PROSTATE DISORDERS AND PROSTATE SPECIFIC ANTIGEN (PSA) LEVELS AMONG PATIENTS ABOVE 50 YEARS OF AGE AT MOI TEACHING AND REFERRAL HOSPITAL ELDORET

BY

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DECLARATION

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DEDICATION

This thesis is dedicated to my Dear Dad and Mum, thank you for paying my School fees all through my years of study and for mentoring me. To my brothers and sisters for their prayers, support and offering me conducive environment for me to learn. To my Wife for her patience and understanding while I committed most of my time in studies.

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LIST OF ABBREVIATIONS

DHT	Dihydrotestosterone
SMCs	Smooth Muscle Cells
ECM	Extra Cellular Matrix
ER	Estrogen receptor
AR	Androgen Receptor
IGF	Insulinlike Growth Factor
TGF	Transforming Growth Factor
EGF	Epidermal growth factor
PCa	Prostate Cancer
LUTS	Lower Urinary Tract Symptoms
BPH	Benign Prostatic Hyperplasia
ED	Erectile Dysfunction
MTRH	Moi Teaching and Referral Hospital
PSA	Prostate Specific Antigen
CPSA	Complexed Prostate Specific Antigen
NiDDK	National Institute of Diabetes and Kidney Diseases
AIP	Asymptotic Inflamatory Prostitis
EPS	Expressed Prostatic Secretions
BEP	Benign Enlargement of Prostate
MRI	Magnetic Resonance Imaging
CT	Computerized Tomography
USA	United States of America

DRE	Digital Rectal Examination
DNA	Deoxyribonucleic Acid
AUA	American Urological Association
ELISA	Enzyme Linked Immunosorbent Assay
OPD	Out Patient Department
TURP	Transurethral Prostatectomy
IQR	Interquartile Range
SPSS	Statistical Package for Social Science
IREC	Institutional Research and Ethics Committee
MUSoM	Moi University School of Medicine
WHO	World Health Organization

ABSTRACT

Title: Prostate Diseases and Prostate Specific Antigen (PSA) Levels among Patients above 50 years of age attending Moi Teaching and Referral Hospital (MTRH) –Eldoret.

Background: The prostate gland is a male reproductive organ that contributes fluids that nourish sperm cells in the ejaculate. Prostate problems encompass benign prostatic hyperplasia (BPH), Prostate cancer and Prostatitis. Troublesome urinary symptoms are sometimes, but not always, symptoms of prostate cancer. PSA has been a good screening Test but not of desired precision and as yet, there is no consensus among experts on the usefulness of this Test for screening asymptomatic men and also there has been no concurrence on what exact cutoff level of PSA is to be considered normal value. Elevated values of PSA are associated with prostate cancer, but they may also be seen with prostatitis and BPH.

Objective: To establish the prevalence of prostate disorders among patients above 50 years of age being attended at MTRH-Eldoret and their associated PSA levels and specifically to describe the demographic and clinical characteristics of patients with prostate disorders; to determine the predictors of elevated PSA levels among patients seen at MTRH.

Methodology: Cross sectional retrospective study design was used. The study population consisted of male in in-patient and out-patient units who had PSA screening as seen at MTRH. A sample of 219 patients' records from 1st April 2012 to 31st March 2013 was reviewed. A checklist was filled by the researcher to collect data relating to the prostate disorders. Ethical clearances were obtained from IREC and permission to carry out the study was sought from the hospital administration.

Results: In the study population, 74.4% were inpatient while 25.6% were outpatients. Those aged between 50-59 years were the majority at 39.7%, followed by those aged between 60-69 years (28.6%). Prevalence of prostate disorders was found to be 18.05% of which BPH had the majority of patients at 76.7%, 64.4% had enlarged prostate while 20.1% had normal prostate. Mean serum PSA among the study subjects was 31.184ng/ml with patients having PSA>4ng/ml constituting 71.7% of the study participants. Out of 54 participants that had been suspected to have prostate cancer, 40 were confirmed to have malignancy. PSA is a significant factor for malignancy $p<0.05$. It was noted that PSA level was rising with age ($p=0.04$). Family history of prostate disorders, urine retention and lower back pain were significant predictors of elevated PSA.

Conclusion: The study findings showed that prevalence of prostate disorders were high among male patients' in their 50s seeking care at MTRH. Men above seventy years of age had the highest reported cases of prostate disorders. It was evident that BPH was the most common prostate disorder seen at MTRH and there were high possibilities of BPH advancing to prostate cancer. The PSA range was significantly higher than those of African-American and Caucasian men. There is need for a population-specific reference range for African and or Kenyan men.

Recommendation: All men should be sensitized and informed on the prostate gland complications and be encouraged to be screened for prostate disorders to prevent advancing complications. Further studies should be done to ascertain the cause of increased prostate complications among young men in their 50s. Health care providers should device more patient management methods that are conservative to take care of the cases that are reported late.

CHAPTER ONE

1.0 INTRODUCTION

1.1 The Prostate Gland

The prostate is a gland found only in males it is located in front of the rectum and below the urinary bladder. The size of the prostate varies with age. In younger men, it is about the size of a walnut, but it can be much larger in older men. The prostate's function is to make some of the fluid that protects and nourishes sperm cells in semen, making the semen more liquid and comprises a major part (15-30%) [1]. Just behind the prostate are glands called seminal vesicles that make most of the fluid for semen. The urethra, which is the tube that carries urine and semen out of the body through the penis, goes through the center of the prostate. The prostate starts to develop before birth. It grows rapidly during puberty, accelerated by male hormones in the body. The main androgen, testosterone, is made in the testicles. The enzyme 5-alpha reductase converts testosterone into dihydrotestosterone (DHT). DHT is the main hormone that signals the prostate to grow. The prostate usually remains at about the same size or grows slowly in adults, as long as male hormones are present.

The normal prostate is composed of glands and stroma. The glands are seen in cross section to be rounded to irregularly branching. This gland represents terminal tubular portions of long tubuloalveolar glands that radiate from the urethra. The glands are lined with two cell layers: an outer low cuboidal layer and inner layer of all columnar mucin-secreting epithelium; these cells project inwards as papillary projections. The fibro

muscular stroma between the glands, accounts for about half of the volume of the prostate [2].

