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Prostatic Specific Antigen (PSA) Relationship to Patients Age, Prostate Volume and Prostate Histology at St Mary's Hospital Lacor.

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Background: ***The use of PSA for the diagnosis of cancer prostate has remained controversial as well as unreliable because many factors affect PSA levels. Included amongst the many factors that can increase PSA level are riding bicycle, rectal exam, sex, age, serum calcium, prostate inflammation, increased prostate volume. This study was aimed at determining the clinic-patho-radiological finding of patients presenting with enlarged prostate and to determine the PSA profile of all patients presenting with enlarged prostate in St. Mary's Hospital Lacor.***
Results: ***Approximate 135 patients were evaluated in the study and significantly, elderly persons constituted 64.5%, compared with Adult (34.5%) and youth 1%, (P=0.00). Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%). When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found that 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%. PSA correlates positively with patients age (r= 0.24, P=0.005). Prostates volume also correlates positively with serum PSA, (Pearson's Correlation r=0.275 and P= 0.002). Age and prostate volume also had a significant relation P=0.054 but there was only a very weak relationship between PSA level and Histological diagnosis, (Pearson's correlation r=0.1).***
Conclusion: ***Age and prostate volume significantly correlate with serum PSA, just as age and prostate volume also correlates significantly.***

Key words: Prostatic specific antigen (PSA), volume, age, histology.

Introduction

The incidence of prostate cancer varies widely between countries and ethnic groups. Whereas native Japanese have the lowest incidence, Black-Americans have the highest rates worldwide[1]. Indeed, prostate cancer is the most commonly diagnosed non–skin cancer and the second leading cause of cancer death in the USA with approximately 241,740 American men diagnosed with the disease in 2012 alone of which 28,170 of them died[2]. Furthermore, the incidence of prostate cancer in the United States and certain western countries has risen sharply during the last decade and the increase is more pronounced in the United States, Canada, Australia, France and the Asian countries[3].

However, the reported incidence of cancer prostate in Asia is much lower than that in African Americans and European Caucasians, and there is somewhat better prognosis in Asian immigrants who develop prostate cancer in the United States[4].It is postulated that Soy food consumption is associated with a 25% to 30% reduced risk of prostate cancer in Asian[4]. In their study, Bjarne, Synnøve, Knutsen, and Gary[5]in 1998 also reported that men with high consumption of soy beans had reduced risk of prostate cancer.

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In developing countries prostate cancer may be less common, however its incidence and mortality has been on the rise[2]. This may be attributed to lack of dedicated efforts to search for the cancer. In fact cancer prostate incidence is influenced by the intensity of diagnostic efforts, mortality reports and active prostate specific antigen (PSA) screening[4]. Even when treated with radical prostatectomy the high PSA relapse rate signifies early metastasis even at low tumor volume[6]. Prostate-specific antigen (PSA) is the only established and routinely implemented clinical biomarker for prostate cancer detection and disease status[2]. The introduction of total prostate specific antigen (total PSA) testing in blood has revolutionized the detection and management of men with prostate cancer because Men who will eventually develop Prostate cancer have increased total PSA levels years or decades before the cancer is diagnosed. However, PSA has limited value for Prostate Cancer screening and prognostication[7].

Prostate cancer screening using PSA has been controversial, as no studies have proven that this strategy reduces mortality from prostate cancer. There is also no cutoff point of PSA with simultaneous high sensitivity and high specificity for detecting prostate cancer, hence PSA may be unrelaible[8]. Serum PSA measurements show variable reliability when it comes to diagnosis of Prostate cancer, given the dynamics of PSA physiology[9]. In general, prostate biopsy has not been recommended unless PSA levels exceed a threshold value of 4.0 ng/mL, with slightly lower values recommended recently by some authors. Indeed 15% of men with a PSA value less than 4.0 ng/mL have prostate cancer and 15% of these cancers are high grade[8]. Even when changes in prostate-specific antigen (PSA) over time (PSA velocity) aid prostate cancer detection, there is little justification for formal calculation of PSA velocity if PSA level is ≥3 ng/ml for cut points to determine biopsy in men[10].

