TO ASSESS THE CORRELATION BETWEENPROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PSA AT KENYATTA NATIONAL HOSPITAL

This dissertation will be submitted as partial fulfillment of the requirements of the Degree of Masters of Medicine in Urology, University of Nairobi.

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DECLARATION

I declare that this research proposal is my original work and has not in my knowledge been presented in any other university for the degree of Master of Medicine in Urology

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ABBREVIATIONS

5 ARI	5 Alpha Reductase Inhibitors
BPH	Benign Prostatic Hyperplasia
DRE	Digital Rectal Examination
fPSA	Free Prostate Specific Antigen
%fPSA	Percentage of free prostate-specific antigen
kD	Kilo Dalton's
KNH	Kenyatta National Hospital
PSA	Prostate Specific Antigen
PSAD	Prostate Specific Antigen Density
TRUS	Trans-rectal ultrasound
UTI	Urinary Tract Infection
UoN	University of Nairobi

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DEFINITION OF TERMS

i) Elevated/Raised PSA – PSA above 4ng/ml

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ABSTRACT

BACKGROUND: PSA density is one of the diagnostic tools used to screen for prostate cancer. Several studies have been done to establish the ideal cut-off for PSAD however no consensus has been established due to the different biological differences between different populations.

OBJECTIVE: Correlate prostate biopsy results with Prostate specific Antigen Density of patients with raised Prostatic Surface Antigen in Kenyatta National Hospital.

METHODOLOGY: The study was a prospective cross-sectional study. It was conducted among patients who presented with PSA >4ng/ml or had abnormal digital rectal examination finding seen at KNH. The study was conducted between May 2019 and August 2019 involved 77 patients with PSA>4ng/ml or suspicious DRE findings. The sample size was met by non-randomized consecutive sampling. They each had PSA value established. Their prostate volume was measured and subsequently a PSA density was calculated. The formula: PSA density = Total PSA/Prostate volume was used. A prostatic core biopsy was then be taken by trans-rectal ultrasound guided method. The results were then compared with the PSA density to determine whether they are in congruity with each other. The inclusion criteria were patients with elevated index PSA or abnormal DRE findings provided they give an informed consent. The exclusion criteria were ongoing UTI, previous prostate surgery, hormonal treatment, use of alpha blockers or 5Alpha Reductase Inhibitors, radiation therapy, and those who will declined to give consent for the study. The data collected was filled in the data collection form after consent was taken from the patient. The collected data was entered into a Microsoft Excel sheet and then a statistical analysis was done using SPSS. The values of the continuous variables were demonstrated

as means +/- Standard deviation. Sensitivity and specificity, positive and negative predictive values of various PSADs were determined. Sensitivity was defined as number of true positive results divided by sum of true positives and false negatives. Specificity was defined as number of true negatives divided by sum of true negatives and false positives. Negative predictive value was defined a proportion of negative results that are true negatives. Positive predictive value was defined as the proportion of positive results that were true positive. The results will be demonstrated using tables, pie charts and graphs.

RESULTS: 77 patients were recruited into the study. The average age was 69.5years. For the IPSS score, 37 (48.1%) had a moderate score, 30 (39.0%) had severe, while 10 (13.0%) had mild score.

PSA levels ranged between 0.78 to 3514 ng/ml with a mean of 94.9 ng/ml and a median of 18 ng/ml. Prostate volumes ranged from 21.0 cc to 464.0cc with a mean value was 89.8 cc while the median value was 73.0cc. PSAD results showed that 50 patients (64.9%) had PSAD values of 0.15 and above, while the 27 (35.1%) had below 0.15. As for biopsy results out of the 77 patients, 41 (53.2%) of the patients had prostate adenocarcinoma, while 30 (39.0%) having benign prostatic hyperplasia alone while the other 6 (7.8%) having a benign prostatic hyperplasia with prostatitis.

Using Receiver Operating Characteristic Curves were used to establish a PSAD cutoff and was established as 0.23.

CONCLUSION:

A PSAD of 0.23 can be used as a cut-off value to predict prostate cancer when evaluating patients with raised PSA in our population. Above this value patients should be subject a prostate biopsy.

1.0 INTRODUCTION

Prostate cancer is the most common cancer among men in Kenya with an incidence of 17 per 100000. It accounts for 17.3% of cancers in the country with most cases affecting males above 65year(1). Early detection of cancers, in general, is ideal for the best chance of cure or decreased morbidity and mortality in the long run. Recently, the focus has been on discovering reliable biomarkers that will assist in accurate diagnosis.(2)

In the case of prostate cancer, several biomarkers have been discovered over the years to enhance the accuracy of diagnosis. One of the most widely used markers is the Prostate-specific antigen(PSA). PSA, also known as Human Kallikrein 3, is a serum biomarker, protein in nature(serine protease), produced by the prostate gland. It is 34 kD in weight, secreted by the prostatic ductal epithelial cells and is detected in prostatic fluid and serum also. PSA is detectable in non-significant levels in other body tissues.

PSA is secreted as pre-pro-PSA, metabolized into pro-PSA and finally secreted as PSA. The body secretes PSA into seminal fluid, and its role is to liquefy the seminal coagulum. PSA exists in two forms; bound and unbound/free. A combination of the two is total PSA. The bound form is bound to alpha-1 antichymotrypsin (ACT – a serine protease inhibitor) and has a half-life of 4-5 days. It is also bound toalpha-2 macroglobulin. The half-life of alpha-2 macroglobulin is also 4-5 days. PSA is a nonspecific biomarker for prostatic disease(Inflammatory, BPH, and cancer). It is raised in prostatic disease however distinguishing which disease becomes a problem. Hence it is said to be organ specific but not cancer specific.

Normal PSA levels are generally 0-4ng/ml for men below 65yrs. There are slight variations between ethnic groups and age groups. (3)(4) According to some studies, due to physiological differences between races, prostate size differs from race to race. For example, PSA levels are lower among some Asian races than Caucasians. (5)Patients with elevated PSA need further evaluation to rule out malignancy. Cancer is best ruled out using biopsy. Prostate biopsy is used to make a tissue diagnosis of prostate cancer and grade prostate cancer. This has a direct bearing on the course of action.

Prostate biopsies are not without complications and risks. Loeb et al. did a systematic review of the complications of prostate biopsy, and some of the most common complications were enumerated therein. These include haematuria(10–84%), rectal bleeding(1.3% and 45%), haemospermia(1.1–93%), infection, pain, erectile dysfunction, and death (4)

Locally a study on the complications of prostate biopsy was done. Seventy-two patients were followed up after prostate biopsy(both TRUS and finger guided). It found that the most common complication was haematochezia at 31.9%, followed by UTI at 15.3% and haematuria at 12.5%. Lastly, there was orchitis at 2.8%.(6)Indications for prostate biopsy bare based on raised PSA level or suspicious DRE findings(nodules, induration, or asymmetry). (7)

One of the less invasive modalities used to diagnose prostate cancer is PSA density.PSA density is a derivative of PSA which helps to screen for prostate cancer. The prostate volume is established using trans-rectal ultrasound. The radiographer measures dimensions of the prostate, i.e., longest width, height, and length. Prostate volume formula is as follows:

Prostate volume= k x width x height x length

Where k(constant) = 0.52

The PSA density formula is as follows:

PSA density (PSAD) = Total PSA/Prostatic volume

PSAD has been shown to be more sensitive in predicting prostate cancer than PSA alone. It is useful in distinguishing between prostate cancer and benign prostate conditions.(8)The cut-off value for PSAD has been proposed as 0.15 above which likeliness of prostate cancer is high.(9)Several studies have been done to establish the ideal cut-off for PSAD however no consensus has been established due to the different biological differences between different populations.

