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Research Article

Low Specificity of Fibroblast Growth Factor 23 in Differentiating Prostate Cancer from Benign Prostate Hyperplasia

Adedapo KS[1], Jimoh MA[1], and Takure AO[2]

[1]*Department of Chemical Pathology University of Ibadan and University College Hospital Ibadan,*
[2]*Division of Urology University College Hospital, Ibadan*

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Abstract

Finding a biomarkers that will be more sensitive and specific for the diagnosis of either prostate cancer or BPH as well as differentiating the two clinical conditions beyond the use of total PSA and all the its modifications has been of considerable interest for the Clinicians and other health care providers. This study here posited some further clarifications in this direction. This work attempted to determine the sensitivity/specificity of fibroblast growth factor23 in prostate cancer and benign prostate hyperplasia (BPH) patients at a tertiary centre in Ibadan Nigeria. Anthropometric characteristics, serum fibroblast growth factor 23 (FGF-23) and total prostate specific antigen (tPSA) were determined in 60 patients with histopathological diagnosis of BPH and Pca and thirty age matched control. Informed consent was obtained from all the participants in the study. Serum FGF-23 was determined using enzyme-linked immunosorbent serologic assay (ELISA) and total PSA was determined using enzyme immunoassay (EIA). The statistical analysis was done using SPSS version 20.0 and Receiver operating characteristics (ROC) curve was used to determine the sensitivity and specificity for both FGF-23 and PSA. A p-value < 0.05 was considered significant. The mean FGF-23 was significantly higher in Pca and BPH compared to control. Expectedly, the mean total PSA was also significantly higher in Pca compared to BPH and control. There was a statistically significant AUC for FGF-23(AUC = 0.697, p = 0.009) between PCa patients and controls while PSA was not statistically significant. (AUC = 0.564, p = 0.391). At FGF-23 cut off of 221.45pg/ml, sensitivity and specificity were 66.7 and 83.3 respectively while at PSA cut off of 1.217ng/ml, sensitivity and specificity were 56.7 and 86.7 for diagnosis of prostate cancer respectively. However, FGF23 has low specificity in distinguishing patients with prostate cancer from BPH. FGF-23 appears more specific in the diagnosis of both PCa and BPH than total PSA and may be promising in differentiate these two disease entities from individuals without them.

Key Words: *Benign prostate hyperplasia, fibroblast growth factor 23, prostate cancer, sensitivity, specificity*

INTRODUCTION

Prostate cancer is the most common male cancer in the developed world, second only to lung cancer worldwide, and is the sixth most common cause of cancer death among men (Adedapo *et al*., 2015). Though prostate cancer, Benign Prostatic Hyperplasia (BPH) and prostatitis are known to afflict the prostate, BPH is the most common urologic disease suffered by elderly men and one of the most common chronic diseases of males (Ejike *et al*., 2008; Parsons *et al*., 2013). Prostate cancer (PCa) has become the number one cancer in men with increasing incidence and morbidity in men of black African ancestry (Delongchamps *et al*., 2007).

Prostate cancer is a disease of the male above the age of 50 years worldwide (Adedapo *et al*., 2014). Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone (Lee *et al*., 1997; Auffenberg *et al*., 2009). Benign Prostatic Hyperplasia is defined in the works of Ian and coworkers (McLaren *et al*., 2011) as a benign enlargement of the prostate gland resulting from a proliferation of both benign epithelial and stromal elements. It might also be defined clinically as a constellation of Lower Urinary Tract Symptoms (LUTSs) in aging men.

BPH may cause physical compression of the urethra and result in anatomic bladder outlet obstruction (BOO) through two distinct mechanisms: First, an increase in prostate volume, termed the static component; second, an increase in stromal smooth muscle tone, termed the dynamic component (McVary *et al*., 2011). BOO, in turn, may present clinically as lower urinary tract symptoms (LUTS), urinary tract infections, acute urinary retention (AUR), renal failure, hematuria, and bladder calculi (Stroup *et al*., 2012). The incidence of AUR is 50% in men aged 50-60 years and 90% in men older than 80 years (Patel and Parsons, 2014). In Nigeria, it has been reported that one-in-four men older than 40 years have symptoms suggestive of BPH (Ezeanyika *et al*., 2006).