The use Prostate-specific antigen (PSA) level typically results in over diagnosis of cancer prostate for a substantial number of men[11]. This is because many factors affect PSA levels. Cycling causes an average 9.5% increase in PSA, when measured within 5 minutes post cycling[11]. In addition in men over 40years a positive PSA screening result is significantly associated with increased age, marital status (married), higher socioeconomic status like higher educational attainment, and health care access[12,18]. Serum calcium and serum parathyroid hormone (PTH) stimulate prostate growth in men without clinical prostate cancer and have implications of increasing PSA level[13]. There is also a tendency of correlation between the presence of inflammatory prostatitis with an elevation of PSA[14] and according to Dong et a1[15], significant relationship also exists between PSA and Prostate volume. Hence use of PSA as a screening tool for prostate cancer leaves a lot to be desired.

There remain gross disparities between the prostate cancer risk and a given PSA level thus posing challenges to the use of PSA-driven algorithms to determine whether biopsy to rule out prostate cancer is indicated or not[16]. Prostate-specific antigen (PSA) lacks both sensitivity and specificity as a serum tumor marker in diagnosis and screening of prostate adenocarcinoma[8]. Its role in diagnosis of active prostate cancer has also remained controversial, yet it is the most prevalently used marker for prostate cancer, hence the need to evaluate other factors that affect serum PSA beside cancer prostate. The main objectives of this study were To determine the clinic-patho-radiological findings and the PSA profile of all patients present with enlarged prostate at St. Mary's Hospital Lacor in Uganda

Patients and Methods

A descriptive study was done on all males patients presenting at the St Mary' hospital Lacor surgical unit between Jan 2012 to Dec 2013 with enlargement of the prostate. St. Mary's hospital Lacor is a rural based 483 bed hospital located in Northern Uganda and is also a teaching hospital for Gulu University medical school. In the 2 years (2012-2013), all patients

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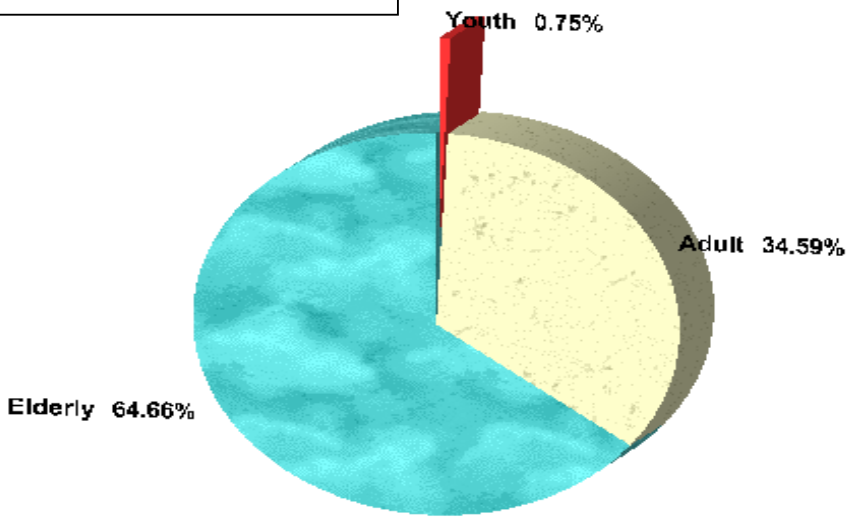
with suspected prostatic enlargement had their main clinical presentation appraised and Digital Rectal Exam done. They also had ultrasonography of the pelvis to assess their prostate volume and they were sent to the laboratory to remove sample for Prostatic specific Antigen (PSA) test prior to being sent for a side room procedure of tru-cut biopsy prostate. No cut off PSA was used; hence every one with enlarged prostate had a biopsy. At least 3 cylindrical samples were obtained at biopsy with a 16 gauge tru-cut gun. The histology samples were analyzed by a pathologist who was blinded but had to diagnose Adenocarcinoma (cancer prostate), Benign Prostatic Hypertrophy (BPH), Prostatitis or Normal tissue. Patient whose sample was insufficient to make histological diagnosis had a repeat tru-cut and those who never did PSA were expunged from the data set for analysis.