The prostate is divided into four anatomical zones; peripheral, transition, central zone and the anterior fibroid muscular stroma. It also has five cell types: the luminal secretory epithelial, basal epithelial, fibromuscular stromal, nerve sheath, and endothelial cells stem cell [3, 4, 5]. Supporting the overlying epithelium, the prostatic stroma consists of smooth muscle cells (SMCs) fibroblasts myofibroblasts, endothelial cells and components of extra cellular matrix (ECM) [5]. As men grow older the walnut size of their prostate grows bigger and bigger until it becomes troublesome as the prostate presses the urethra which in turn blocks the urine flow [6]. Growth of the prostate is therefore regulated by systemic and locally-produced steroid hormones and growth factors. Differentiated secretory epithelial cells express androgen receptor (AR) and estrogen receptor beta (ERβ), which promote the expression of sex steroid hormone-responsive genes [7]. It is epithelially-derived growth factors such as insulin like growth factor (IGF), transforming growth factor (TFG) and epidermal growth factor (EGF) that act in a paracrine manner on the underlying stream [8]. Stromal fibroblasts are responsive to sex steroid hormones via expression of AR and ER, which promote cellular proliferation and stimulate the production of stromal-derived factors that act in an autocrine and paracrine fashion. In addition, stromal cells express aromatase and 5-α-reductase enzymes which catalyze the local synthesis of bioactive steroid hormones. Prostate gland, however, like other organs in the body, can get infected with some diseases or develop some problems making it less effective.

There are several types of the prostate problems and among them are: Prostatitis which is an inflammation of the prostate gland. The three types of prostatitis are; acute bacterial, chronic bacterial and chronic nonbacterial [9, 10, 11]. Acute prostatitis is often caused by a bacterial infection, but only about 5 percent of chronic prostatitis cases are caused by bacterial infection. Chronic prostatitis is often related to frequent urinary tract infections. Other possible cause of chronic prostatitis is an enlarged prostate [12].

Benign prostate hyperplasia (BPH) is a noncancerous enlargement affected by the male hormone testosterone and by aging. Starting at about the age of 50 years, the prostate gland naturally begins to enlarge in most men and almost 90 percent of men age 80 years or older have an enlarged prostate [13]. Some men have BPH but have no problems as a result. In others however, the enlarged prostate may begin to press inward on the urethra, partially or completely blocking the flow of urine and causing detectable clinical symptoms. If the bladder never completely empties a buildup of old urine can lead to bladder or urinary tract infection and in severe cases the enlarged prostate may stop the flow of urine so much that it may cause kidney dysfunctions.

Prostate cancer, which is also considered as a prostate disorder, may take many dimensions as it develops. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease

and if not realized early may lead to death. Rates of detection of prostate cancers vary widely across the world, with South and East Asia detecting less compared to Europe and more commonly detected especially the United States [14]. Prostate cancer tends to develop in men over the age of fifty years and many never have symptoms. Although many undergo no therapy and unlike most prevalent types of cancer in men, many have symptoms, undergo no therapy and eventually die of other causes. This is because cancer of the prostate is, in most cases, slow-growing, symptom-free and since men with the condition are older they often die of causes unrelated to the prostate cancer such as prostate associated conditions e.g. orchitis, hydrocele, Cancer of the bladder, heart/circulatory diseases, pneumonia, other unconnected cancers or old age. On the other hand, the more aggressive prostate disorder accounts for more cancer-related mortality than any other cancer except lung cancer. About two-thirds of cases are slow growing the other third more aggressive and fast developing.

1.2 Problem Statement

Prostate in ageing men is known to have problems associated with difficulties in voiding however, various attempts have been carried out to find out the specific causes of the prostate problems such as; prostate cancer, prostatitis and the benign prostatic hyperplasia (BPH). PSA is a protein produced primarily by cells of the prostate and it has in the past been used as a tumor marker and in the monitoring of the prostate cancer. PSA has been a good screening test, but not about preferred precision and currently there is no concurrence among experts on the usefulness of this test for screening asymptomatic men. Currently, there has been no consensus on what exact cutoff level of PSA is to be

considered normal value. Elevated values of PSA are associated with prostate cancer, but they may also be seen in prostatitis and BPH. Since PSA screening is not a diagnostic tool for cancer, patients found with elevated levels and also happen to present with abnormal Digital Rectal Examination (DRE) are further referred for biopsy which is a gold standard for identifying prostate disorders. Other studies have suggested complexed PSA (CPSA) and use of electric fluorescence to detect accurately the cancer related PSA but have not been of any distinctive difference with the free PSA. This study, therefore was aimed at establishing the elevated PSA levels in patients with prostate problems and its relation to the prostate cancer, BPH and prostatitis.

1.3 Justification of the Study

Moi Teaching and Referral Hospital (MTRH) is the second largest National Referral Hospital after Kenyatta National Hospital in Kenya. MTRH is also a Teaching hospital with diverse researches going on. Despite the rich research background there has been no study findings and/or background information on the institution to ascertain the proportions of prostate disorders. Prevalence and proportions of prostate disorders have been reported widely in scientific findings both in the developed and developing countries. As yet, there are limited updates and/or research findings available in Kenya more so in the Western Kenya and the entire East Africa region for both guidance and reference as far as prostate disorders and prostate associated disorders are concerned. Most quoted data relating to prostate disorders is from studies done in the developed countries. These populations have different demographic features of the patient population in relation to our environmental setup and context as a developing Nation. In MTRH, approximately twenty samples are screened for PSA per week. As such, the

screening results help in quantifying the amount of prostate specific antigens present in blood circulation for detection of enlargement of the prostate (BPH). Almost half the number of patients' screened for PSA are sent for biopsy. Biopsy in MTRH is used to confirm whether the enlarged prostate is cancerous or non-cancerous and it is done in the histopathology lab. Therefore, it would be important to understand the elevated PSA levels in patients with prostate problems and its relationship with prostate cancer, BPH and prostatitis for the patients seeking care at MTRH.

1.4 Significance of the Study

This study was set to determine the case proportions of prostate problems and whether men in Kenya had a similar profile as their counterparts in other countries. There was no direct benefit of the study to the participants, but a considerable interest in finding strategies to encourage disclosure to the public health benefits that may accrue from its interventions. Further, the study was meant to provide reference material for future studies that may be of great importance in the monitoring of prostate and other associated illness. In addition, the study results will assist the clinicians/Hospital management to get to know their statistics of the conditions also the community will benefit from the research and get to understand the dynamics of prostate disorders and possible health preventive measures that would be of benefit. Likewise, the findings of the study will enhance the understanding of the magnitude of prostate disorders more so prostate cancer; and help in monitoring and detection in early stages enabling the management to develop appropriate strategies to improve the diagnostic process and possible evaluation of the treatment nationally and in other developing countries at large.

