sensitivity	94.6	75.7	70.3
Specificity	20.2	44.7	64.9
PPV	48.3	51.9	61.2
NPV	82.6	70.0	73.5
Accuracy	53.0	58.0	67.3

The performances of these tools were calculated from three groups namely: all patients with elevated PSA (irrespective of DRE findings), abnormal DRE (irrespective of their PSA values) and those with both indications. Table 1 shows the performances of PSA, DRE and combinations of both indications calculated using standardized two by two tables based on the test and outcome positives and negatives.

Cancer detection stratified with PSA levels shows different cancer detection at different PSA values with highest detection of 85.7% (18/21) in the range of PSA above 50ng/ml and lowest detection of 17.4% (4/23) in PSA values < 4ng/ml. (Table 2) There was an increasing positive correlation between the diagnosis of CaP and PSA as PSA value increases.

Cancer detection at various PSA levels considered along with findings on DRE findings is depicted in Table 3 below. The increases in detection rates were statistically significant in all the PSA ranges in patients who had both elevated PSA and abnormal DRE. (P values < 0.05).

The performance of PSA as a diagnostic tool at 4ng/ml and 10ng/ml cut-offs is depicted in Table 4.

The range of Gleason score was 3–10 with a mean score of 6.82± 1.39. Of 74(100%) cancers detected, 21(28.4%) had low grade (2–4), 34 (45.9%) had moderate grade (5–7) while 19 (25.7%) had high grade (8–10) tumours.

Of 168 patients, 39 had at least one complication with the overall complication rate of 23.2%. Altogether, there were 64 complications recorded in all the 39 patients. Haematuria was the commonest occurring in 29(17.3%) patients while the least was haematospermia in 1(0.6%). Other complications recorded are as follow: rectal bleeding, 14 (8.3%); urinary tract infection, 8 (4.8%); deep perineal pain, 7 (4.2%); acute urinary retention, 3(1.8%); and epididymo-orchitis, 2(1.2%).

DISCUSSION

Currently, screening for CaP by PSA and DRE to enhance earlydetection is widely supported[12,13,15] but yet to be embraced fully in some countries where these tools are used only when patients

Table 2: Cancer Detection at Different PSA Levels

PSA levels	Malignant (+ve)	Benign (-ve)	Total
<4.0	4 (17.4)	19 (82.6)	23
4.1 – 10.0	13 (28.9)	32 (71.1)	45
10.1 – 20.0	10 (37.0)	17(63.0)	27
20.1 – 30.0	11 (52.4)	10 (47.6)	21
30.1 – 40.0	8 (50.0)	8 (50.0)	16
40.1 – 50.0	10 (67.7)	5 (33.3)	15
>50.0	18 (85.7)	3 (14.3)	21
Total	**74**	**94**	**168**

Table 3: Detection Rates at Different PSA Levels Versus DRE Findings

Range of PSA	DRE Findings	Malignant (N/%)	Benign (N/%)	Total (N/%)
<4	Normal	0 (0)	0 (0)	0 (0)
	Abnormal	4 (17.4)	19 (82.6)	23(100)
4.1 – 10.0	Normal	5 (21.7)	18 (78.3)	23(100)
	Abnormal	8 (36.4)	14 (63.6)	22(100)
10.1 – 20.0	Normal	3 (25.0)	9 (75.0)	12(100)
	Abnormal	7 (46.7)	8 (53.3)	15(100)
20.1 – 30.0	Normal	2 (28.6)	5 (71.4)	7 (100)
	Abnormal	9 (64.3)	5 (35.7)	14(100)
30.1 – 40.0	Normal	3 (33.3)	6 (66.7)	9 (100)
	Abnormal	5 (71.4)	2 (28.6)	7 (100)
40.1 – 50.0	Normal	2 (40.0)	3 (60.0)	5 (100)
	Abnormal	8 (80.0)	2 (20.0)	10(100)
>50	Normal	3 (80.0)	1 (20.0)	4 (100)
	Abnormal	15 (88.2)	2 (11.8)	17(100)
Total		**74**	**94**	**168**

Table 4: Performance of PSA at Different Cut-offs

PSA cut-off ì	>4ng/ml	>10ng/ml
No of patients	145	100
Malignant biopsies	68	56
Benign biopsies	77	44
Sensitivity	91.9	75.7
Specificity	18.1	53.2
PPV	46.9	56.0
NPV	73.9	53.0
Accuracy	50.6	63.1

present with symptoms of prostatic diseases commonly lower urinary tract symptoms. This is particularly true in Nigeria and most sub-Saharan countries where there are no organized prostate cancer screening programmes despite the high prevalence of CaP in these countries.[5–7, 9]

In this study, most of the patients (86.3%) had biopsy for elevated PSA either as a sole indication or in combination with abnormal DRE. All patients had PSA analysis unlike in an earlier study in the same centre few years ago where about 13% of patients did not have PSA analysis due to cost and unavailability of the test.[16] This represents an increasing awareness, availability and affordability of this marker as a diagnostic tool in our urologic practice.