2.0 LITERATURE REVIEW

2.1 PROSTATE SPECIFIC ANTIGEN

Prostatic Surface Antigen (PSA) was discovered by Albin et al. in 1970. It is a tumour marker for prostate cancer. When PSA was able to be detected and quantitated using assays, it was used to diagnose prostate cancer.(10). Further studies noted that patients with PSA levels of 4ng/ml and less were very unlikely to have prostate cancer(less than 1.4%). (9) It is was also established that the prevalence of prostate cancer among patients with PSA levels above 10ng/ml was 53.3%(11). In patients with an intermediate range of PSA (4-10ng/ml) the prevalence of cancer was estimated at 30-35% (NCCN clinical practice guidelines in oncology: prostate cancer.)

A PSA values between 4-10ng/ml is said to be in a "grey zone" in prostate cancer diagnosis. This means that it is not clearly a positive predictor of prostate cancer nor is it a predictor of benign prostate disease.PSA assay alone is not very reliable in diagnosing prostate cancer. At this range, it is not possible to distinguish between BPH and prostate cancer without doing a biopsy. As noted by Graham et al. PSA alone can give a false positive result. (10)

Furthermore, PSA levels can be affected by manipulation of the prostate gland in one way or another. Prostate massage or manipulation may raise PSA levels very slightly as noted by Yuan et al. (11) The ultrasound probe used in TRUS also increases PSA values slightly(approximately 1ng/ml). This is due to secretion of PSA into the bloodstream after manipulation. Ejaculation is also known to cause a rise in PSA levels slightly and remain

elevated for about 24hours afterward. Prostate biopsy, on the other hand, may increase PSA value significantly. Stamey et al. noted that the value of PSA might increase by approximately 57 fold after the transrectal biopsy. (12) Other conditions other than BPH or prostate cancer may influence PSA levels like prostatitis and the like.

Apart from diagnosis, clinicians can use the PSA levels for monitoring of disease and response to treatment. A rise in PSA could indicate a recurrence of disease or disease progression.

2.2 PROSTATE SPECIFIC ANTIGEN DENSITY

In 1989 Whang et al. discovered the concept of PSAD. He discovered PSAD while looking for a way to increase the sensitivity of PSA. PSAD is now used to increase the sensitivity of PSA.PSAD is useful in those patients with PSA levels between 4-10ng/ml due to the overlap between BPH and prostate cancer within this range. At this range, it is most effective.

Studies done by Babaian et al. (9) found that there was a correlation between PSA, age, and volume of the prostate gland. He concluded that when PSA value was between 4.1 and 20 ng/ml, the prostate volume should be determined. He recommended that patients with PSA between 4-10ng/ml, with a volume of 25cc or less, should undergo biopsy since no cancer-free man with a gland volume below 25 ccs had a PSA value above four ng/ml.

Veneziano reiterated that there was a correlation between PSA and prostate volume. He noted that PSAD also correlates with prostate cancer. Babaian recommended that clinicians should use the PSA/Volume ratio(now termed PSAD) as an alternative to PSA alone in distinguishing between prostate cancer and benign prostate conditions. In the study, he recommended the cut-off value of 1.73 as predictive of prostate cancer. (13)

Benson et al. also suggested that PSAD could be used to diagnose prostate cancer more accurately especially in the intermediate PSA range of 4-10ng/ml. He recommended the use of PSAD in this range to decrease unnecessary biopsy(9),(15). Bazinet noted that PSAD was a useful tool to diagnose early prostate cancer.(16)The previous practice of systematic biopsies after getting a raised PSA result is no longer the standard of practice. Systematic biopsies although more accurate is invasive and relatively expensive. Some of the complications include bleeding pain and psychological trauma. Also, many patients with elevated PSA(4-10ng/ml) who undergo biopsy may not require biopsy in the first place. Systematic biopsies may also miss some cancers depending on the location. (16)

In a study by Catalona et al. (17) in 2000, in a bid to increase the specificity of PSA, found that PSAD and percentage of free PSA (%fPSA) were equally useful in diagnosis and staging of prostate cancer. The Percentage of free PSA(%fPSA) was more practical than the use of PSAD in the low economic setup because TRUS is not required. The percentage of free PSA value below 0.10 indicates 49-65% risk of prostate cancer while values above 0.25 are more predictive of benign prostate hyperplasia. This is because benign prostate tissue produces more free PSA than cancerous tissue.

In a study done in China, PSAD was found to be a useful tool in the diagnosis of prostate cancer. It is even more useful when used in combination with other modalities like DRE. They recommended that patients who have a PSA between 4-20ng/ml should only undergo biopsy if the DRE is suspicious. It also recommended a PSAD cutoff of >0.20. (18)

The cut-off value for PSAD was recommended to be 0.15 according to studies done by Benson et al. (19)(5) He concluded that PSAD above 0.15 is a positive predictor of cancer and warrants a biopsy assuming the DRE and TRUS findings were not suggestive of cancer. However, this value is not consistent in all studies. According to Lujan et al. (20), the value may vary from population to population. The variation, like that of PSA, has been hypothesized to be due to biological differences between various races.

PSAD is not without its limitations. In a study by Kim et al., it was found that several factors affect PSAD and thus its predictive value for diagnosing prostate cancer. One of the factors is obesity. While obese men have an increased overall PSA, they tend to have larger prostate volumes. However, overall there is a significant difference in the ability of PSAD to predict cancer-positive versus cancer-negative biopsy results between non-obese and obese men. Clinicians might also assess the aggressiveness of cancer. (22)Hence it could be used as a prognosticator in the early detection and management of prostate cancer. (23)

2.3 PROSTATE SPECIFIC ANTIGEN DENSITY OF TRANSITIONAL ZONE

PSAD can further be modified to yield a more accurate result. Instead of using the PSA/total prostate volume ratio, radiographer should use the volume of the transitional zone instead of the total prostate volume. The rationale behind this is that the zone of the prostate where BPH arises is the transitional zone. Higher PSA with low transitional zone volume is predictive of prostate cancer.

Naya et al. differentiated between total PSAD and PSAD of transitional zone (PSAD-tz) both enhancing prostate cancer detection compared to PSA alone. (24) Graham et al. did a study comparing PSAD and PSAD-tz and concluded that PSAD-tz is more accurate than PSA or PSAD in predicting prostate cancer(12).

3.0 STUDY JUSTIFICATION

Prostate cancer research has experienced great strides in the last few years. There is a constant need for ways to make an accurate and timely diagnosis in order to initiate treatment. The purpose of this study was to evaluate whether the PSAD of patients with raised PSA at KNH was in keeping with their biopsy results in our setup and hence a good predictor of prostate cancer. PSAD can be used to give a distinction between BPH and prostate cancer. In resource-poor setups where access to biopsy is not widespread, the PSAD may help distinguish between BPH and prostate cancer hence reduce unnecessary biopsies.