Multiple observational studies from Europe, the United States of America and Asia have demonstrated older age to be a risk factor for BPH onset and clinical progression by several different metrics (Taylor *et al*., 2006; Wei *et al*., 2005; Kok *et al*., 2009; Jacobsen *et al*., 1997; Bosch*et al*.,1995; Fong *et al*., 2005; Guess*et al*.,1990; Tantiwong *et al*., 2002).Serum PSA should be measured and dig ital rectal examination (DRE) performed in appropriately counseled patients in whom there is clinical suspicion of prostate cancer or in those who wish to be screened (Horwich *et al*., 2010). It has been found that the PSA test had a sensitivity ranging from 0.78 to 1.00, which

**Author for Correspondence:* +234 807 888 7386 E-mail: ksadedapo@yahoo.com

means it potentially fails to diagnose over 20% of prostate cancers (Philip *et al*., 2009). Though organ specific, PSA is not cancer specific and circulating PSA levels often rise in the presence of conditions that disrupt prostate basal membrane epithelial cells such as prostatitis, benign prostatic hyperplasia (BPH), prostate biopsies and surgeries (Romero *et al*., 2014; Cary and Cooperberg, 2013).

The fibroblast growth factor (FGF) family consists of 22 members with varied functions (Itoh and Ornitz, 2004). FGF23 is an approximately 32-kD (251 amino acids) protein with an N-terminal region that contains the FGF homology domain and a novel 71–amino acid C-terminus that was originally discovered by homology-based PCR screening of a mouse embryonic cDNA library (Yamashita *et al*., 2000). FGF-23 may be also produced by some tumors leading to hypophosphatemia (Kocełak *et al*., 2012).

FGF23 is normally expressed in osteocytes and has a critical role in phosphate homeostasis as key component of an endocrine feedback loop between bone and the kidney, along with the vitamin D metabolite 1,25(OH)2D3 (Quarles, 2012). To date there is only limited evidence linking FGF23 to cancer, although it is well established that tumor induced osteomalacia is a result of FGF23 secretion by a number of tumor types, including prostate cancer (Mak *et al*., 2012). Recently, three single nucleotide polymorphisms (SNPs) in the FGF23 gene were found to be associated with the development of prostate cancer (Kim *et al*., 2014). Hence FGF-23 may be a discriminative marker between prostate cancer and BPH. As a result of striking similarity in presentation of prostate cancer and BPH and similar diagnostic profile using PSA however, the former has a much more grave consequences. It is therefore necessary to have a diagnostic modality that is sensitive and specific enough to distinguish between the two close related prostate pathology. This study was aimed at assessing the sensitivity/specificity of fibroblast growth factor23 in plasma in the diagnosis of PCa and BPH compared to total PSA with a view to providing another diagnostic tool in the management of PCa and BPH.

MATERIALS AND METHODS

Serum fibroblast growth factor 23 (FGF-23) and total prostate specific antigen (tPSA) were determined in two groups of 30 patients each with histopathological diagnosis of BPH and PCa and thirty age matched control subjects selected from the same community whose informed consent were obtained. The patients were recruited from the urology clinic of the hospital for symptoms referable to prostate disease. Informed consent was obtained from all the patients that participated in the study.

Serum FGF-23 was determined using enzyme-linked immunosorbent serologic assay (ELISA) kit for the quantitative determination of FGF-23 in human plasma on the principle of double-antibody sandwich enzyme-linked immunosorbent one-step process.

Total PSA was determined using enzyme immunoassay (EIA) for the quantitative determination of total PSA in human serum on the principle of sandwich assay between the two antibodies to form coated antibody-antigen-enzyme complex. Statistical package for social sciences version 20.0 was used for the statistical analysis. Analysis of Variance (ANOVA) and Post hoc tests was used for comparison of quantitative variables. Receiver operating characteristics (ROC) curve was used to determine the sensitivity and specificity for both FGF-23 and PSA. Two-tailed independent t-test of significance at 95%confidence limit with $p < 0.05$ was considered significant for the variables. Chi-Square test (X^2) was be used to find relationship between two qualitative variables

