**KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, KUMASI**

# INDICATORS FOR THE ASSESSMENT OF PROSTATE DISORDERS AT KOMFO ANOKYE TEACHING HOSPTIAL (KATH)



**A THESIS SUBMITTED IN FULFILLMENT**

**OF THE REQUIREMENTS FOR THE**

**DEGREE OF**

**MASTER OF PHILOSOPHY**

**(CHEMICAL PATHOLOGY)**

**In the**

**Department of Molecular Medicine,**

**School of Medical Sciences**

**College of Health**

**By**

**EMMANUEL ACHEAMPONG**

**PG2403614**

**NOVEMBER, 2016**

## DECLARATION

With the exception of references and quotations from other sources which have all been duly acknowledged. I solemnly declare that this piece of work is the original research work I personally undertook and that no part of this work has been presented elsewhere apart from novel publication emanating from this work. Also, I would like to say that any errors of judgment, facts, omissions and style remain my liability.



…… ……

**EMMANUEL ACHEAMPONG** **Date (STUDENT)**

…… ……

**PROF. F. A. YEBOAH** **Date**
**(SUPERVISOR)**

…… ……

**PROF. F.A. YEBOAH** **Date (HEAD, Department of Molecular Medicine)**

## ABSTRACT

**Aims:** This study evaluated the diagnostic accuracy of various diagnostic tools for prostate cancer and also developed nomogram for the prediction of biopsy outcome among Ghanaian men presenting with prostate disorder at Komfo Anokye Teaching Hospital. **Study design/Methodology**: A hospital-based cross-sectional prospective study conducted at the Department of Surgery (Urology Unit) Komfo Anokye Teaching Hospital (KATH) December, 2014 to March, 2016. A total of 241 patients suspected of having prostate disorder based on abnormal digital rectal examination (DRE) and, or elevated prostate specific antigen (PSA) level underwent Trans rectal ultrasonography guided biopsy of the prostate. Evaluation of PSA, Prostate Specific Antigen Density (PSAD), DRE, prostate volume was done using receiver operating characteristics curve (ROC) analysis. These four diagnostic tools were combined into a single score to improve the diagnostic performance. Lower urinary tract symptoms (LUTS) related characteristics and questions pertaining to international prostate symptom score (IPSS) was also employed to obtain relevant data. Stepwise logistic regression was used to determine the independent predictors of a positive initial biopsy. Two nomogram models were developed to predict the likely clinical outcome of prostate biopsies. ROC was used to assess the accuracy of the nomograms and PSA levels alone for predicting positive prostate biopsies.

**Results**: Prostate cancer was diagnosed in 63 patients out of 241 (26.1%). Benign prostatic hyperplasia was diagnosed in 172 (71.4%) patients and the remaining 6 (2.48%) had chronic inflammation. PSA on its own had a sensitivity of 98.4% and specificity of 16.3% respectively. PSAD had sensitivity and specificity of 84.1% and 56.7% respectively. DRE had a specificity of 69.8% but sensitivity of 67.4%. Significantly elevated levels of PSA and PSAD were observed among patients with PCa compared to patients without PCa. PSAD showed better accuracy (AUC=78.9) than PSA (AUC=77.8) and DRE (AUC=68.6) respectively for the individual diagnostic tools. Among the different combination of diagnostic tools, bioscore combination of DRE+PSAD+PSA had better accuracy (AUC=80.6) than PSAD+DRE (AUC=78.1) PSA+PSAD+DRE+ Prostate Volume (AUC= 76.7), and PSAD+PSA (AUC=71.5) respectively. PSAD+DRE had significant higher odds (19.52) than PSA+PSAD (19.52) and PSA+DRE (13.67). The prevalence of LUTS was 88.89%. Bladder storage symptoms was recorded at 88.59%, prostate enlargement based on DRE was 60.4%. PSA levels ≥4ng/ml gave a prevalence of 81.5% while prostate enlargement defined as PSA ≥1.5ng/ml gave a prevalence of 85.23%. The accuracy of nomogram I and II for predicting a positive initial prostate biopsy were 87.5% and 84.9% respectively