4.0 STUDY QUESTION

Are the Prostate Specific Antigen Density results among patients in KNH consistent with the biopsy results?

5.0 NULL HYPOTHESIS

Prostate Specific Antigen Density results of patients in KNH are not consistent with biopsy results.

6.0 OBJECTIVES

6.1 PRIMARY OBJECTIVE

The primary objective was to establish the correlation between prostate biopsy results with Prostate Specific Antigen Density of patients with raised Prostate Specific Antigen at Kenyatta National Hospital.

6.2 SECONDARY OBJECTIVES

1. To determine the PSAD of patients with raised PSA at KNH.
2. To determine of prostate biopsy results of patients with raised PSA at KNH.
3. To determine the correlation between PSAD and prostate biopsy results.
4. To determine whether the PSAD of 0.15 is a suitable cutoff for Prostate cancer for patients seen at KNH.

7.0 METHODOLOGY

7.1 STUDY DESIGN

The study adopted a cross-sectional study design.

7.2 STUDY SETTING

The study was carried out in the Urology Clinics, Interventional Radiology clinics, and the in-patient wards at Kenyatta National Hospital. KNH is a teaching hospital for the University of Nairobi, Faculty of Medicine and visiting students from other institutions. The hospital offers comprehensive specialty services including surgical and obstetrics and gynecology departments. In addition, it has a private wing for both inpatient and outpatient services (the Doctors Plaza). These departments also run specialty clinics including urology clinics. The study will be carried out at the KNH general outpatient urology clinics. Three clinics are run per week by three different firms on Monday afternoon, Tuesday morning and Wednesday afternoon at clinic 24.

7.3 STUDY POPULATION

Patients with raised PSA findings were eligible for recruitment into the study. Patients with suspicious DRE findings were also recruited. Informed consent will be sought from the recruited patients.

7.4 SAMPLING METHOD AND SAMPLE SIZE DETERMINATION

Kenyatta National Hospital records and the authors rapid audit of the same, indicate a probable annual turnover of at most 110 patients with elevated index PSA. This study

utilized this indicative patient turnover as its population. The sample size is then calculated using Krejcie's formula as follows[26];

$$s = \frac{Z^2(1-\infty/2) \times NP(1-P)}{d^2 (N-1) + Z^2(1-\infty/2) P(1-P)}$$

Where;

s = sample size to be determined

$Z^2(1-\infty/2)$ =is the standard error of the mean corresponding to a 95% confidence interval and the corresponding value from a t-table is 1.96.

N = *E*stimated population size (110)

P =is the expected prevalence of the event to occur. Value of P was 0.173.

d = is the target margin of error which will be 5 % (0.05) to increase precision.

Therefore, the sample size is calculated as follows:

$$s = \frac{1.96^2 \times 110 \times 0.173 (1 - 0.173)}{0.05^2 \times 109 + 1.96^2 \times 0.173 \times 0.827}$$

Hence s = **74**.

Sequential sampling of eligible patients was be used until the sample size is reached.

7.5 INCLUSION CRITERIA

Patients with elevated index PSA or abnormal DRE findings. The researchers included only those patients who give informed consent in the study.

7.6 EXCLUSION CRITERIA

The principal investigator excluded patients who have ongoing UTI had previous prostate surgery, hormonal treatment, been on alpha blockers or 5Alpha Reductase Inhibitors, radiation therapy, and those who will decline to give consent form the study.

7.7 STUDY PROCEDURES

7.7.1 PROSTATESPECIFIC ANTIGEN SAMPLING

PSA tests were done at the KNH lab in order to standardize the results.

The Elecsys PreciControl Tumour marker 1 and 2 used for quality control. PreciControl Tumor Marker is used for quality control of Elecsys immunoassays on Elecsys immunoassay systems.

7.7.2 TRANS-RECTAL PROSTATE BIOPSY

For this study, we collected biopsy samples according to the standard protocol employed by the Interventional Radiology department at KNH

Procedure materials:

- A biopsy gun (disposable)
- Suitable disposable needle-guides
- Suitable disposable sheaths to cover the TRUS probes
- Ultrasound-specific lubricating gel
- A suitable specimen collection system to prevent fragmentation and damage to the biopsy cores
- Specimen pots

- Lubricating jelly
- Disposable gloves
- Wipes/gauze
- Clinical waste bin
- 10% Formalin

The biopsies were done by the qualified Interventional Radiologists at KNH Interventional radiology department.

Each biopsy was a minimum of 12-cores. Tissue samples were preserved in 10% formalin solution.

7.7.3 PATHOLOGICAL TESTS

The pathological analysis was done according to the standard protocol employed at the KNH histology lab. The prostatic cores were put in wax cassettes and analyzed under a light microscope. The histological diagnosis will be made by either a Pathology resident or a registered pathologist, and confirmed by two additional pathologists. The final report was be typed and printed.

7.8 ETHICAL CONSIDERATIONS

Ethical approval was sought from the University of Nairobi, Department of Surgery and the UON /KNH Ethics and Research Committee. Informed consent was obtained by the principal investigator(s) from all the participants before being enrolled in the study. The participants did not incur any extra costs and will be free to withdraw from the study at any time. All information and data obtained during the study was kept confidential.

7.9 DATA COLLECTION

The principal investigator and study assistants collected data using a structured questionnaire/data collection form. The variables that were analyzed were age, duration, and type of symptoms and presence of symptoms related to metastasis, PSA and prostate volume.

7.10 QUALITY ASSURANCE

The principal investigator or research assistant identified potential research subjects based on the inclusion criteria of abnormal DRE findings and/or raised PSA. The next step was to inform the patient about the study and ask for consent to participate in the study. This was done by administering the consent form and clarification of any points the patient does not understand.

For patients who have PSA results from KNH, the PSA values were recorded on the data collection sheet. They were then sent to the Interventional radiologist for imaging and prostate sampling.

For those patients with suspicious DRE findings, they were sent to the lab for PSA testing. The samples were drawn by phlebotomists and sent to the lab as per standard protocol at KNH.

The samples were collected and taken to the lab by the principal investigator and the samples processed and analyzed. The results were recorded in the data collection sheet in order to complete it.

7.11 DATA ANALYSIS

The data collected was filled in the data collection form after consent taken from the patient. The collected data was entered into a Microsoft Excel sheet and then a statistical analysis done using SPSS. Socio-demographic characteristics of the study participants was analyzed and presented as proportions. The values of the continuous variables such as PSA levels and age were analyzed and presented as means +/- Standard deviation.

Sensitivity and specificity, positive and negative predictive values of various PSADs was determined. Sensitivity is defined as number of true positive results divided by sum of true positives and false negatives. Specificity is defined as number of true negatives divided by sum of true negatives and false positives. Negative predictive value is defined as proportion of negative results that are true negatives. Positive predictive value is the proportion of positive results that were true positive. The results were demonstrated using tables, pie charts and graphs. Statistical analyses was performed using statistical software (SPSS version 23.0) with P values < 0.05 were considered statistically significant. Further analysis to establish the best cut off point for the PSAD test, taking prostate biopsy results as the standard diagnostic test was done using Receiver operating characteristic curves to estimate the sensitivity of different PSAD categories in predicting prostate cancer. The researcher

communicated the findings of the study to the KNH clinicians and management, and other bodies within the medical fraternity.