RESULTS

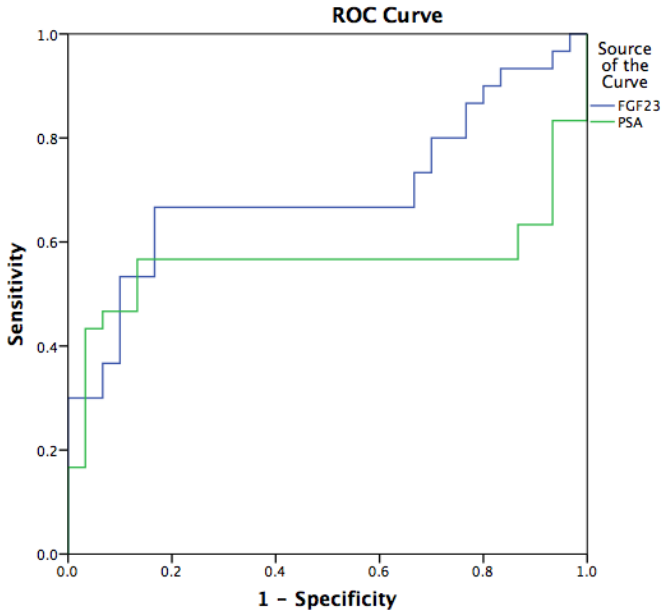
Table 1 shows the comparison of the anthropometric characteristics and biochemical variables of patients with PCa, and BPH as well as controls (mean ± SD). There was a significant decrease in the mean systolic blood pressure (SBP) in PCa, when compared to BPH and control. The mean diastolic blood pressure (DBP) was significantly lower in PCa and BPH compared to control. However, the mean FGF-23 was significantly higher in PCa and BPH compared to control. Expectedly, the mean total PSA was significantly higher in PCa compared to BPH and control. There was no significant difference in the age, height, weight, body mass index (BMI) and waist circumference (WC) between the three groups.

Figure 1 shows the receiver operating characteristics (ROC) and the area under curve (AUC) between PCa and control. There was a statistically significant AUC for FGF-23 (AUC = 0.697, p = 0.009) while PSA was not statistically significant (AUC = 0.564, p = 0.391) between PCa and controls. At FGF-23 cut off of 221.45pg/ml, sensitivity and specificity was 66.7 and 83.3 respectively while at PSA cut off of 1.2ng/ml, sensitivity and specificity was 56.7 and 86.7 respectively.

Table 1:
Mean comparison of Anthropometric and biochemical variables in patients with PCa, BPH and controls.

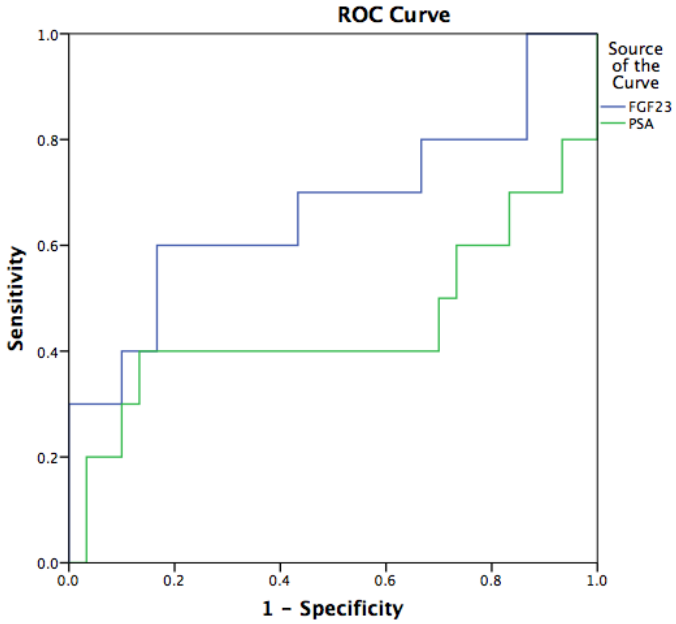
Variables	PCa	BPH	Controls	F	P
Age	71.70 ± 8.09	70.20 ± 10.41	67.77 ± 9.96	1.299	0.278
SBP(mmHg)	126.33 ± 12.17[a,b]	137.20 ± 26.57	140.60 ± 22.10	3.722	0.028*
DBP(mmHg)	82.00 ± 8.34[a]	81.00 ± 12.42[a]	90.17 ± 11.22	6.504	0.002*
HEIGHT(M)	1.67 ± 0.09[a]	1.68 ± 0.08	1.72 ± 0.08	3.109	0.050*
WEIGHT(Kg)	62.23 ± 10.16	65.20 ± 9.85	68.10 ± 8.58	2.828	0.065
BMI(Kg/M^2)	22.42 ± 3.23	23.25 ± 3.31	23.17 ± 2.85	0.635	0.532
WC(CM)	87.00 ± 8.10	79.95 ± 14.55	84.45 ± 12.54	2.638	0.077
FGF-23(pg/mL)	224.12 ± 24.47[a]	222.88 ± 25.74[a]	207.33 ± 21.40	4.581	0.013*
PSA(ng/mL)	17.78 ± 26.56[a,b]	5.07 ± 10.25	2.33 ± 7.61	7.041	0.001*