**Conclusion:** Combined diagnostic performance of DRE+PSAD+PSA poses a better diagnostic accuracy. Bioscores for the combination of the diagnostic tools were significantly associated with increasing odds of prostate cancer detection upon logistic regression analysis**.** The most prevalent urinary tract symptoms (LUTS) were bladder storage symptoms and urgency. The accuracy of nomogram I and II for predicting a positive initial prostate biopsy was better than using individual diagnostic tools.

## DEDICATION

This work is dedicated to my dad Mr. Isaac Acheampong, my mum Mrs. Victoria Akomah Acheampong and my elder brother Master Alphred Delton Acheampong. They have been the motivational strength behind this work. Again I dedicate this work to Prof F. A. Yeboah (FAY), Dr. Ken Aboah, Dr. E F. Laing and Dr. C.K. Gyase-Sarpong my wonderful supervisors for all the sacrifices they have all made on my behalf towards this project



**ACKNOWLEDGEMENT**

To the one who strengthens me to do all things; to he who is able to complete whatsoever he has begun in me; the Omnipotent God for bringing me this far, may His name be praised. My sincere gratitude goes to my supervisors, Prof F. A. Yeboah, Dr. Ken Aboah, Dr. E F. Laing and Dr. C.K. Gyase-Sarpong for their immense support, advice; guidance and patience from the beginning of the project to the end. It took time though, but I think I have finally "responded to treatment". God richly bless you all. I wish to show my sincere gratitude to my colleagues and friends Enoch Odame Anto, Emmanuella Nsenbah Batu, and Bright Amankwaah for all the support and advice you offered me throughout this project, you are part of this success. I say a big thank you to the entire staff and postgraduate students of the Department of Molecular Medicine, School of Medical Sciences, KNUST, the staff of Urology Unit of Komfo Anokye Teaching Hospital. God richly bless you.

## TABLE OF CONTENTS

**Contents**

## LIST OF TABLES

## LIST OF FIGURES

## LIST OD EQUATIONS



## LIST OF ABBREVIATIONS

| | |
|---|---|
| AIC | Akaike Information Criterion |
| ASAP | Atypical Small Acinar Proliferation |
| AR | Androgen Receptors |
| AUA | America Urological Association |
| AUR | Acute Urinary Retention |
| AUC | Area Under Curve |
| BMI | Body Mass Index |
| BPH | Benign Prostatic Hyperplasia |
| CI | Confidence Intervals |
| CZ | Central Zone |
| DHT | Dihydrotestosterone |
| DRE | Digital Rectal Examination |
| DV | Dependent Variable |
| IARC | International Agency for Research and Cancer |
| IGF -1 | Insulin Growth Factor-1 |
| IQR | Interquartile Range |
| KATH | Komfo Anokye Teaching Hospital |
| LUTS | Lower Urinary Tract Symptoms |
| MRI | Magnetic Resonance Imaging |
| NE | Neuroendocrine |
| NIH | National Institute of Health |
| OAB | Overactive Bladder |
| OR | Odds Ratio |
| PAP | Prostatic Acid Phosphatase |
| PCa | Prostate Cancer |
| PIN | Prostatic Intraepithelial Neoplasia |
| PSA | Prostate Specific Antigen |
| PSAD | Prostate Specific Antigen |
| PV | Prostate Volume |
| PZ | Peripheral Zone |
| QOL | Quality of Life |
| ROC | Receiver Operational Characteristic |
| SEER | Surveillance Epidemiology End Results |
| STD | Sexual Transmitted Disease |
| SSA | Sub-Sahara Africa |
| TNM | Tumour Node Metastasis |
| TRUS | Trans Rectal Ultrasonography |

| | |
|---|---|
| TZ | Transitional Zone |
| UTI | Urinary Tract Symptoms |

# CHAPTER 1

## 1.0 INTRODUCTION

The size of the prostate gland at birth is like a small pea and remains so until puberty when there is a spurt of growth as it starts producing hormones (Rogers, 2010). The increment in size causes problems and the common problems are prostatitis, benign prostatitis hyperplasia and prostate cancer (Arthur *et al.*, 2006; Rogers, 2010).