The patient's biographic data, main presenting symptom, clinical diagnosis, prostate volume, serum PSA level and histological findings were collected, coded, entered and analyzed using SPSS.

Results

Approximate 135 patients were evaluated in the study. The youngest person was 33years and the oldest was 98 years, Mean age 68.5year (SD+/- 13years). Significantly, elderly persons constituted 64.5%, compared with Adult who made up to 34.5% and approximately 1% was a youth (P=0.00) (Figure 1). The high proportion of elderly persons in this study is because as one ages, the prostate also tend to enlarge as a result of decrease in androgen hormone level. Prostate volume often increases with age[17].

Figure 1. Age Distribution



Presenting symptoms

Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%) and this observed difference was significant P=0.00 (Table 1). On examination, 80% of the patients had clinical evidence of BPH and cancer prostate was 13%.

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(P=0.00). However, of the patient who were clinically diagnosed with BPH, 46% correlated well with the histological finding While for those diagnosed with clinical caner prostate, 72% were found to have a positive histology findings, (P= 0.04). Therefore clinical evaluation is emphasized and complementary to PSA marker.

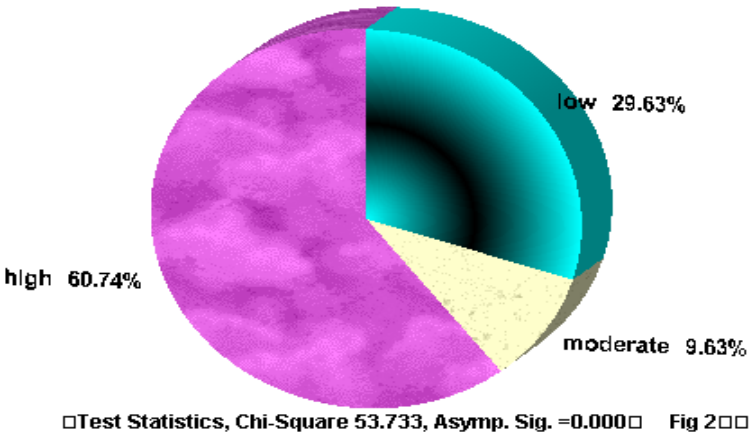
Table 1 Presenting Main symptom

Symptom	Frequency	Percent (%)
Urinary retention	40	29.6
Dysuria	18	13.3
Dribbling of urine	31	23.0
straining to pass urine	9	6.7
Difficulty passing urine	22	16.3
Frequency	6	4.4
Others	6	4.4
Hematuria	2	1.5
Metastasis	1	.7
Total	**135**	**100.0**

PSA Analysis.

Of the 135 patients enrolled in the study, the serum PSA ranged from 0.1ng/ml to 88.7ng/ml with average of 15.6ng/ml. When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found the 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%, (P value=0.00). Therefore when PSA is taken for all patients with enlarged prostate, a significant proportion of patients tend to have a high PSA P=0.000 (Fig 2).

Fig ure 2. Serum PSA



□Test Statistics, Chi-Square 53.733, Asymp. Sig. =0.000□ Fig 2□□

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Prostate Histology

Histological examination of prostate biopsy revealed BPH (39%), Cancer prostate (33%), inflamed prostate (15%) and intraepithelial neoplasms (12%). These observed difference in histology finding is significant (P=0.00), (Table 2 below). Therefore a great proportion of those patients who presented with enlargement of the prostate had cancer prostate, hence the need to biopsy all the enlarged prostates.