*Significant at p<0.05
[a]Significantly different from controls
[b]Significantly different from BPH



Variables	AUC	p	Cut-Off (Pg/Ml; Ng/Ml)	Sens (%)	Spec (%)
FGF-23	0.697	0.009*	221.45	66.7	83.3
PSA	0.564	0.391	1.217	56.7	86.7

Figure 1:
ROC Curve: sensitivity and specificity of FGF-23 and PSA in patients with Pca and controls.
Spec = specificity; Sens = sensitivity

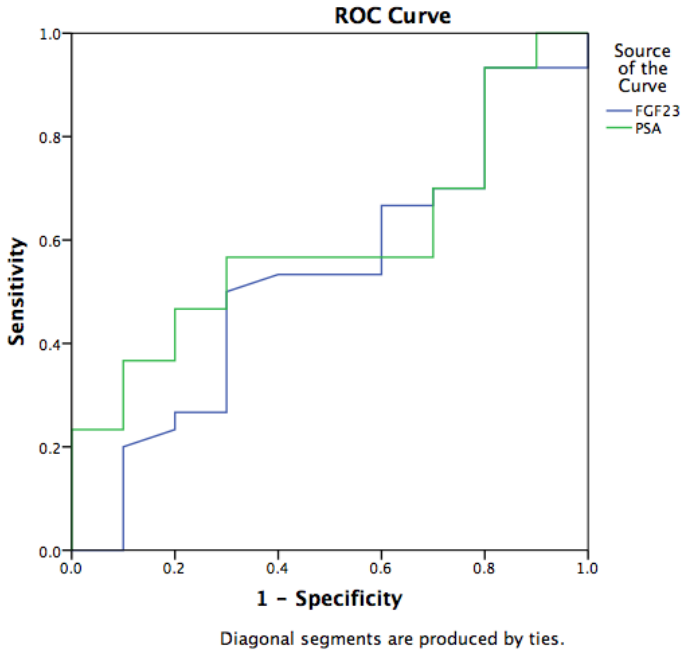


Variables	AUC	p	Cut-Off(Pg/Ml; Ng/Ml)	Sens (%)	Spec (%)
FGF-23	0.673	0.021*	224.52	60.0	83.3
PSA	0.450	0.506	1.016	40.0	86.7

Figure 2
ROC Curve: sensitivity and specificity of FGF-23 and PSA in patients with BPH and controls
Spec = specificity; Sens = sensitivity

Figure 2 shows the receiver operating characteristics (ROC) and the area under curve (AUC) between BPH and control. There was a statistically significant AUC for FGF-23 (AUC = 0.673, p = 0.021) while PSA was not statistically significant (AUC = 0.450, p = 0.506) between BPH and controls. At FGF-23 cut off of 224.52pg/ml, sensitivity and specificity was 66.0 and 83.3 respectively while at PSA cut off of 1.016ng/ml, sensitivity and specificity was 40.0 and 86.7 respectively.

Figure 3 shows the receiver operating characteristics (ROC) and the area under curve (AUC) between PCa and BPH. There was no statistically significant AUC for FGF-23 (AUC = 0.530, p = 0.690) between PCa and BPH and PSA was not statistically significant (AUC = 0.597, p = 0.198).At FGF-23 cut off of 229.45pg/mL, sensitivity and specificity were 53.3 and 60.0 respectively while at PSA cut off of 0.770ng/mL, sensitivity and specificity were 56.7 and 60.0 respectively.



Variables	AUC	p	Cut-Off (Pg/Ml; Ng/Ml)	Sens (%)	Spec (%)
FGF-23	0.530	0.690	229.45	53.3	60.0
PSA	0.597	0.198	0.770	56.7	60.0

Figure 3:
ROC Curve: sensitivity and specificity of FGF-23 and PSA in patients with PCa and BPH
Spec = specificity; Sens = sensitivity

There were statistically significant differences in the smoking habit, alcohol use, red meat intake, dairy product intake, hypertension and use of anti-hypertensive agents among PCa patients, BPH patients and controls. Similarly there was statistically significant differences in the smoking habit, alcohol use, red meat intake, dairy product intake, hypertension and use of anti-hypertensive agents between PCa patients and BPH patients (Table 2 and 3)

There were significant differences in urinary patterns between PCa, BPH and controls; there was significant difference in urinary patterns between PCa and BPH patients. (Table 4).