1.5 Research Questions

1) What are the common prostate disorders in MTRH?

2) What are the factors associated with prostate disorders?

3) How do the PSA levels correlate with the prostate diseases?

1.6 General objective

To establish the prevalence of prostate disorders among patients above 50 years of age seen at MTRH-Eldoret and to determine the associated PSA levels.

1.6.1 Specific Objectives

i. To describe the demographic and clinical characteristics of patients with prostate disorders.
ii. To determine the prevalence of prostate disorders and PSA levels among patients seen at MTRH.
iii. To determine the predictors of elevated PSA levels.

1.6.2 Hypothesis

Ho

There is no association between prostate disorders and the related PSA levels among patients above 50 years of age seen at MTRH-Eldoret.

H_1

There is an association between prostate disorders and the related PSA levels among patients above 50 years of age seen at MTRH-Eldoret.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 The Prostate

The main function of the prostate is to produce a thin, milky fluid that contains citric and acid phosphatase (PH 7.29) that is added to the seminal fluid at the time of ejaculation that constitutes 10-30% of the volume of the seminal fluid which along with spermatozoa constitutes Semen [15]. The rest of the seminal fluid is produced by the two Seminal vesicles. The smooth muscle which surrounds the gland squeezes the secretion into the prostatic urethra. The alkalinity of seminal fluid helps neutralize the acidity of the vaginal tract, prolonging the lifespan of sperm. The prostatic fluid is expelled in the first ejaculate fractions together with the most of the spermatozoa. In comparison with the few spermatozoa expelled together with mainly seminal vesicular fluid those expelled in prostate fluid have better motility, longer survival and better protection of the genetic material (DNA). The prostate also contains some smooth muscles that help expel semen during ejaculation.

2.2 Epidemiology of Prostate Disorders

2.2.1 Prostatitis

The traditional classification of prostatitis includes acute and chronic prostatitis, which affects less than 5% of men with prostatitis and for which treatment and management are usually successful [16]. In 1995 National Institute of Diabetes and Kidney Diseases (NiDDK) of the US National Institute of Health gave various definitions of prostatitis as [17].

I. Acute bacterial prostatitis, acute infection of the prostate.

II. Chronic bacterial prostatitis recurrent infection of the prostate.

III. Chronic nonbacterial prostatitis/chronic pelvic pain syndrome where there is no demonstrable infection.

IV. Asymptotic inflammatory prostatitis (AIP) where there are no subjective symptoms, but white blood cells are found in prostate secretions or in prostate tissue on evaluation for other disorders.

Unlike patients in category I and II, patients in category III do not have detectable colonization or infection of the prostate as determined by conventional microbiological technique. Abnormalities in the EPS (expressed prostatic secretions) are the primary features of category III prostatitis. Chronic pain is the primary subjective symptom. The majority of the patients are in category III. The prostate may also become infected, resulting in a painful condition which sometimes is difficult to eradicate. This infections cause inflammation and swelling, resulting in partial or complete urinary obstruction, pain and fever. Prostate cells put out a small amount of protein, called prostatic specific antigen (PSA) that may be detected using a blood test. Since the amount of prostate tissue increases with age, PSA levels normally increase with age, and so the normal range gradually increases. Elevated levels of PSA can be caused by prostatic enlargement, infection, manipulation or prostate cancer [17].

2.2.2 Benign Prostatic Hyperplasia

Benign enlargement of the prostate (BEP) /benign prostatic hypertrophy, is an increase in the size of the prostate. BPH involves hyperplasia (an increase in the number of cells) rather than hypertrophy (a growth in the size of individual cells [18] it involves hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large,

fairly discrete nodules in the periurethral region of the prostate. When sufficiently large, the nodules compress the urethral canal to cause partial, or sometimes virtually complete, obstruction of the urethra, which interferes with the normal flow of urine. It leads to symptoms of urinary hesitancy, frequent urination, dysuria, increased risk of urinary tract infections, and urinary retention. Although prostate specific antigen levels may be elevated due to increased organ volume and inflammation due to urinary tract infections, BPH does not lead to cancer or increase the risk of cancer. An estimated 50% of men have histological evidence of BPH by age 50 years and 75% by 80 years; in 40- 50% of these men, BPH becomes clinically significant [19]. Benign prostatic hyperplasia symptoms are classified as storage or voiding. Storage symptoms include urinary frequency, urgency (compelling need to void that cannot be deffered) urge incontinence, and voiding at night (nocturia).

BPH can be a progressive disease, especially if left untreated. Incomplete voiding results in stasis of bacteria in the bladder residue and an increased risk of urinary tract infection. Urinary bladder stones are formed from the crystallization of salts in the residual urine. Urinary retention termed acute or chronic, is another form of progression. Acute urine retention is the inability to void, while in chronic urinary retention may eventually progress to renal failure, a condition termed as obstructive uropathy. Causes of BPH according to most experts are considered to be androgens (testosterone and related hormones) that play a role, although the overall role of androgens in BPH is incompletely understood [7]. This means that androgens have to be present for BPH to occur, but do not necessarily directly cause the condition. This is supported by the fact that castrated

boys do not develop BPH when they age. On the other hand, administering exogenous testosterone is not associated with a significant increase in the risk of BPH symptoms [20]. Dihydrotestosterone (DHT) a metabolite of testosterone is a critical mediator of prostatic growth. DHT is synthesized in the prostate form circulating testosterone by the action of the enzyme 5α-reductase, type 2. This enzyme is localized principally in the stromal cells; hence those cells are the main site for the synthesis of DHT which act in an autocrine fashion on the stromal cells or in a paracrine fashion by diffusing into nearby epithelial cells. In both of these cell types DHT binds to unclear androgen receptors and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells. DHT is 10 times more potent than testosterone because it dissociates from androgen receptor more slowly. The importance of DHT in causing nodular hyperplasia is supported by clinical observation in which an inhibitor of 5α reduces such as finasteride is given to men with this condition. Therapy with a 5α reductase inhibitor markedly reduces the DHT content of the prostate and, in turn, reduces prostate volume and, in many cases BPH symptoms. Testosterone promotes prostate cell proliferation [20] but relatively low levels of serum testosterone are found in patients with BPH [21, 22]. Various studies have shown that medical castration lowers the serum and prostate hormone levels unevenly, having less effect on testosterone and Dihydrotestosterone levels in the prostate [23].