7.12 STUDY LIMITATIONS

The study was hospital-based and depended on the number of patients with raised PSA that come to the urology clinic during the study period. This will make the results obtained less representative of the Kenyan population.

RESEARCH FINDINGS

PATIENT CHARACTERISTICS

This section describes the patient characteristics.

Table 1: Patient and Clinical Characteristics

	Frequency	Percent
Age		
45-54	7	9.1
55-64	14	18.2
65-74	33	42.9
75-84	18	23.4
85-94	5	6.5
IPSS Score		
Mild	10	13.0
Moderate	37	48.1
Severe	30	39.0
Prostate exam		
Soft	2	2.6
Firm	47	61.0
Hard	28	36.4

The mean age of the patients was 69.7 (SD=10.7) years, with majority of the patients belonging to the 65-74 age bracket (42.9%). For the IPSS score, 37 (48.1%) had a moderate score, 30 (39.0%) had severe, while 10 (13.0%) had mild score. The prostate exam had 47 (61.0%) with a firm prostate, 28 (36.4%) had a hard prostate, while 2 (2.6%) had a soft prostate.

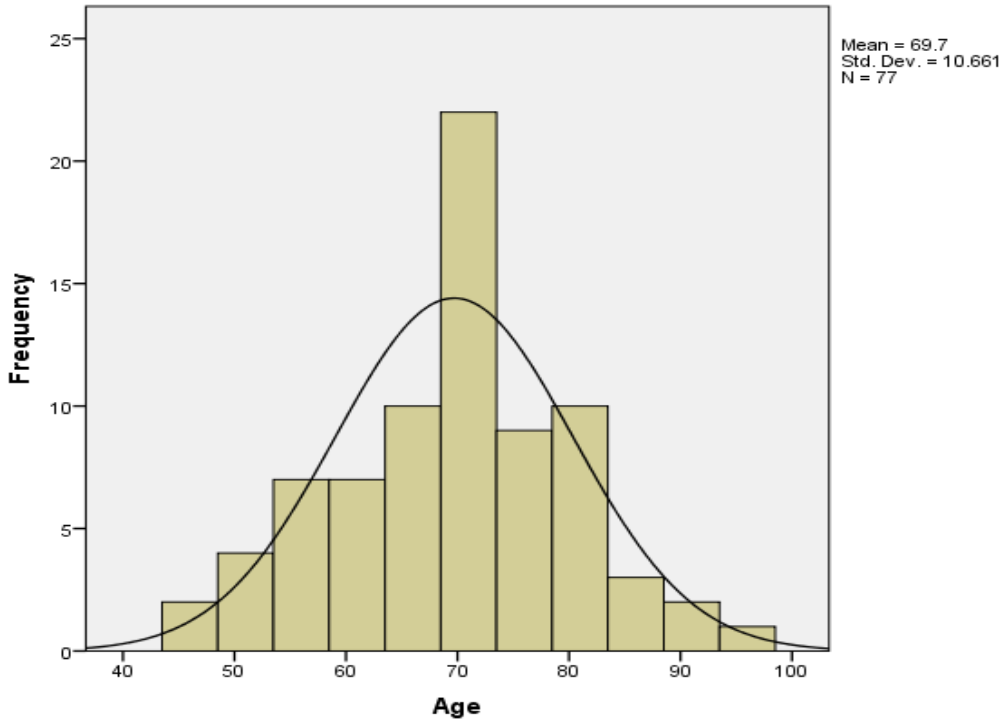


Figure 1: Distribution of Age

PROSTATE SPECIFIC ANTIGEN DENSITY

This section presents the results of PSAD of patients with raised PSA at KNH.

PSA:

The overall mean PSA level was 94.9 (SD=415.14), while the median PSA level was 18 (IQR=44.9). The minimum value was 0.78 while the maximum was 3,514.For those with

a positive biopsy result, the mean PSA value was 166.7 (SD=562.1), while those with negative biopsy result had a mean PSA value of 13.1 (SD=14.3).

PROSTATE VOLUME:

For the prostate volume the mean value was 89.8 (SD=75.5), while the median value was 73.0 (IQR=49.0). The minimum volume was 21.0 and maximum was 464.0.

The PSA Density was calculated using the following formula and was applied to all patients:

PSA density (PSAD) = Total PSA/Prostatic volume

The PSA densities were calculated and found to range between 0.012 to 3.326. The distribution of patients in reference to the accepted cutoff of 0.15 is represented in the table below:

Table 2: Prostate Specific Antigen Density

	Frequency	**Percent**
Less than 0.15	27	35.1
0.15 and above	50	64.9

The results of Table 2 indicate that 50 (64.9%) had PSAD values of 0.15 and above, while the 27 (35.1%) had below 0.15.

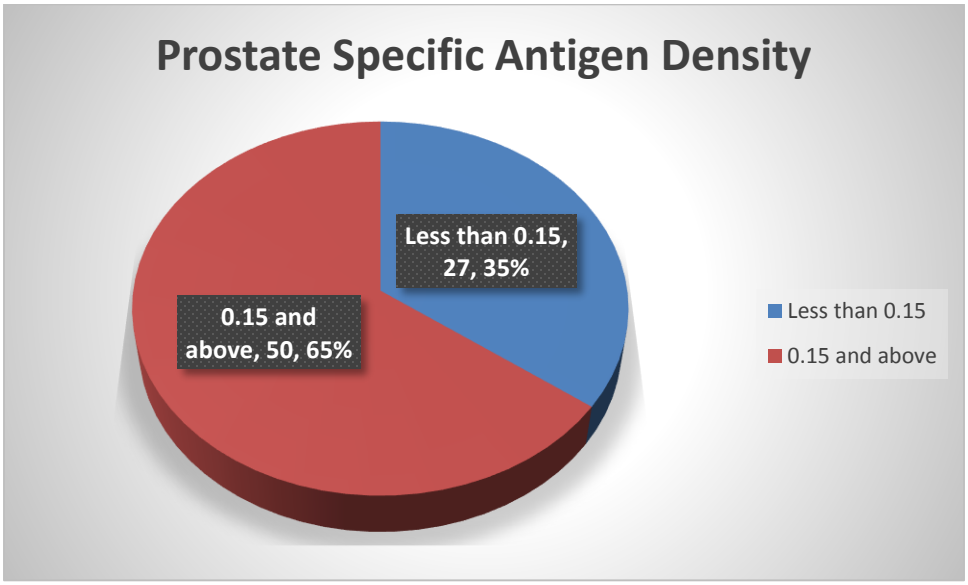


Figure 2: Prostate Specific Antigen Density

PROSTATE BIOPSY RESULTS

This section presents the prostate biopsy results of patients with raised PSA at KNH.