Cancer of the prostate (PCa) is the sixth leading cause of mortality and second most frequently diagnosed cancer among males globally (Ferlay *et al.*, 2010). It is the number one cancer in both incidence and mortality in Africa, consisting of 13% of all male cancer occurrence and 11.3% of all male cancer related mortalities. The worldwide incidence rates vary considerably among different regions with the highest incidence noted among males from advanced countries which was attributed to the utilization of the prostate specific antigen (PSA) test as a screening tool (Center *et al.*, 2012; Jemal *et al.*, 2012). In African countries where registers exist such as Nigeria, Uganda, South Africa and Zimbabwe, it has been observed that the incidence of prostate cancer is increasing between the ages of 40 to 70 years (Wabinga, 2003). Rretrospective analysis of all cancer cases have demonstrated that, prostate cancer was the second leading cause of cancerrelated mortality among their male patients in Ghana (Klufio, 2004; Wiredu and Armah, 2006; Laryea *et al.*, 2014).

Prostatitis is defined as the inflammation of the tissue of the prostate gland. It is estimated that 50% of men experience this disorder during their lifetime (Habermacher *et al.*, 2006). Benign prostatic hyperplasia is the presence of hyperplastic glands on pathological inspection of the prostatic tissue which arises in the periurethral and transition zones of the prostate gland (Untergasser *et al.*,

2005). The reported prevalence of microscopic, macroscopic and clinical BPH differs significantly (Girman, 1998; Irani *et al.*, 2003). In Ghana, the prevalence of BPH using ultrasound detected enlarged prostate was 40.0% (Obu, 2014). Autopsy studies conducted in the Western countries shows that 40% of men in their 50s and up to 90% of men in their 80s have histological evidence of BPH (Girman, 1998). Lower Urinary Tract Symptoms (LUTS) are used to define the complex of symptoms which includes bladder storage, sensation or voiding symptoms affecting the lower urinary tract (Skolarikos *et al.*, 2004; Parsons, 2010). However, BPH is thought to account for the vast majority of LUTS. BPH causes symptoms in approximately 90% of men over the age of 80 and one third of men will develop urinary tract symptoms once in their life (Peters *et al.*, 1997; Rosen *et al.*, 2003). Recent data from a population-based study in the capital of Ghana on LUTS reported a prevalence of 19.9%, 62.3% and 13.3% respectively for international prostate symptom score (IPSS), PSA and an enlarged prostate on DRE(Chokkalingam *et al.*, 2012) .

The clinical factors used in the assessment of prostate disorders and the differentiation of malignant and benign prostatic conditions includes prostate specific antigen (PSA) , digital rectal examination (DRE), clinical symptoms, heterogenic echo lesion on trans rectal ultrasound, PSA derivatives such as age specific PSA, PSA density (PSAD), PSA velocity, and free PSA percentage, international prostate symptoms score (IPSS) and identified risk factors such as age, family history, race, body mass index (BMI), prior prostatitis and medications respectively (Kamoi and Babaian, 1999; Reiter and De Kernion, 2002). DRE is regarded as the basic tool for screening and early detection of prostate cancer and is estimated to have about 59% overall accuracy (Basler and Thompson, 1998). DRE is the oldest and most commonly used screening test for prostate cancer, and

its use has been recommended by several expert groups, including the American Cancer Society (ACS, 1980) and the American Urological Association (American Urological Association, 1992).