The clinical significance of PSA as a parameter in the diagnosis of CaP has increased over the last several years and PSA can be considered the best and most sensitive tumor marker in clinical oncology today.[17] However, a well-documented limitation of PSA is its poor specificity.[10,18,19] Like the findings of otherstudies,[10, 17–19] we found PSA to be highly sensitive with a sensitivity of 94.6% but poorly specific with a value of 20.2% at a cut-off value of 4ng/ml. In terms of sensitivity, PSA outperformed DRE as a diagnostic tool for CaP in this study. This conforms to the findings of many studies.[10, 13, 20] Elevated PSA levels (>4ng/ml) were found in 79.8%(75/94) of patients with BPHin the present study, which againdemonstrates the specificity problem.

DRE has been used in diagnosis and screening for CaP for many decades and its importance is well established.[21] Its sensitivity and specificity in this study were 75.7% and 44.7% respectively. Haid *et al*[22] in their series documented a similar sensitivity of 77.4% for DRE which was inferior to the 93.3% sensitivity of PSA documented in the same study. They also reported low specificity of 18.8% and 21.2% for DRE and PSArespectively. The sensitivity and specificity in their study and ours were significantly higher than reported in many other studies.[13,14,21] These higher values may be due to similar previously unscreened populations common to these two studies as opposed to other studies conducted amongst asymptomatic populations.

The accuracy of a test is the proportion of the screened population that will be correctly labeled as either diseased or disease free. We found the accuracy of PSA and DRE to be 53% and 58%respectively with no significant difference. The accuracy of DRE in the diagnosis of CaP was documented to be 39–45% in clinical studies. The higher accuracy of DRE is because the patients in this study were never screened and referred from peripheral centres having had an elevated PSA and or suspicious DRE in addition to other symptoms of prostate disease in contrast to the other studies carried out amongst asymptomatic populations. In this study, even though the specificity of both PSA and DRE are poor, combination of the two indications for biopsy in patients increased the specificity of the diagnostic tools significantly to 64.9%. Though there are reports that DRE is not a very useful tool in asymptomatic populations,[23, 24] this study suggests that DRE is currently as useful an examination as PSA in the detection of CaP in

unscreened populations. Therefore, DRE is still strongly recommended in environments where routine screening programmes are not well established.

It has been previously documented that DRE increases the predictive value of PSA in predicting cancer and vice versa.[12,20,22] The importance of the additive values of these tools was further strengthened in this study when the cancer detection or PPV was determined separately in patients with elevated PSA alone with normal DRE, abnormal DRE alone with normal PSA level and both in combination. Detections in the first two categories of patients were 17.4% and 30.0%respectively. There was a statistically significant increase in detection rate to 61.2% which is more than the arithmetic additions of the two detection rates in patients who had both indications. Though detection was highest in patients with both indications, it is obvious that only 29.7% (22/74) of all cancers in this study were detected in patients with only one indication (either abnormal PSA or DRE). These cancer cases could have been missed if presence of both were to be mandatory for prostate biopsy. This study like other studies suggests that both tools should be utilized in all patients and patients with at least one indication with or without the other deserve a biopsy.

A significant parameter in determining the value of cancer detection tests is the PPV which also equals the cancer detection rate. Previous studies showed that the PPV of an abnormal PSA utilizing a cut-off value of 4ng/ml is higher than that of an abnormal DRE and that PPV was highest when both PSA level and DRE were abnormal.[12, 20, 25] The PPV of 48.3% and 51.9% for PSA and DRE respectively in this study implies that the PPV have similar values amongst unscreened patients. However, the PPV increases significantly to 61.2% in patients that had the two indications together. This study like others[22] demonstrates the additive values of both diagnostic modalities. The higher values in this study may be due to higher number of advanced cases evidenced by a high mean PSA of 33.6ng/ml. In an earlier study in the same centre, withmore than two-third of the patients presented with features of systemic or locally advanced disease,[16] the PPV of both PSA and DRE were even higher, 68.6% and 88.9% respectively. These higher values were however, in sharp contrast to the lower cancer detection rates or PPVs of 0.8–13.6% documented in community screening studies.[13,14]