Table 2:
Smoking, alcohol, and diet history

VARIABLES	RESPONSES	PCa	BPH	CONTROLS	X^2	p
Smoking	Before	17(56.7)	12(40.0)	3(10.0)	17.33	0.008*
	Present	0(0.0)	0(0.0)	1(3.3)		
	Never	13(43.3)	18(60.0)	26(86.7)		
Alcohol	Daily	2(6.7)	0(0.0)	1(3.3)	32.05	0.000*
	Weekly	0(0.0)	6(20.0)	0(0.0)		
	Occasionally	17(56.7)	12(40.0)	3(10.0)		
	Never	11(36.7)	12(40.0)	26(86.7)		
Vegetables	Daily	10(33.3)	15(50.0)	14(46.7)		0.421
	Weekly	9(30.0)	9(30.0)	5(16.7)		
	Occasionally	11(36.7)	6(20.0)	10(33.3)		
	Never	0(0.0)	0(0.0)	1(3.3)		
Red meat	Daily	1(3.3)	9(30.0)	7(23.3)		0.007*
	Weekly	7(23.3)	12(40.0)	14(46.7)		
	Occasionally	20(66.7)	9(30.0)	8(26.7)		
	Never	2(6.7)	0(0.0)	1(3.3)		
Dairy product	Daily	4(13.3)	0(0.0)	1(3.3)		0.002*
	Weekly	3(10.0)	9(30.0)	7(23.3)		
	Occasionally	17(56.7)	21(70.0)	22(73.3)		
	Never	6(20.0)	0(0.0)	0(0.0)		

*Significant at $p<0.05$

Table 3:
Analysis of health history

VARIABLES	RESPONSES	PCa	BPH	CONTROLS	X^2	p
Diabetes	Yes	3(10.0)	0(0.0)	2(6.7)	2.965	0.227
	No	27(90.0)	30(100.0)	28(93.3)		
Hypoglycemic agents	Yes	3(10.0)	0(0.0)	1(3.3)	3.663	0.160
	No	27(90.0)	30(100.0)	29(96.7)		
Hyperlipidemia	Yes	1(3.3)	3(10.0)	0(0.0)	3.663	0.160
	No	29(96.7)	27(90.0)	30(100.0)		
Hypolipidemic agents	Yes	1(3.3)	3(10.0)	0(0.0)	3.663	0.160
	No	29(96.7)	27(90.0)	30(100.0)		
Hypertension	Yes	12(40.0)	18(60.0)	8(26.7)	6.923	0.031*
	No	18(60.0)	12(40.0)	22(73.3)		
Antihypertensive agents	Yes	11(36.7)	18(60.0)	5(16.7)	12.006	0.002*
	No	19(63.3)	12(40.0)	25(83.3)		

*Significant at $p<0.05$

Table 4:
Analysis of urinary pattern

VARIABLES	RESPONSES	PCa	BPH	CONTROLS	X^2	P
Incomplete emptying	Yes	17(56.7)	21(70.0)	2(6.7)	27.090	0.000*
	No	13(43.3)	9(30.0)	28(93.3)		
Frequency	Yes	22(73.3)	21(70.0)	5(16.7)	24.375	0.000*
	No	8(26.7)	9(30.0)	25(83.3)		
Intermittency	Yes	21(70.0)	12(40.0)	2(6.7)	25.340	0.000*
	No	9(30.0)	18(60.0)	28(93.3)		
Urgency	Yes	18(60.0)	24(80.0)	7(23.3)	19.980	0.000*
	No	12(40.0)	6(20.0)	23(76.7)		
Straining	Yes	16(53.3)	15(50.0)	1(3.3)	20.463	0.000*
	No	14(46.7)	15(50.0)	29(96.7)		
Nocturia	Yes	23(76.7)	30(100.0)	13(43.3)	24.886	0.000*
	No	7(23.3)	0(0.0)	17(56.7)		

*Significant at $p<0.05$

DISCUSSION

Finding biomarkers that will be more sensitive and specific for the diagnosis of PCa or BPH as well as differentiating the two clinical conditions aside the use of total PSA and all its modifications has been a great quest for the Clinicians and other health care providers. This study here posited some further clarifications in this direction.