Table 2 Histology findings

		Frequency	*%*
Valid	BPH	53	39.3
	Adenocarcinoma	44	32.6
	Prostatitis	20	14.8
	PIN 1	11	8.1
	PIN 2	1	.7
	PIN 3	3	2.2
	Normal	1	.7
	Total	133	98.5
Missing	Bad sample	2	1.5
Total		**135**	**100.0**

Relationship between PSA, Prostate volume, Age, and Histology (Correlations)

As shown in table 3 below and using Figure 2, PSA correlates positively with patients age (r= 0.24, P=0.005). Therefore as age advances, PSA also tends to increase. Hence elderly persons (more than 65years old) presenting with enlarged prostate should have a tru-cut biopsy of prostate irrespective of the PSA level.

In this study, prostate volume ranged from 18 to 236 mls with mean prostate volume was 78.8mls (SD+/-41mls). Prostates volume correlates positively with serum PSA, Pearson's Correlation r=0.275 and P= 0.002.Therefore as prostate volumes increases, PSA also increases. Furthermore prostate volume also correlates positively with increasing age (Pearson's correlation r= 0.176 and P= 0.054 (table 3). There is a weak relationship between PSA level and Histological diagnosis, (Pearson's correlation r=0.1, Table 3).

As shown in Table 4,of all the patients whose PSA ranged within the low prostate cancer detection levels of 0-2.4ng/dl, 54% had BPH and 15.4% were found to be having cancer prostate.Of those whose PSA was considered high (≥4ng/dl), 32% had BPH and 42% had cancer prostate. This finding was not statistically significant Chi square 13.561, P= 0.33.

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Table 3. PSA, Prostate Volume and Histological findings

		Cancer Detection rate of PSA	Histology findings	Prostate volume	Age Group
Cancer Detection rate of PSA	Pearson Correlation	1	.097	.275(**)	.240(**)
	Sig. (2-tailed) (P value)		.265	.002	.005
	N	135	133	120	133
Histology findings	Pearson Correlation	.097	1	.074	-.188(*)
	Sig. (2-tailed) (P value)	.265		.424	.031
	N	133	133	118	131
Prostate volume	Pearson Correlation	.275(**)	.074	1	.176
	Sig. (2-tailed) (P value)	.002	.424		.054
	N	120	118	120	120
Age Group	Pearson Correlation	.240(**)	-.188(*)	.176	1
	Sig. (2-tailed) (P value)	.005	.031	.054	
	N	133	131	120	133

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table 4 Cancer Detection rate of PSA and Histology findings

Cancer Detection rate of PSA	Histology findings							Total
	BPH	Adeno-carcinoma	Prostatitis	PIN 1	PIN 2	PIN 3	Normal	
Low (N)/%	21 53.8%	6 15.4%	8 20.5%	4 10.3%	0 .0%	0 .0%	0 .0%	39 100.0%
Moderate (N)/%	6 46.2%	4 30.8%	2 15.4%	1 7.7%	0 .0%	0 .0%	0 .0%	13 100.0%
High (N)/%	26 32.1%	34 42.0%	10 12.3%	6 7.4%	1 1.2%	3 3.7%	1 1.2%	81 100.0%
Total	53 39.8%	44 33.1%	20 15.0%	11 8.3%	1 .8%	3 2.3%	1 .8%	133 100.0%

Discussion

In this study, Approximate 135 patients were evaluated in the study. The youngest person was 33years and the oldest was 98years, Mean age 68.5year (SD+/- 13years) Fig 1. Significantly, elderly persons constituted 64.5%, compared with Adult who made up to 34.5% and approximately 1% was a youth (P=0.00). Other authors have reported similar mean age,and that prostate volume increase with age[17]. This is because as one ages, the prostate also tend to enlarge as a result of decrease in their androgen hormone level. Older Age at biopsy can be predictive of the disease[8]. PSA measurements before age 50years has been reported to help risk-stratify men for intensity of Prostate Cancer screening[19].

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Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%) and this observed difference was significant P=0.00 (Table 1). On examination, 80% of the patients had clinical evidence of BPH and cancer prostate was 13%. (P=0.00). However, of the patient who were clinically diagnosed with BPH, 46% correlated well with the histological finding While for those diagnosed with clinical caner prostate, 72% were found to have a positive histology findings, (P= 0.04). Therefore clinical evaluation is emphasized besides PSA because when taken together with a man's age, family history, ethnicity, and digital rectal exam results, PSA levels add to the overall estimate of the risk of cancer[19]and abnormal DRE result and older age at biopsy are often predictive for high-grade prostate cancer[8].