2.2.3 Prostate Cancer

This is a form of cancer that develops in the prostate gland in the male reproductive system. Most prostate cancers are slow growing [24] however; there are cases of

aggressive prostate cancers [25] where the cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse or erectile dysfunction. Other complications can potentially develop during later stages of the disease. Since prostate cancer prevalence vary with regions due to various demographic and other social factors [26] Prostate cancer is more common in the developed countries with increasing rates in the developing countries [27]. However, many men with prostate cancer never have symptoms, undergo no therapy, and eventually die of other unrelated causes. Many factors, including genetics and diet, have been implicated by symptoms, physical examination and prostate cancer. The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. Prostate specific antigen testing increases cancer detection but does not decrease mortality [28]. The United States Preventive Services Task Force in 2012 recommended against screening for prostate cancer using the PSA test, due to the risk of over-diagnosis and over-treatment with most prostate cancer remaining asymptomatic and further concluded that the that the potential benefit of testing does not outweigh the expected harms [29].

Prostate cancer is therefore a significant health problem in most industrialized Western countries where it is the most commonly diagnosed cancer affecting men after middle age. The worldwide 5 year prevalence of prostate cancer has been estimated at 1,554,700 cases. It is estimated that in Western countries about 30% of all men will develop microscopic prostate cancer during their lifetime. However, as most prostate cancers tend

to grow slowly, the risk of developing overt clinical diseases is 8% (lifetime risk) and the risk of accuracy. Dying from prostate cancer is only 3% whereas the autopsy based prevalence is 80% by the age of 80 years. Therefore most men die with prostate cancer, rather from it [30]. Based on US data for a 50 year old man with a life expectancy of 25 years, there is a 42% lifetime risk of having microscopic cancer, a 9.5% risk of having clinically evident cancer and a 2.9% risk of dying of prostate cancer. In Kenya the prevalence of prostate cancer is 9.4% being the third leading form of cancer after breast and cervical cancer with 23.20% respectively [31]. In recent years, the veritable epidemic of prostate cancer has probably resulted from the widespread use of PSA testing which allows the earlier diagnosis in men who have not yet developed symptoms. As an example, it was estimated at 2005 in the USA that there would be approximately 235,000 new diagnoses of prostate cancer and 29,000 deaths [20]. Prostate cancer is primarily a disease of men over the age of 50 years, and the trend towards an ageing worldwide population is likely to lead to an increased incidence of cases of prostate cancer. Prevalence is however, increasing in men in their early 50s, a study spanning 20 years has found an increase of approximately 50% in the number of cases in men less than 60 years of age and that the incidence of prostate cancer varies from country, with the highest incidences being found in the Western world and the lowest being found in Asia. Data for the year 2000 identify that the incidence in the USA was 2400 per 10,000, Japan was 220 per 100,000 and for China was 15 per 100,000 [32]. Prostate cancer has become one of the leading male cancers in some Asian countries with the incidence having risen rapidly in the last 20 years. The reasons for this high degree of variability between ethnic

groups are probably multi factorial and include the availability of improved detection methods, increasing westernization of lifestyle and in particular genetic risk factors.

The state distribution at the time of diagnosis also varies around the world. In the U.S.A in 2001 only 135 of the tumors were diagnosed as Stage 3 or 4, whereas the corresponding figures in 2000 for the South Korea were 72% and in Taiwan in 1998 they were 58%. However, in most Asian countries, there is evidence that there is a trend towards diagnosing cancer with more favor.

2.3 Laboratory Diagnosis

A physical examination, patient history, an evaluation of symptoms provides the basis for a diagnosis of a prostate disorder. The physical examination includes a digital rectal examination (DRE) and symptom evaluation is obtained from the results of the AUA symptom index.

2.3.1 Digital rectal examination

In DRE examination, the doctor inserts a lubricated, gloved finger into the patient's rectum to feel the surface of the prostate gland through the rectal wall to assess its size, shape and consistency. Healthy prostate tissue is soft, like the fleshy tissue of the hand where the thumb joins the palm. Malignant tissue is firm, hard, and often asymmetrical or stony, like the bridge of the nose. If the examination reveals the presence of unhealthy tissue or any abnormality, additional tests are performed to determine the nature of the abnormality, these includes massaging the prostate during the DRE to obtain fluid to

examine with a microscope and taking a blood test to measure prostate-specific antigen (PSA) and if DRE or the PSA blood test indicates a problem may exist, additional tests, including urinalysis, urodynamic tests, cystoscopy, abdominal ultrasound, transrectal ultrasound with prostate biopsy, and imaging studies such as magnetic resonance imaging (MRI) or computerized tomography (CT) scan may be done[33].

2.3.2 American Urological Association Symptom Index

The American Urological Association (AUA) Prostate Symptom Index is a questionnaire designed to determine the seriousness of a man's urinary problems. The patient answers questions related to common symptoms of prostate disease. How frequently the patient experiences each symptom is rated on a scale of 1 to 5. These numbers added together provide a score that is used to evaluate the condition. An AUA score of 0 to 7 means the condition is mild while a score of 8 to 19 means moderate; and 20 to 35 shows the condition is severe, [33].

2.3.3 Prostate Specific Antigen

PSA is a protein made only by the prostate gland. This test is often included in routine physical exams for men older than age 50. Because African American men have higher rates of getting, and dying from prostate cancer than men of other racial or ethnic groups in the United States, medical organizations recommend a PSA blood test be given starting at age 40 for African American men. A PSA blood test is performed to detect or rule out prostate cancer. The amount of PSA in the blood is often higher in men who have prostate cancer. However, an elevated PSA level does not necessarily indicate prostate

cancer. The US Food and Drug Administration has approved the PSA blood test for use in conjunction with a DRE to help detect prostate cancer in men age 50 or older and for monitoring men with prostate cancer and other infections of the prostate after treatment. However, much remains unknown about how to interpret a PSA blood test, its ability to discriminate between cancer and problems such as BPH and prostatitis, and the best course of action if the PSA level is high [12].

The test measures the amount of PSA in the blood in Nanograms per milliliter (ng/ml). A PSA of 4 ng/ml or lower is normal; 4-10 ng/ml is slightly elevated; 10-20 is moderately elevated; and above 20 is highly elevated. Most men with slightly elevated PSA levels do not have prostate cancer but some have normal PSA levels yet having cancer [18]. A highly elevated level may indicate the presence of cancer. The PSA test can produce false results. A false positive result occurs when the PSA level is elevated and there is no cancer. False negative result occurs when the PSA level is normal and there is cancer. Because of this, a biopsy is usually performed to confirm or rule out cancer when the PSA is high [10].