Elevations of PSA level above normal range are not necessarily diagnostic for CaP.[13,19] In this study, about 51.7% (75/145) of patients with elevated PSA had benign prostatic lesions. Mean PSA amongst patients with CaP and BPH were 33.6ng/ml and 10.3ng/ml respectively. The findings of this study show that benign prostatic conditions like BPH and prostatitis are common causes of elevated PSA in our environment. This also agrees with the recent findings of Anunobi *et al*[26] in Lagos and Abbiyesuku *et al*[6] in Ibadan amongst Nigerian men with BPH. In addition, PSA values greater than 20 ng/ml is strongly indicative of CaP with about three quarters diagnosed of having cancer while there were just few exceptions at PSA level of $\geq$40ng/ml. We found no benign disease in patients with PSA values greater than 54.6 ng/ml. About one fifth of those with normal PSA in this study were found to harbor malignancies. This is consistent with many other studies.[25,27,28] In view of this significant risk of CaP in patients with normal PSA values, prostate biopsy is recommended for all men who have abnormal DRE abnormalities regardless of PSA level.

The PPV was noted to be increasing with increasing PSA values from overall detection rate of 28.9% amongst patients with PSA of 4.1–10.0ng/ml to 85.7% in patients with PSA values above 50ng/ml. The only exception was in the ranges of PSA of 30.1– 40ng/ml where detection was lower (50.0%) than PSA range of 20.1–30.0ng/ml (52.4%). This conforms to the general consensus that PPV of PSA increases with increasing values.[17, 19, 22] When cancer detection in patients with abnormal PSA was considered with DRE findings, the detection rates or PPVs were enhanced amongst patients who had combination of PSA and DRE compared to PSA alone at every level of PSA from 21.7 to 36.4% in PSA range of 4–10ng/ml and from 80% to 88.2% in the patients with PSA >50ng/ml. A critical look into the exception stated above revealed that greater percentage (82.4%) of patients in the 20.1–30ng/ml group had both PSA and DRE abnormalities as indications for biopsy than the former group (30.1–40ng/ml) of 43.8%. This might be responsible for higher detection in the lower PSA range of 20–30ng/ml and further strengthens the greater and additive predictive value of combination of these tools.

Determining a "normal range" of PSA has been a difficult task[17]. While most authorities have suggested that a value of 4ng/ml or less should be regarded as normal, a much lower cut-off of 2.5ng/ml has been suggested in order to increase the sensitivity of PSA.[10, 17] In a study by Oesterling,[19] the sensitivity of PSA at 2.5ng/ml cut-off was 100% but its specificity was extremely poor. We similarly noted that the sensitivity of PSA at cut-off of 2.5ng/ml was 100% as the lowest PSA amongst cancer patients in our study was 2.7ng/ml. A PSA cut-off of 10ng/ml in this study shows an increased specificity, PPV and accuracy but poorer specificity and NPV than a cut-off of 4ng/ml amongst the patients evaluated. Even though the performance of PSA cut-off of 10ng/ml is generally better than at 4ng/ml in terms of overall accuracy, an important drawback for the use of this cut-off is the significant drop in the sensitivity from 91.9% to 75.7% which will lead to failure to diagnose many tumours in patients with PSA lower than 10ng/ml. In this series, about 23% (17/74) of all patients with cancer had PSA values of less than 10ng/ml which is unacceptably higher than just 5.4% (4/74) of 4ng/ml cut-off. Therefore, a PSA cut-off of 4ng/ml is still recommended in Nigerian patients.

All patients diagnosed to have CaP in this study had adenocarcinoma as the histological type in conformity with other studies.[22,29] The mean age 67.4 years amongst cancer patients and peak age range of seventh decade of life are both consistent with other studies.[7,26] Average Gleason score of 6.34 implies that most of the patients had at least moderate grade histology. This also agrees with earlier reports from the West Africa sub region.[7–9]

The overall complication rate of 23.2% is within the range documented in literature.[30, 31] Transient haematuria was found to be the commonest complication which occurred in 19(15.2%) patients followed by rectal bleeding in 10 (8%).This agrees with other studies[31, 32] that bleeding complications are the commonest complications of prostate biopsy. There were no major infective complications. Antibiotic prophylaxis and rectal wash out adopted in this study might be responsible.

CONCLUSION

This study has shown that neither PSA nor DRE alone yielded a satisfactory diagnostic value for CaP.Only when these methods were combined was an accuracy rate of 67.3% achieved. Neither PSA nor DRE is sensitive, specific and accurate on its own to be an ideal screening or diagnostic test for CaP. Therefore,optimal evaluation of the prostate gland for cancer is best achieved with both PSA measurement and DRE even in previously unscreened populations.A PSA cut-off of 4ng/ml is recommended in Nigerian men.

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