According to Figure 2, of the 135 patients, the serum total PSA ranged from 0.1ng/ml to 88.7ng/ml with average of 15.6ng/ml. When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found the 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%, (P value=0.00). Young *et al*[6] (2011) had earlier classified the cancer detection level of PSA as below 2.5ng/ml, from 2.5 to 4.0ng/ml, and above 4.0ng/ml, as 13.3%, 13.6% and 26.5%, respectively[6]. Therefore when PSA is taken for all patients with enlarged prostate, a significant proportion of patients tend to have a high PSA P=0.000 (Fig 2). Most other studies on PSA analysis have used a cut-off level of 4ng/ml, and they have reported high cancer detection rate if PSA is more than 4ng/ml [6,20,21].

As shown in Table 2, Histological examination of prostate biopsy revealed BPH (39%), Cancer prostate (33%), inflammation of prostate (15%) and intraepithelial neoplasms (12%). These observed difference in histology finding significant is (P=0.00). These finding contrast with the findings of those who biopsied the prostate only if the PSA was more than 4ng/ml. For example the finding of prostate cancer prevalence of 20.9%, benign prostatic hypertrophy of 4.7%, prostatitis of 74.4% by Young *et al*[6] (2011)suggest a low cancer detection rate by limiting biopsy to a PSA cut-off of 4ng/ml yet that is an unreliable cut off [8,9].This finding suggests that we should biopsy all clinically symptomatic enlarged prostate.

Table 3 shows a positive correlation ship between PSA and patients age (r= 0.24, P=0.005). Therefore as age advances, PSA also tends to increase and most of the elderly persons have PSA ≥4ng/ml.This finding in our study is also similar to the report of Ornstein*et al*[7] (1998) that PSA levels correlated significantly with age[7]. Collins *etal*[17] (2008) also found an independent association between PSA and age when controlled for volume[17]. Liu, Wang, Su, *et al*[20] (2013) found that males with a baseline PSA 3–3.99 ng ml^{-1} have a 57.81% chance, that their PSA would increase above 4.0 ng ml^{-1} over the following 4 years (P<0.0001)[20], thus emphasizing how advancing age correlate with PSA increase. Furthermore it was established that Serum PSA levels show an exponential increase with advancing age[21].However PSA value of ≥4ng/ml is suspicious and must be biopsied[8]. Other authors independently reported that PSA concentration in men with a prostate volume <25 cc also showed a continuous increase with aging[22].

Although our study found a mean prostate volume 78.8mls and others reported a lower value 32 mls[17]which may be attributable to our poor health seeking behavior, the study found that Prostates volume correlates positively with serum PSA, Pearson's Correlation r=0.275 and P= 0.002. In 1998, Ornstein *et al*[7], reported prostate volume as being significant predictors PSA. The positive relation between PSA and prostate volume was also reported independently by many other authors[15,19,22,23]. Furthermore the study also found that prostate volume also correlates with increasing age (Pearson's correlation r= 0.176 and P= 0.054. Collins, Lee, Mckelvieet al[21] 2008 got a similar finding just as Berges, and Oelke[22] in 2011 and Mettlin, Littrup, Kane *et al*[24] (2006) also got a similar findings.

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There is a weak relationship between PSA level and Histological diagnosis, (Pearson's correlation r=0.1, table 3 and table 4 (Chi square 13.561, P= 0.33). This can be attributed to the fact the PSA is unreliable and controversial when used in diagnosis of cancer prostate and can be misleading if entirely relied upon[8,9,10,11,12,14,19, 23, 25,26.]

Conclusion

Age and prostate volume significantly correlate with serum PSA and age and prostate volume also correlates significantly. Since PSA correlates weakly with histological findings, it should therefore be used in in-conjunction with other clinico-biographic parameters to diagnose cancer prostate.

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