Table 3: Prostate Biopsy Results

	Frequency	**Percent**
Benign Prostatic Hyperplasia	30	39.0
Prostate Adenocarcinoma	41	53.2
Benign Prostatic Hyperplasia and Prostatitis	6	7.8

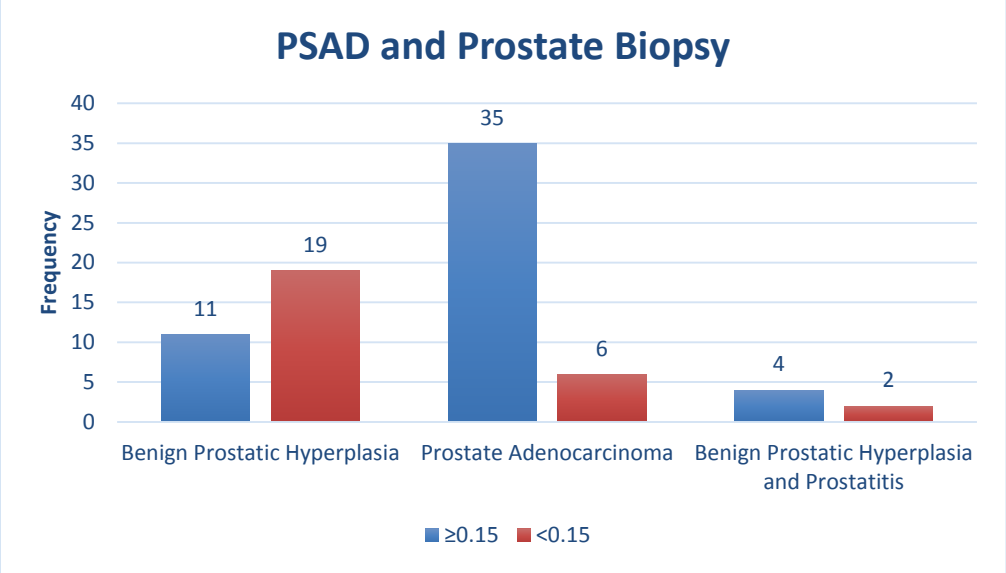
Out of the 77 patients, 41 (53.2%) of the patients had prostate adenocarcinoma, while 30 (39.0%) having a benign prostatic hyperplasia, while the other 6 (7.8%) having a benign prostatic hyperplasia and prostatitis.

CORRELATION BETWEEN PSAD AND PROSTATE BIOPSY

This section presents the results of the correlation between PSAD and prostate biopsy results. Pearson chi-square test and Fishers exact were used.

Table 4: Correlation between PSAD and Prostate Biopsy

	PSAD ≥0.15	**PSAD <0.15**	**Total**	**p-value**
Benign Prostatic Hyperplasia	11 (22.0)	19 (70.4)	30 (39.0)	**<0.001**
Prostate Adenocarcinoma	35 (70.0)	6 (22.2)	41 (53.2)	**<0.001**
Benign Prostatic Hyperplasia and Prostatitis	4 (8.0)	2 (7.4)	6 (7.8)	1.000



There were significant differences between the ≥0.15 and <0.15 for the benign prostatic hyperplasia ($p<0.001$), which was also the case for the prostate adenocarcinoma ($p<0.001$), but no statistical difference was detected for those with benign prostatic hyperplasia and prostatitis ($p<1.000$).

Contingency Tables:

The following table is a representation of the PSAD results compared to biopsy findings.

The positive PSAD result is one >0.15 which is predictive of Prostate cancer while <0.15 is taken to be a negative result indicative of benign prostate disease.

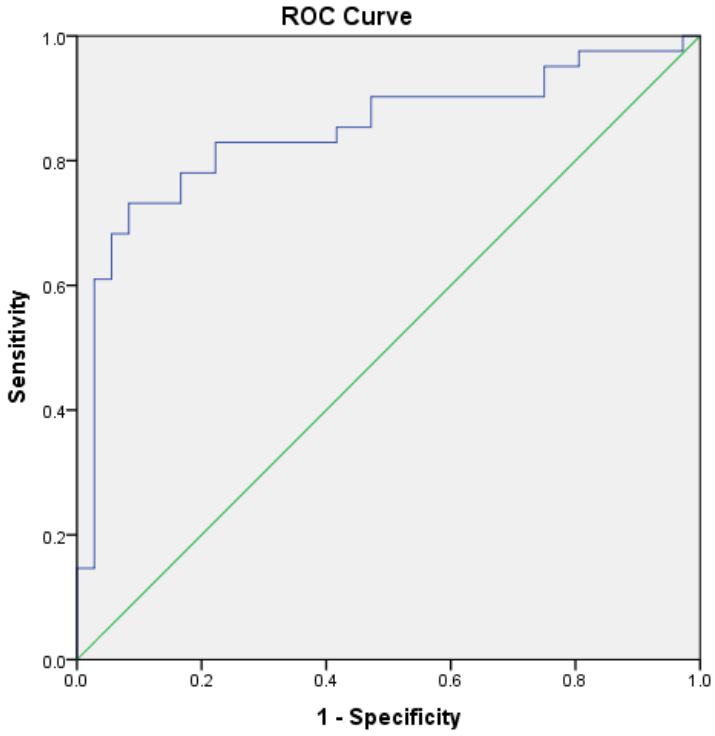
BIOPSY RESULTS

PSA DENSITY		POSITIVE	NEGATIVE	
	POSITIVE	34	15	49
	NEGATIVE	7	21	28
		41	36	

CUTOFF VALUE FOR PSAD

This section presents the results for the cutoff value for PSAD.

ROC Curve



The Receiver Operated Characteristic curves analysis was used to integrate the sensitivity and specificity of the PSAD in diagnosing prostate cancer (confirmed on biopsy).

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error**	**Asymptotic Sig.**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
PSAD value	.847	.047	.000	.755	.938

	Cut off	**Sensitivity**	**Specificity**
PSAD value	**0.233**	82.9%	22.2%

The Area under the Curve (AUC) was calculated and noted to be approaching 1. This indicates that the cut off value has favorable predictive value for patients at risk of prostate cancer. The value of the area under the curve (AUC) has achieved statistical significance with p-value < 0.005, which means it has a favorable sensitivity and specificity characteristics.

Table 5: Gleason Groups

The Gleason groups of the 41 patients were as follows:

	Frequency	Percent
1. 3+3=6	4	9.8
2. 3+4=7	8	19.5
3. 4+3=7	7	17.1
4. 4+4=8; 3+5=8	7	17.1
5. 4+5=9; 5+4=9 OR 5+5=10	15	36.6

Of the 41 patients, 15 (36.6%) belonged to group 5.

Table 6: Univariate Analysis on Selected Factors

	≥0.15	<0.15	Total	OR (95% CI)	p-value
Age					
<65	13 (61.9)	8 (38.1)	21 (100)	0.8 (0.3-2.4)	0.733
65-74	22 (66.7)	11 (33.3)	33 (100)	1.1 (0.4-2.9)	0.783
≥75	15 (65.2)	8 (34.8)	23 (100)	1.0 (0.4-2.8)	0.973
IPSS score					
Mild	6 (60.0)	4 (40.0)	10 (100)	0.8 (0.2-3.1)	0.734
Moderate	22 (59.5)	15 (40.5)	37 (100)	0.6 (0.2-1.6)	0.333
Severe	22 (73.3)	8 (26.7)	30 (100)	1.9 (0.7-5.1)	0.217
Prostate exam					
Soft	1 (50.0)	1 (50.0)	2 (100)	0.5 (0.03-8.8)	1.000
Firm	24 (51.1)	23 (48.9)	47 (100)	0.2 (0.05-0.5)	**0.001**
Hard	25 (89.3)	3 (10.7)	28 (100)	8.0 (2.1-30.0)	**0.001**

For prostate exam, those who had Firm were found to be statistically significantly different in respect to the other groups (p=0.001), this was the case for the Hard (p=0.001). The Soft was not statistically significantly different. Other factors i.e. age and IPSS score were not significant.