Free and total PSA (also known as PSA II) in the blood may be bound molecularly to one of several proteins or may exist in a free or unbound state. Total PSA is the sum of the levels of both forms; free PSA measures the level of unbound PSA only. Studies suggest that malignant prostate cells produce more bound PSA; therefore, a low level of free PSA in relation to total PSA might indicate a cancerous prostate, and a high level of free PSA compared to total PSA might indicate a normal prostate. Age-specific PSA Evidence

suggests that the PSA level increases with age. PSA of up to 2.5 mg/ML for men age 40-49 is considered normal, as is 3.5 mg/ML for men 50-59,4.5 ng/ml for men age 60-69, and 6.5 mg/ML for men 70 and older. Nevertheless, the use of age-specific PSA levels have not been fully endorsed [32].

2.3.4 Urinalysis

Urinalysis entails testing of urine sample for abnormal substances or signs of infection. In suspect of an infection, urine samples are collected in duplicate or triplicate during a single urination to help locate the infection site as the urethra, prostate or the bladder.

2.3.5 Trans rectal Ultrasound with Prostate Biopsy

Trans-rectal ultrasound entails insertion of a transducer slightly larger than a pen into the man's rectum next to the prostate. The ultrasound image shows the size of the prostate and any abnormal-looking areas such as tumors. In determining whether a tumor is cancerous or non-cancerous the needle is used to remove a piece of prostate tissue for microscopy examination [34].

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Area

The study was carried out at the Moi Teaching and Referral Hospital (MTRH) which serves as a Teaching Hospital for Moi University School of Medicine (MUSoM). It is situated in Eldoret Town, Uasin-Gishu County, Kenya. The catchment area is over 13 million people, which are roughly 40% of the Kenyan population.

3.2 Study Population

The study population comprised of records of both in patients and out patients who attended MTRH and had PSA screening in Immunology laboratory and biopsy in the Histology laboratory.

3.3 Study Design

A retrospective cross sectional study design was used to assess the causes and categories of the prostate disorders among men above fifty years attending MTRH.

3.4 Sample Size Determination

Based on the data in the outpatient and inpatient departments, in a day, approximately 30 patients are attended to and provided with care. The estimated prevalence of prostate disorders in Kenya as according to KEMRI findings is 17.3% [35]. Therefore the sample size was reached using the formula by Fisher's et al (1998).

$$N=Z^2 \frac{P(1-P)}{D^2}$$

Where; **Z**=Confidence level at 95% =1. 96, **D**=Expected error = 0.05, **P**=17. 3% is the estimated prevalence of prostate disorders [35], **1-P** = 0.827 and **N**=219.

Thus the sample size was 219 patients. The sampling technique used was simple random sampling, whereby from the list of patients, who reported for medical attention in the outpatient and inpatient urology sections, each was assigned a number and the numbers picked at random to constitute the sample size. Selected patients' names were recorded and their record files from the Health Records and Information System (H.R.I.S) reviewed for data mining.

3.6 Inclusion Criteria

1. Records of those already under diagnosis.
2. Records of those patients who attended MTRH urology OPD clinic and inpatients from 1st April 2012 to 31st March 2013.
3. Records of Men Aged above 50 years and had PSA screening.

3.7 Data Collection

1. Demographic data including MTRH numbers, age, marital status, economic activity were captured.
2. No names were indicated in the data collection tool for privacy.

3. Patient's medical history was obtained; presence or absence or prostate problems such as; weak flow of urine, frequent urination at night, lower back pain among others were captured.

Records of patients who were sent for PSA screening with urine retention symptoms and reported to have elevated PSA levels, and were further sent to the histology lab for biopsy were also considered. The examination finding was sorted such as those with urine blockage, burning sensation or pain during urination. PSA levels, DRE results and data from the histopathology lab were also used to confirm those with suspected enlarged prostate and with elevated PSA levels. All patients' data with symptoms suggestive of prostate disorders had equal chances of being sampled. Systematic random sampling was applied in selecting every second subject name and/or MTRH patient number to be included in the study.

3.8 Preparation/Training

Data collection was done by the researcher with the aid of two assistants from the records department and a laboratory Technician who were informed of the purpose of the study and the kind of information to be collected. They were involved in filling the checklist.

3.9 Data management and Statistical analysis

All data collected were entered, organized and managed using SPSS spreadsheet for Windows XP. Data were analyzed using SPSS version 17. Descriptive statistics such as mean, median, standard deviation and inter-quartile range (IQR) was used for continuous data while frequency listings were used for categorical variables. To assess whether there

was any association between the outcome of interest (elevated PSA) and categorical predictor chi square test was used. In cases where the expected cell count was below 5 the Fishers' exact test was used. In all the analysis a p-value below 5% was considered to be significant.

3.9.1 Ethical considerations

Approval to carry out the study was obtained from the Institutional Research and Ethics Committee (IREC) of the MUSoM and MTRH. There was no actual contact made with the patients, files of both the inpatients and out patients were reviewed as the checklist was filled to capture the required information. All the study records obtained were kept confidential and not disclosed to anyone not involved in the study. The study findings will be made available to interested individuals and groups, but with authority from Moi University and MTRH. The findings will be sent for publication in peer reviewed journals upon seeking permission from the relevant bodies.

CHAPTER FOUR

4.0 RESULTS

4.1 Results overview

The study findings have been highlighted and presented in figures, tables and synthesized texts. The first part presents the demographic information of the research subjects. The socio demographic factors are presented under various topics; descriptive statistics, clinical characteristics, associated findings, surgeries done and testing of association of various variables.