The finding of a significant increase in the level of FGF-23 in both PCa and BPH participant compared to that of control groups may assist when considering the use FGF-23 as a diagnostic tool for either PCa or BPH. Although, there is dearth of literature on the usage of FGF-23 in the diagnosis either PCa or BPH, this study serves as one of the preliminary findings in this direction. Expectedly, there was a significance increase in the level of total PSA in both PCa and BPH participants compared to that of controls as many researches have established. It has been stated by Stamey *et al*.,(1987) that rising levels of PSA in serum are associated with prostate cancer. Likewise, strong evidence exists showing that baseline serum total PSA level, like baseline prostatic volume, predicts future prostate growth (Roehrborn *et al*., 2000).

Receiver operative characteristics (ROC) transformation on the present data supports serum FGF-23 greater than 221.45pg/mL(0.221ng/mL) and total PSA of 1.2ng/mL as increased risk for development of prostate cancer as well as serum FGF-23 greater than 224.52pg/mL(0.225ng/mL) and total PSA of 1.0ng/mL as increased risk for development of BPH. This finding agrees partly with the work of Amayo and Obara, (2004) that sets total PSA cutoff for BPH as 0.34-36ng/mL and that of PCa at 1.78-4339ng/mL. This study demonstrated FGF-23 high sensitivity to both PCa and BPH than total PSA, but low specificity. While FGF-23 may be promising in the early diagnosis of both PCa and BPH, it was unable to differentiate PCa from BPH just like PSA previously. This is in line with the work of Ellis and Brawer, (1993) which stated that the distribution of serum PSA levels in men with benign prostatic hyperplasia is similar to the distribution in men with organ-confined prostate cancer.

The finding of no significant difference in the BMI of PCa participants compared to that of controls corroborates the study of Edward *et al*.,(2003) who stated that there was no association between BMI and the development of prostate cancer. This study shows that there was no association between BMI and the development of BPH. BMI is a measure of adiposity which probably indicates that adiposity does not have much relationship with development of BPH. Contrary to this finding however, a cluster of published epidemiological evidence demonstrates that obesity may increase the risks of BPH and LUTS (Parsons, 2007; Parsons *et al*., 2009; Nandeesha, 2008). Likewise, Adedapo *et al*.,(2012) observed significant variations in the weight, hip circumference, and body mass index (BMI) across the group but the post hoctest did not show any difference between patients with prostate cancer and BPH.

The significant difference in the smoking habit of previous and present smokers and those that had never smoked among PCa, BPH patients and controls confirms previous studies indicating that the degree of cigarette smoking was associated with the persistence of the effects on the prostate. Light or moderate smokers were less likely to have moderate to severe prostatism and BPH unlike heavy smokers (Roberts *et al*., 1994; Platz *et al*., 1999). However the study by Berroukche *et al*.,(2012), opined that there was no evidence that tobacco smoking increased the risk for BPH. This study agrees with previous submission that cigarettes contain significant levels of cadmium, which has been linked to prostate carcinogenesis (Kalcher *et al*., 1993; Saldivar *et al*., 1991; Yeargan *et al*., 1992). This study demonstrated significant difference in the use of alcohol among participants with PCa, BPH and controls. Thus, this finding is contrary to the work of Hak*et al*., (2017) that male alcohol consumer have lower risk of developing prostatic hyperplasia and it agrees with submission of Howard *et al*., (2001), which states that men who maintained or increased their total alcohol consumption during an 11-year period had an approximate twofold increased risk of prostate cancer compared to men with no consumption during the same period.

The study demonstrated significant difference in the red meat intake among PCa patients, BPH patients and controls. The study therefore agrees with the work of Sinha *et al*., (2009) which stated that approximately 30% increases in risk of advanced prostate cancer is associated with high intakes of red and processed meat.

There has been a link between diary product intake and development of prostate cancer (Gao *et al*., 2005). The finding in this study thus buttresses the submission that high dairy intake contributes significantly to the development of both BPH and prostate cancer probably through its ability to increase serum calcium level and this in turn down regulate the production of vitamin D that normally inhibits cellular proliferation and promote cellular differentiation in the prostate leading to increase in prostate volume which may results into prostate cancer (Chan *et al*., 2001). This study is also in line with the work of Adedapo *et al*.(2015) which stated that consumption of milk/dairy and smoked food was associated with increased risk of prostate cancer.

In conclusion, FGF-23 is more sensitive in the diagnosis of both PCa and BPH than the total PSA, and can indeed differentiate these two disease entities from individuals without them.

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