DISCUSSION:

Prostate specific antigen was discovered by Albin in 1970 and used since then as a screening tool for Prostate cancer. A Prostate specific antigen value of < 4ng/ml has been used as a cut off for PSA values above which the likeliness of Prostate cancer begins to rise. PSA sensitivity at 4 ng/ml has an approximate sensitivity of 67.5-80% and a specificity of values above 4ng/ml is 60-70%.

Other derivatives of PSA have been used to increase the sensitivity and specificity of PSA. These include free to total PSA ratios (f/t PSA), PSA velocity and PSA doubling times. There is PSA density which is among the PSA derivatives used to increase the predictive value of PSA.

PSA density cutoff has traditionally been proposed to be 0.15 however PSA values and prostate volumes vary from population hence the justification for this study hence the PSAD values for our population are likely to differ.

In this study the ages of the patients enrolled in the study ranges from between 45-94yrs old. The mean age was found to be 69.7years of age with most patients (approximately 50%) within the 65-74 years age bracket. This is in keeping with the average age of patients who develop prostate disease (both benign and malignant). There are a few case reports of patients presenting with prostate cancer at <40 years but it is a rare occurrence.(24)

According to the study regarding the IPSS score, 37 (48.1%) had a moderate score, 30 (39.0%) had severe, while 10 (13.0%) had mild score. Hence majority of the patients seen at Kenyatta National hospital with raised PSA value have moderate to severe lower

urinary tract symptoms and require some sort of intervention. It is also likely that these patients present with advanced disease.

As for the prostate examination on DRE, 47 (61.0%) had a firm prostate, 28 (36.4%) had a hard prostate, while 2 (2.6%) had a soft prostate. According to clinical practice a firm prostate on exam correlates with BPH while a hard prostate is common in prostate cancer patients. When compared with biopsy results. For prostate exam, those who had Firm prostate were found to be statistically significantly different in respect to the other groups ($p=0.001$), this was also the case for the Hard ($p=0.001$). The Soft examination finding was not statistically significantly different. Other factors i.e. age and IPSS score were not significant.

The PSA levels for the patients in the study were ranging from a minimum value of 0.78 ng/ml while the maximum was 3,514 ng/ml. The overall mean PSA level was 94.9 ng/ml while the median PSA level was 18 ng/ml. This shows that our patients usually present with high PSA results warranting intervention.

Several studies have shown that very high levels of PSA (>50) has a greater than 90% predictive value in diagnosing Prostate cancer. Yang and colleagues concluded in their study that PSA > 100ng/ml had a 100% predictive value in diagnosing Prostate cancer.(25)

For those with a positive biopsy result for prostate cancer, the mean PSA value was 166.7ng/ml. The mean PSA value for patients with benign disease was 13ng/ml. This is indicative of the fact that our population may have higher PSA values even in benign disease.

The Prostate volumes of patients enrolled in our study ranged from 21.0 cc to 464.0cc. For the prostate volume the mean value was 89.8 cc while the median value was 73.0cc. This is indicative of larger prostates than the average population.

PSAD results show that 50 patients (64.9%) had PSAD values of 0.15 and above, while the 27 (35.1%) had below 0.15.

As for biopsy results out of the 77 patients, 41 (53.2%) of the patients had prostate adenocarcinoma, while 30 (39.0%) having a benign prostatic hyperplasia, while the other 6 (7.8%) having a benign prostatic hyperplasia and prostatitis. This indicates that the PSAD of 0.15 did not capture Prostate cancer in about 9 patients out of the 77.

It was also noted that none of the patients were diagnosed with Prostatic Intraepithelial Neoplasia (PIN). This may indicate that PIN is a rare occurrence in our population.

Of the patients with prostate cancer there were various Gleason cores and groupings. All Gleason groups were represented with the largest percentage being Gleason group 5 at 36.6%. This shows that of the patients with Adenocarcinoma of the prostate that present at Kenyatta national hospital, most patients have poorly differentiated tumors and hence more aggressive tumors. The second most common group was Gleason group 2 (19.5%) followed by Groups 3 and 4(17.1% each) while the least common group is Gleason group 1(9.8%).

When comparing the PSAD and the biopsy results there were significant differences between the ≥ 0.15 and <0.15 for the benign prostatic hyperplasia ($p<0.001$), which was also the case for the prostate adenocarcinoma ($p<0.001$), but no statistical difference was detected for those with benign prostatic hyperplasia and prostatitis ($p<1.000$). This

indicates a positive correlation between PSAD levels and prostate biopsy results. It was noted that more patients with Adenocarcinoma had PSAD > than 0.15 while more patients with PSAD <0.15 had Benign prostate Hyperplasia.

For the PSAD cutoff the value with the highest specificity and sensitivity would be ideal. In our study the value with the highest sensitivity and specificity was found to be 0.23 with a sensitivity and specificity of 82.9% and 22.2% respectively. Thus, in our population a PSAD of <0.23 was likely to be negative for prostate cancer while a PSAD of >0.23 was likely to be positive for prostate cancer.

This value is close to but not identical to the cutoff recommended by Benson et al.(5)(19).

The discrepancy in the variation of PSAD cutoff values among different populations may be attributed to the variation in size of the prostate, ratio of epithelial to stromal tissue and higher PSA levels in our population.

LIMITATIONS

1. Sample size was small due to the limited number of patients that fit the inclusion criteria of the study.
2. Some patients declined biopsy for various reasons hence making it difficult to conduct further study of the patients.
3. The study costs were high.

RECOMMENDATIONS

1. A PSA density of 0.23 should be adopted as the cut-off value for screening patients for Prostate cancer in our setup. This would help to reduce the number of unnecessary biopsies.

CONCLUSION:

The PSAD cut-off for our population is slightly higher than the internationally accepted value. This may be attributed to the different biological attributes like larger prostate sizes and higher PSA values. The value for PSAD that we established as the cut-off to predict Prostate cancer can be used for screening. This may reduce the number of unwarranted biopsies during diagnostic evaluation. It may be used as predictive tool in screening for prostate cancer especially in a resource poor setting.

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APPENDIX:

DATA COLLECTION WORKSHEET

STUDY TITLE: TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PSA AT KENYATTA NATIONAL HOSPITAL

DATE _____

PATIENT NUMBER _____

AGE _____

RESIDENCE _____

CONTACT NO. _____

PRESENTING SYMPTOMS:

IPSS SCORE

i. ☐ Mild (1-7)

ii. ☐ Moderate (8-19)

iii. ☐ Severe (20 – 35)

PROSTATE EXAM

1. Soft
2. Firm
3. Hard

TOTAL PSA VALUE

PROSTATE VOLUME:

PSAD VALUE

_____

BIOPSY RESULTS:

I. Benign Prostatic Hyperplasia

II. Prostate Adenocarcinoma

III. Prostatitis

IV. High-Grade PIN

V. Low-Grade PIN

GLEASON GROUP

1. 3 + 3 = 6
2. 3 + 4 = 7
3. 4 + 3 = 7
4. 4 + 4= 8; 3 + 5 = 8
5. 4 + 5= 9; 5 + 4 = 9 OR 5+5= 10

INFORMED CONSENT FORM

STUDY TITLE: TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PSA AT KENYATTA NATIONAL HOSPITAL

This informed consent form is for male patients who have raised PSA in KNH. I am inviting you to participate in this research on a voluntary basis.