4.2. Demographic and Clinical characteristics of Patients with prostate disorders

There were 219 patients records involved in the study; 74.4% (n = 163) were inpatient and 25.6% (n = 56) outpatients. The age range was between fifty and ninety six years. Majority of the patients 29.7% (n = 65) were within the age bracket of 70-79 years with most of them being self-employed. Pertinent characteristics of the study subjects are presented in Table 1. On evaluation of marital status, 78.5% (n = 172) were married with more than half (n = 128) being married to one spouse**.**

Table 1: Demographic profile of patients

Variable	Frequency	Percentage
Age in years	N=219	
50-59	63	28.80%
60-69	49	22.40%
70-79	65	29.70%
Above 79	42	19.20%

Marital status	N=219	
Married	172	78.50%
Single	9	4.10%
Divorced	3	1.40%
Widowed	35	16.00%
Number of spouses	N=219	
One	128	58.40%
Two	54	24.70%
More than two	7	3.20%
None	30	13.70%
Occupation	N=219	
Farmer/Self Employed	179	81.70%
Civil servant	12	5.50%
Others	28	12.80%
Clinic/ward	N=219	
Inpatient	163	74.40%
Outpatient	56	25.60%

Source: Author, 2014

The clinical characteristics of the study subjects revealed that 149 (68.03%) patients had had urine retention in the course of their urological problem of which 32.9% were on suprapubic catheter and 67.1% on urethral catheter. Among the 219 study participants, 141(64.4%) had enlarged prostate and 44(20.1%) had normal prostate upon digital rectal examination. On further clinical assessment of the study subjects, 35.2% were suspected to have cancer of the prostate while 48.4% and 0.9% were suspected to have benign prostate hyperplasia and prostatitis respectively. The leading complaints were lower back pain followed by urine retention then weak flow of urine. The associated clinical features are as seen in the Table 2.

Table 2: Clinical features of the patients at presentation

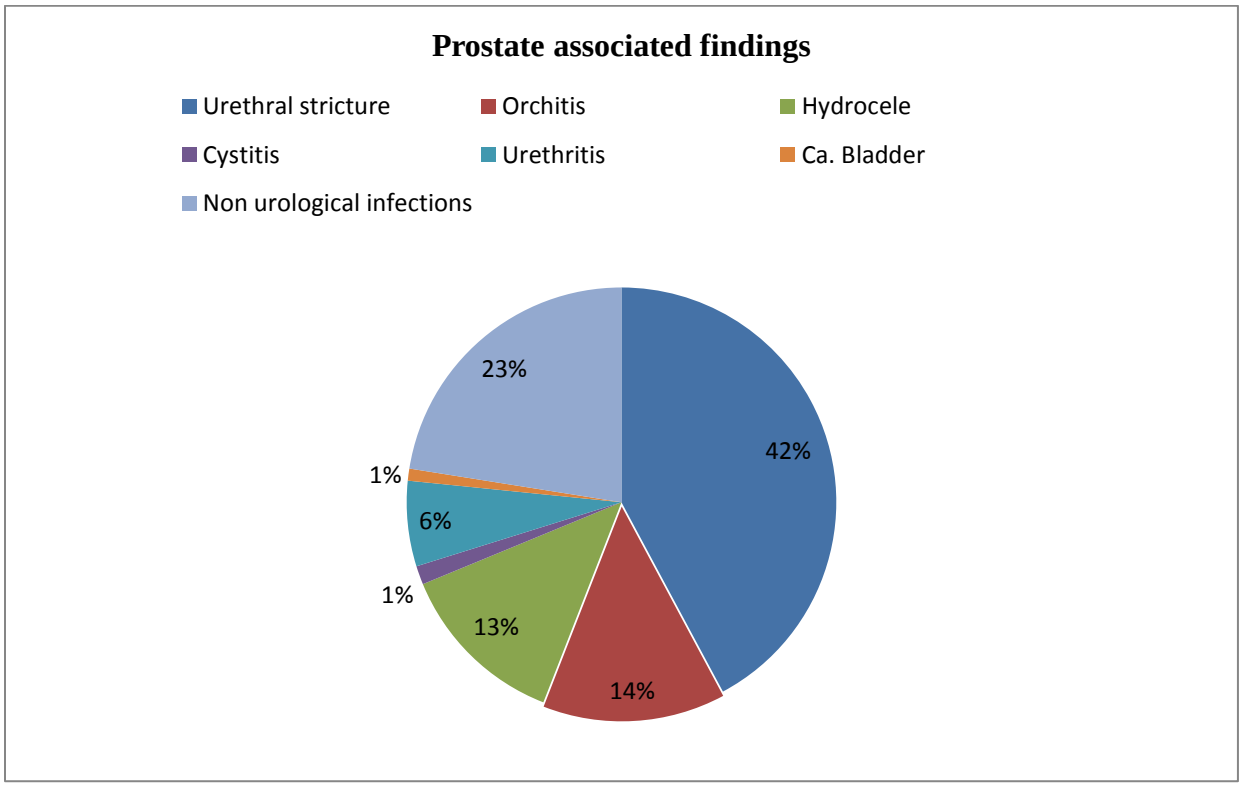
	Frequency	
Variable	**N=219**	**Percentage**
Frequent urination at night	109	49.80%
Urine retention	149	68.03%
Burning sensation during urination	71	32.42%
Lower back pain	166	75.80%
Incomplete voiding	147	67.10%
Weak flow of urine	149	68.00%
Family history	73	33.30%
Nature of the prostate	N=219	
Normal	44	20.10%
Enlarged	141	64.40%
Not done	34	15.50%
Suspicion on DRE	N=219	
Ca prostate	77	35.20%
Prostatitis	2	0.90%
BPH	106	48.4%
Not done	34	15.50%
Form of catheterization	N=219	
Suprapubic catheter	49	22.40%
Urethral catheter	100	45.70%
No catheter	70	32.00%

Source: Author, 2014

4.2.1 Prostate associated findings

Episodes of prostate associated findings alongside prostate disorders were also evident among 67 patients. The commonly prostate associated findings were urethral stricture

42.5% (n = 29), Orchitis 13.7% (n=9) and Hydrocele 12.8% (n=9) with non-urological infections representing 22.4% (n = 15) as shown in Figure 1.



Source: Author, 2014

Fig 1: The prostate associated findings

4.0 Prevalence of prostate disorders and PSA levels among patients seen at MTRH

During the study period, 842 patients did attend Urology Clinic at MTRH. A total of 152 patients was confirmed to have prostate disorders and as such, the prevalence of prostate disorders among patients seen at MTRH during the study period (1st April 2012 to 31st March 2013) was 18.05%. The 219 study participants, had a mean PSA level of 31.184ng/ml, 62 patients had PSA within the normal range of 0-4ng/ml with an average

of 1.762 ng/ml while 157 had elevated PSA levels with a mean of 42.287 ng/ml. Study participants with either of the three prostate disorders having PSA levels within the normal range were 30 while those with PSA levels above cutoff and had prostate disorders were 122 (Table 3). BPH was found to be the most prevalent prostate condition at 43.83% as opposed to prostate Cancer and Prostatitis at18.3% and 0.01% respectively. Further observation showed that there was a close relationship between enlarged prostate and prostate cancer ($p<0.001$).