Principal Investigator: Dr. Carrey Ochieng' Abonyo

Institution: The University of Nairobi, School of Medicine, Department of Surgery.

This Informed Consent Form has three parts:

1) Information Sheet (to share information about the research with you).
2) Certificate of Consent (for signatures if you agree to take part).
3) Statement by the researcher/person taking consent.

The researcher will give you a copy of the full informed consent form.

PART I: Information Sheet

Introduction

My name is Dr. Carrey Ochieng' Abonyo, a postgraduate student in Urology at the University of Nairobi. I am carrying out research to determine the " TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PSA AT KENYATTA NATIONAL HOSPITAL."

Purpose of the research

Prostate cancer is the most common cancer among men in Kenya with an incidence of 17 per 100000. It accounts for 17.3% of cancers in the country with most cases affecting males above 65year(1). Early detection of cancers, in general, is ideal for the best chance at cure or decreased morbidity and mortality in the long run. Recently, the focus has been on discovering reliable biomarkers that will assist in accurate diagnosis (2) . In the case of prostate cancer, several biomarkers have been discovered over the years to enhance the accuracy of diagnosis.

One of the most widely used markers is the Prostate-specific antigen (PSA). The PSA is a serum biomarker, protein in nature, produced by the prostate gland. However, it is a nonspecific biomarker for prostatic disease (Inflammatory, BPH, and cancer). Apart from diagnosis PSA level may also be used in monitoring treatment.

Normal PSA levels are generally 0-4ng/ml for men below 65yrs. There are slight variations between ethnic groups and age groups. Patients with elevated PSA need further evaluation to rule out malignancy. One of the ways to rule out malignancy is to use PSA density. PSA density is a derivative of PSA which helps distinguish between benign prostate disease and malignancy. I am going to give you information and invite you to be a participant in this research. There may be some words that you do not understand or that you may need clarification. Please ask me to stop as we go through the information and I will explain or clarify.

Type of Research Intervention

This research will involve examination of your medical records with your doctor's permission [or their representative] to obtain the symptoms of your illness, the results of your total PSA, biopsy results, clarification of your symptoms and their duration. I will also interview you to obtain this and any other additional information. The interview may take about 25 minutes.

Voluntary participation/right to refuse or withdraw

You are free to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue, and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this hospital for your condition. You have a right to refuse or withdraw your participation in this study at any point.

Confidentiality

The information you volunteer, or we obtain will be treated with confidentiality and only be available to the principal investigator and the study team. Your name will never be used. Any information about you will have a number on it instead of your name. We will not be sharing the identity of those participating in this research.

Sharing the results

The knowledge that we get from this study will be shared with the policymakers in the Ministry of Health, KNH, and doctors through publications and conferences. Confidential information will not be shared.

Risks

There is no direct risk resulting from participation in the study.

Cost and compensation

There will be no extra cost incurred for participating in this study nor is there compensation offered. However, your time will be required to participate in the interview. This proposal has been reviewed and approved by the UON/KNH Ethics Committee, which is a Committee whose task is to make sure that research participants are protected from harm.

Whom to contact

If you wish to ask any questions later, you may contact:

1. Principal Researcher:

   Dr. Carrey Ochieng Abonyo

   Department of Surgery, School of Medicine, University of Nairobi

   P.O. Box 19676 KNH, Nairobi 00202.

   Mobile no. 0724773976

2. University of Nairobi Supervisors:

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Kenyatta National Hospital,

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Tel 0722642661

If you have any ethical concerns, you may contact:

- Secretary,

  KNH/UON - ERC,

  P.O. Box 20723 KNH, Nairobi 00202

  Tel +254-020-2726300-9 Ext 44355

  Email: KNHplan@Ken.Healthnet.org

Part II: Certificate of Consent

I …….. Freely give consent of myself/ proxy (Name ……..) to take part in the study conducted by Dr. Carrey Ochieng' Abonyo, the nature of which has been explained to me by him/ his research assistant. I have been informed, and I understand that my participation is voluntary and I am free to withdraw my consent at any time if I so wish and this will not in any way alter the care being given to me/ proxy. The results of the study may be of benefit to other patients with LUTS and aid in better care of such patient's outcome in the future.

……

Signature

Date ……...

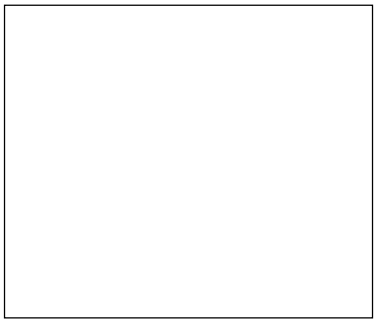
Statement by a witness if the guardian or proxy is illiterate.

I have witnessed the accurate reading of the consent form to the participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness……

Signature of witness……..

Date……



Part III: Statement by the Researcher

I have accurately read out the information sheet to the participant, and to the best of my ability made sure that the participant understands the following:

- Participation is voluntary, and failure to participate will not deny the patient right to optimal management.
- The researcher will not introduce any management other than the usual management procedures.
- Personal Information and results will be kept confidential.
- Results of this study may be published to enhance scientific knowledge

. I confirm that the participant was given an opportunity to ask questions about the study. Questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has given voluntary informed consent.

A copy of this Informed Consent Form has been provided to the participant.

Name of the researcher taking consent……..……

Signature of the researcher taking the consent……

Date……

Swahili Version of the Consent Form

Sehemu ya Kwanza

Utangulizi:

Jina langu ni Dk. Carrey Ochieng 'Abonyo, wa Urology katika Chuo Kikuu cha Nairobi. Ninafanya utafiti wa kuamua

"TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PSA AT KENYATTA NATIONAL HOSPITAL''

Kusudi la utafiti

Saratani ya Prostate ni kansa ya kawaida kati ya wanaume nchini Kenya yenye matukio ya 17 kwa kila mwaka 100,000. Inachukua asilimia 17.3 ya saratani nchini na kesi nyingi zinazoathiri wanaume zaidi ya 65

Early detection of cancers, in general, is ideal for the best chance at cure or decreased morbidity and mortality in the long run. recent years focus has been on discovering reliable biomarkers that will assist in accurate diagnosisKatika kesi ya saratani ya kibofu ya prostate, biomarkers kadhaa wamegundulika zaidi ya miaka ili kuongeza usahihi wa uchunguzi.

Mojawapo ya alama za kutumika sana ni antijeni maalum ya Prostate (PSA). PSA ni biomarker ya damu, protini katika asili, iliyotengenezwa na kibofu ya prostate. Hata hivyo, ni biomarker isiyo na maana ya ugonjwa wa prostate (uchochezi, BPH na saratani). Mbali na uchunguzi wa kiwango cha PSA pia inaweza kutumika katika ufuatiliaji.

Viwango vya kawaida vya PSA kwa jumla ni 0-4ng / ml kwa wanaume chini ya 65yrs. Kuna tofauti kidogo kati ya makundi ya kikabila na makundi ya umri.

Wagonjwa wenye PSA ya juu wanahitaji tathmini zaidi ili kuondokana na saratani. Mojawapo ya njia za kudhibiti uharibifu ni kutumia wiani wa PSA.

Wiani wa PSA husaidia kutofautisha kati ya saratani na uvimbe ya prostate usiyo saratani. Nitawapa taarifa na kukualika uwe mshiriki katika utafiti huu. Kunaweza kuwa na maneno ambayo hujui au kwamba unahitaji ufafanuzi. Tafadhali niulize kuacha tunapopitia maelezo na nitasema au kufafanua

Aina ya Uingizaji wa Utafiti

Utafiti huu utahusisha uchunguzi wa rekodi zako za matibabu na idhini ya daktari wako [au mwakilishi wake] kupata dalili za ugonjwa wako, matokeo ya PSA, biopsy matokeo ya ufafanuzi wa dalili zako na muda wao. Mimi pia nitakuuliza mahojiano ili kupata hii na maelezo mengine yoyote ya ziada. Mahojiano inaweza kuchukua muda wa dakika 25.

Ushiriki wa hiari

Wewe ni huru kushiriki au la. Ikiwa unachagua kushiriki au la, huduma zote unazopata katika hospitali hii itaendelea na hakuna kitu kitakachobadilika. Ikiwa unachagua kushiriki

katika mradi huu wa utafiti, utapewa matibabu ambayo hutolewa mara kwa mara katika hospitali hii kwa hali yako. Una haki ya kukataa au kuondoa ushiriki wako katika utafiti huu wakati wowote.

Usiri

Taarifa unayejitolea au tunayopata itachukuliwa kwa siri na inapatikana kwa uchunguzi mkuu na timu ya utafiti pekee yao. Jina lako halitatumiwa kamwe. Taarifa yoyote kuhusu wewe itakuwa nayo nambari badala ya jina lako. Hatuwezi kugawana utambulisho wa wale wanaoshiriki katika utafiti huu.

Kushiriki matokeo

Maarifa tunayopata kutokana na utafiti huu yatashirikiwa na watunga sera katika Wizara ya Afya, KNH na madaktari kupitia machapisho na mikutano. Maelezo ya siri hayatashirikiwa.

Hatari

Hakuna hatari moja kwa moja kutokana na ushiriki wako katika utafiti.

Gharama na fidia

Hakutakuwa na gharama ya ziada iliyopatikana kwa kushiriki katika utafiti huu wala kuna fidia inayotolewa. Hata hivyo, wakati wako utahitaji kushiriki katika mahojiano.

Pendekezo hili limepitiwa na kupitishwa na Kamati ya Maadili ya UoN / KNH, ambayo ni Kamati ambayo kazi yake ni kuhakikisha kuwa washiriki wa utafiti wanalindwa dhidi ya madhara.

Kuwasiliana:

Ikiwa unataka kuuliza maswali yoyote baadaye, unaweza kuwasiliana

1. Mtafiti Mkuu:

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Barua pepe: KNHplan@Ken.Healthnet.org

Sehemu ya pili – Idhini ya mgonjwa

Nimeisoma habari hapo juu, au imesomezwa. Nimekuwa na fursa ya kuuliza maswali kuhusu hilo na maswali yoyote niliyoyaomba yamejibiwa kwa kuridhika kwangu. Ninakubali kwa hiari kushiriki kama mshiriki katika utafiti huu.

Jina la Mshiriki

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Sahihi la Mshiriki

_____

Tarehe

_____

Nimeona usomaji sahihi wa fomu ya kibali kwa mshiriki mwenye uwezo, na mtu huyo amepata fursa ya kuuliza maswali. Ninathibitisha kwamba mtu huyo ametoa ridhaa kwa uhuru.

Jina la Mshiriki

_____ Thumb print

Sahihi la Mshiriki

_____

Tarehe

_____

Sehemu ya tatu : Dhibitisho la mtafiti

Nimesoma kwa usahihi karatasi ya habari kwa mshiriki, na kwa uwezo wangu bora kuhakikisha kwamba mshiriki anaelewa kuwa zifuatazo zitafanywa:

- Kukataa kushiriki au kujiondoa kutoka kwenye utafiti hakutapoteza huduma ya matibabu kwa namna yoyote.
- Taarifa zote zilizotolewa zitashughulikiwa kwa siri.
- Matokeo ya utafiti huu yanaweza kuchapishwa ili kuwezesha matibabu na uchunguzi wa kansa ya prostate.

Ninathibitisha kwamba mshiriki huyo alitolewa fursa ya kuuliza maswali kuhusu utafiti huo, na maswali yote aliyoulizwa na mshiriki amejibu kwa usahihi na kwa uwezo wangu mkubwa. Ninathibitisha kwamba mtu huyo hakujazimishwa kutoa idhini, na ridhaa imetolewa kwa uhuru na kwa hiari.

Fomu ya Fomu hii ya Ruhusa ya Ruhusa imetolewa kwa mshiriki.

Jina la mtafiti

_____

Sahihi la mtafiti

_____

Tarehe

_____

Table 2:

	Gold (Biopsy)	**Standard**
PSAD	**Positive**	**Negative**
Positive	True positive (TP)	False positive (FP)
Negative	False Negative (FN)	True negative (TN)

1. **Measures of Diagnostic Accuracy**

a. Sensitivity (True Positive – TP)

$$\text{Sensitivity} = \frac{TP}{TP+FN} \times 100$$

b. Specificity (True Negative – TN)

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100$$

c. Positive Predictive Value (False Positive – FP)

$$\text{Positive Predictive Value} = \frac{TP}{TP+FP} \times 100$$

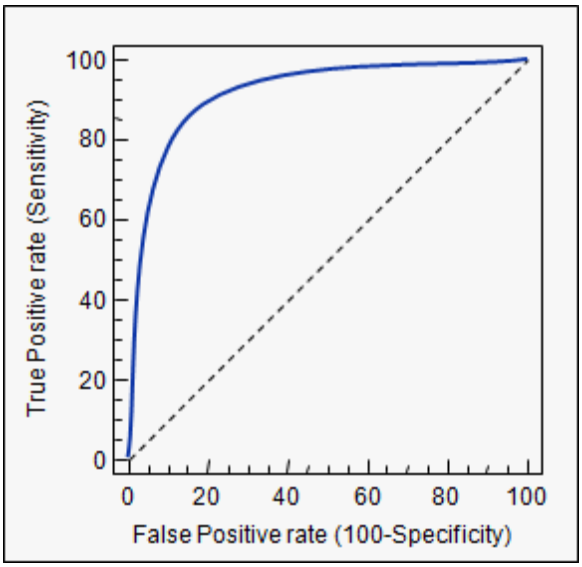
d. Negative Predictive Value (False Negative – FN)

$$\text{Negative Predictive Value} = \frac{TN}{TN+FN} \times 100$$

2. Measures of Diagnostic Effectiveness

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \times 100.$$

3. Receiver Operation Curve



STUDY TIME FRAME

Activity/ Time	Dec 2018- Jan 2019	Feb 2019	March 2019	April 2019	.May 2019	June. 2019	July 2019	August 2019
Proposal Development								
Ethical Approval								
Data Collection								
Data Analysis								
Dissertation Submission								

STUDY BUDGET

Item	**Amount (Ksh)**
Statistician	30,000
Stationery	30,000
Contingencies	20,000
Research fee	2,500
Research assistants	30,000
Printing and binding	30,000
Radiology	340,000
Pathology Lab	238,000
Total	**720,500**