Table 3 PSA levels and DRE findings of the study subjects

	PSA ≤4	**%**	**DRE**			
			Normal	**%**	**Enlarged**	**%**
BPH	**23**	24	19	82.6	4	17.4
Prostitis	**1**	50	0	0	1	50
Ca Prostate	**6**	11.1	2	33.3	4	66.7
Associated findings	**32**	0	0	0	0	0
Total	**62**					

	PSA >4	**%**	**DRE**				
			Normal	**%**	**Enlarged**	**%**	**Not done**
BPH	**73**	76	7	9.5	66	90.5	0
Prostatitis	**1**	50	0	0	1	50	0
Ca prostate	**48**	88.9	2	4.2	46	95.8	0
Associated findings	**35**	0	0	0	0	0	67
Total	**157**						

Source: Author, 2014

4.3.1 Prostate Specific Antigen levels and interventions

Urological interventions were done in 71 patients with Trans-Urethral Prostatectomy (TURP) being the most frequently performed surgery at 57.8% (n=41) of which majority (n=36) had elevated PSA levels and the rest had normal PSA. Open prostatectomy

represented 26.8% of urological interventions done while Orchitectomy was the least performed surgery (15.4%). Majority of the patients 71.7% (n=157) had elevated PSA levels (at a cut-off point of 4 ng/ml) of which 73 of them had BPH on clinical evaluation using DRE. Fifty-four patients had prostate biopsy done whereby 40 (74.1%) were confirmed to have malignancy while 25.9% were benign. Majority of those found with malignancy were between 50-59 years of age (n= 12). Only 2 of the study subjects were found to have malignancy yet their PSA levels were within the cut-off point. It was noted that presence of malignancy was significant to PSA (*p=0.001*).

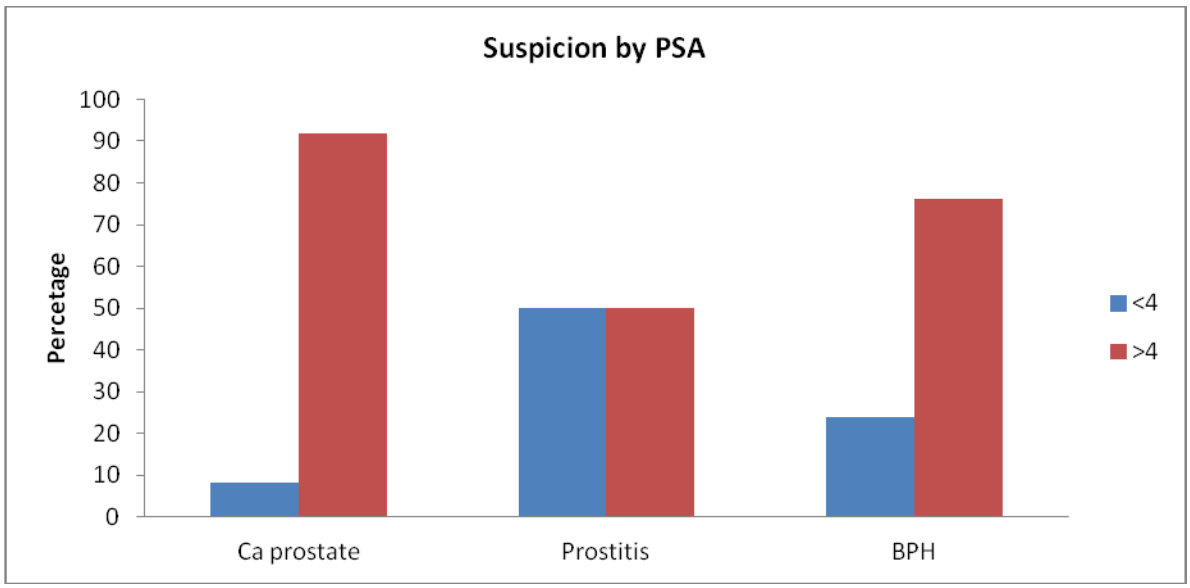
Table 4: PSA levels and managements interventions

Variable	Frequency	Percentage
PSA levels	N=219	
0 to 4.0	62	28.30%
Above 4	157	71.70%
Biopsy results	N=219	
Cancerous	40	18.30%
Non cancerous	14	6.40%
Biopsy not done	165	75.30%
Surgery/operation done	n= 71	
Open prostatectomy	19	26.8%
TURP	41	57.8%
Orchitectomy	11	15.4%
Other forms of surgery	17	
No surgery	131	

Source: Author, 2014

4.4 Predictors of elevated PSA Levels

Among the study participants, patients aged between 70-79 (29.6%) years were the majority of those having elevated PSA followed by those aged between 50-59 (28.8%) years. It was further observed that increase in age was significantly related to elevated PSA (*p=0.041*). Urine retention, burning sensation, family history of prostate disorders together with frequent urination at night were found to be significant to elevated PSA ($p<0.001$). Those with PSA > 4, were more likely to be found having either Ca prostate or BPH ($P<0.001$) and were about five times as compared to those with prostatitis. Comparison of the three prostate disorders to the PSA levels showed that study subjects with Ca prostate had the highest PSA levels (> 4 ng/ml) followed by those with BPH (Figure 2).



Source: Author, 2014

Fig. 2: Rate of PSA elevation in the three prostate conditions

On evaluation of demographics of malignancy versus PSA and occupation, it was observed that majority of the malignancies were among the married patients. Of those

subjected to histology majority had presented with elevated PSA and confirmed to have malignancy. It was further noted that those with elevated PSA were likely to have cancer of the prostate and were about five times more compared to those with PSA levels ≤ 4. The study findings further suggested that malignancy was statistically significant to age and elevated PSA (p=0.041), while age and PSA were found to be non-significant (p=0.172).

CHAPTER FIVE

5.0 DISCUSSION

The study demonstrated that the percentile of the inpatients (74.4%) was almost thrice that of the outpatients which was at 25.6%. This implies that many prostate disorders are unnoticed until they are at an advanced stage where conservative management is almost impossible therefore critical care and management is required. It was evident that digital rectal examination is a good diagnostic procedure for the enlarged prostate as 141 patients showed prostate enlargement upon DRE examination. There was a strong association between urine retention and prostate enlargement which is comparable to the findings by Lane et al, 2007 [36] where majority of the patients with urine retention were found to have enlarged prostate. According to the study, mean serum PSA was significantly high, but slightly lower than that of Causasian-American men with mean PSA of 35.5 ng/ml [37] and far much higher compared to the Afro-Caribbeans of Tobago Island (14.8ng/ml) [38]. This therefore poses challenges in making the international comparison that can be made at any time while the prevalence of PSA testing is not well documented in Kenya and Africa. It appears then that cancer of the prostate is also commonly detected where PSA is performed which corresponds well to Caribbean men [38].

The prevalence of prostate disorders among patients as seen at MTRH was found to be 18.05%, which was almost equal to the prevalence of prostate cancer, 18.3%. Prostate cancer prevalence was slightly higher compared to a report given by KEMRI; cancer incidence report,Nairobi, 2012 as the prevalence of prostate cancer in Kenya (17.3%)

[35] But seven fold higher compared to Ghana and fivefold in comparison to Senegal [39]. The difference is due to variability in geographical locations and environment, lifestyle and specific to the facility. Frequently performed urological interventions was TURP and open prostatectomy which is similar interventions done to up to 25% of patients with urine retention symptoms as demonstrated in England and Wales studies [40]. In this study, PSA levels were relatively high with some of the malignant cases having PSA levels of less than 4 ng/ml which is similar to developed countries where cancer of the prostate has been found in patients with PSA values as low as 1.1 ng/ml [41] and this therefore needs debate to determine the exact cut off point to values below 4.0ng/ml with respect to, particularly, age and race of the patient (42, 43).

Majority of those found with malignancy were age between 50-59 years (n= 12). The revelation, therefore does not concur with the projection by Washington, DC, U.S. Census Bureau, Statistical [44] that men to be diagnosed of prostate cancer between 2010 and 2050 will be aged above 65 years. The malignancy rate (18.3%) is lower than that previously found by Nassanga, 2001 [45] with a rate of 32.5% but close to findings by Men *et al.,2000*- [46] in Turkish men with a rate of 23.1%. The difference is attributed to the use of different methods of biopsy collection and detection rates. In the Nassanga series, all patients were subjected to systematic six core biopsies regardless of DRE findings but in this scenario patients undergo DRE and PSA screening for them before resolving to have biopsy done. DRE was the most commonly done diagnostic procedure with the majority being done to those having elevated PSA. This shows that the trend in which DRE and PSA as used in MTRH-Kenya is similar to USA where PSA is majorly

used for the detection of prostate cancer [47] and the WHO recommendation that the two be primary core investigations in dealing with prostate disorders.

Urine retention, burning sensation, family history of having prostate disorders together with frequent urination at night was found to be significant to elevated PSA, which compares well to Carter, 2007 [48] that frequent nighttime urination and having related family history points to likelihood of PSA elevation.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

From the study it was concluded that the prevalence of prostate disorders was 18.05%. Men above seventy years had the highest reported cases of the same. BPH was the most common prostate disorder seen at MTRH. Urine retention, burning sensation and family history were found to be the significant predictors of elevated PSA. The PSA range of the patients were significantly high than those of African-American or Caucasian men. The study concluded that prostate cancer prevalence in Kenya was high as compared to other sub-Saharan countries.

Age and prostate enlargement significantly correlate with serum PSA and age and prostate enlargement 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.

6.1 RECOMMENDATIONS

All men should be sensitized and educated on the prostate gland complications and be encouraged to be screened for PSA once they attain the age of 50 years. The health care providers should devise more patient management methods that are conservative to take care of the cases that are reported late. There is need to adopt modern methods of detecting prostate disorders e.g. use of radioisotope scans and electric pulse to detect the malignancies in early stages.

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APPENDICES

APPENDIX I: Check list

1. Demographic Data

   MTRH Patient Number……..

   a) Date ……..……

   b) Age…… (Yrs)

   c) Marital status: (i) Married [ ], (ii) Single [ ], (iii) Divorced [ ], (iv) Widower [ ]

   d) Number of spouses : (i) One.[ ], (ii) Two [ ], (iii) More than two [ ] (iv) None[ ]

   e) Occupation : (i) farmer/self [ ], (ii) civil servant [ ] Others [ ]

   f) Ward / Clinic…….

2. Medical History

   i. Frequent Urination at night……. Yes [ ] No [ ]

   ii. Urine Retention …….. Yes [ ] No [ ]

   iii. Burning sensation during urination ……..……...…Yes [ ] No [ ]

   iv. Feeling of un-empty bladder after void……. …Yes [ ] No [ ]

   v. Lower Back pain……...…… Yes [ ] No [ ]

   vi. Weak flow of urine ……..……..… Yes [ ] No [ ]

   vii. Any family member with the same symptoms/signs before…. Yes [ ] No [ ]

3. Examination, DRE;

(a) Prostate: Normal [ ] Enlarged [ ], Moderately enlarged [ ], Not done [ ]

(b) Suspicious: Ca Prostate [ ], Ca bladder [ ] BPH [ ], :Hemorrhoids [ ], Hydrocele [ ] , Cystitis [ ], Urethritis [ ], Other [ ]

4. On Catheter: (i) Supropubic catheter……..….[ ]

(ii) Urethral catheter……..…. [ ]

(iii) No catheter ……..[ ]

5. Any other infection past and or current

a) Syphilis ……Yes [ ] No [ ]

b) Gonorrhea……..…. Yes [ ] No [ ]

c) HIV/AIDS……..Yes [ ] No [ ]

Others (specify)……

6. Other diagnosis?

a) Urethral stricture/urine retention.…..[ ]

b) Testicular swelling (Orchitis)…….[ ]

c) Hydrocele ……..….[ ]

d) Cystitis ……...[ ]

e) Others …….[ ]

7. Surgery/operation done:

a. Prostatectomy……..... [ ]

b. Transurethral resection (TURP).....…[ ]

c. Orchitectomy……...[ ]

d. Hydrocelectomy …….…....[ ]

e. Cystostomy ……[ ]

f. Others ……...……..[ ]

8. Laboratory results

Table 1.

Immunology Lab. PSA LEVELS

Age:	
PSA values	

Table 2.

Histology Lab

Biopsy Results/Report

(a). Cancerous…….……Yes [ ] No [ ]
(b). None cancerous……. ……... Yes [ ] No [ ]

APPENDIX II: Ethical approval by Institute of Research and Ethics Committee (IREC)

APPENDIX III: Approval to conduct research by Moi Teaching and Referral Hospital