Prostate specific antigen (PSA) has unequivocally proved its clinical usefulness as a serum marker for prostate cancer. Higher PSA values have also been observed in African American men with newly diagnosed prostate cancer when compared with newly diagnosed Caucasian men (Moul *et al.*, 1995). The presence of an abnormal digital rectal examination (DRE) or an elevated PSA level (>4.0ng/ml) is currently used to select men for prostate biopsy (Catalona *et al.*, 1994; Krumholtz *et al.*, 2002).

Previous study conducted among the Ghanaian population observed that 83.6% of the subjects had their PSA levels above the upper limit of the reference range (4.0ng/ml) with their ages ranging between 56 to 85 years (Arthur *et al.*, 2006). However, the sensitivity and specificity of PSA are insufficient to make it an ideal screening test for prostate cancer, since elevated PSA (greater than 4.0ng/ml) may also occur in patients with prostatitis and benign prostatic hyperplasia (BPH) (Partin and Oesterling, 1994). PSAD was introduced to correct PSA levels associated with prostate volumes, on the basis of the fact that prostate cancers release more PSA per unit volume into circulation than BPH (Benson *et al.*, 1992; Stephan *et al.*, 2005).

Furthermore, with the advent of evidence-based medicine, bias-free prediction models such as nomogram has started to emerge in aiding clinical decision making (Chun *et al.*, 2007). A nomogram is able to quantify probability of the event of interest by multivariate analysis of combined contribution of identified risk factors and clinical parameters (Garzotto *et al.*, 2003). Nomograms are widely used for cancer prognosis, primarily because they reduce statistical predictive models into a single numerical estimate, tailored to the profile of an individual patient, of the probability of an event, such as death or recurrence (Iasonos *et al.*, 2008; Shariat

*et al.*, 2008). Therefore evaluating the indicators for assessment of prostate disorders and developing a prostate nomogram to predict prostate biopsy outcome among a Ghanaian population will be immensely

helpful.

## 1.1 STATEMENT OF PROBLEM I

The discovery of the PSA revolutionized the management of PCa as a sensitive marker of early disease. However, its specificity can be improved upon. Management of patients with increased levels seem to be controversial since it is elevated in benign pathologies like prostatitis and benign prostatic hyperplasia (BPH) (Bozeman *et al.*, 2002; Punglia *et al.*, 2006). Previous studies have reported high specificity but low sensitivity of DRE as a diagnostic tool in detecting prostate cancer (Richie *et al.*, 1993).

In an attempt to reduce unnecessary biopsies and detect PCa, several methods have been employed to improve the accuracy of PSA test, including measurement of PSA density (PSAD), transitional zone PSA density, Age specific PSA, PSA velocity, free-total PSA ratio, and PSA isoforms. However, there have been inconsistencies in accuracies among various reports from several studies (Aslan *et al.*, 2005; Kefi *et al.*, 2005; Sözen *et al.*, 2005). The emerging use of the combination of DRE, PSA and PSAD for diagnosis have been shown to be promising, however these studies have mainly come from the advanced countries. Previous studies have explored the accuracy of total PSA (Arthur *et al.*, 2006; Agyei-Frempong *et al.*, 2008), and DRE (Hsing *et al.*, 2014) in

the Ghanaian population, however combinations of these with PSAD have received little attention.

## 1.2 STATEMENT OF PROBLEM II

Early detection of prostate cancer using DRE, prostate specific antigen (PSA) screening and its derivatives has major limitations (Barry, 2009). This diagnostic

gap exposes men to intensive diagnostic screening and invasive management strategies that affect quality of life. Although invasive and costly prostate biopsies provide a definitive diagnosis, they should be avoided in men with a low probability of disease because of the possible complications and associated pains (Rodriguez and Terriz, 1998; Suzuki *et al.*, 2006).

Efforts to develop predictive models for prostate cancer using clinical, laboratory and ultrasound parameters have been directed to improve the rates of prostate cancer detection and to reduce associated complications (Potter *et al.*, 2001; Djavan *et al.*, 2002b; Ohori and Swindle, 2002). Previous models has been developed to predict positive prostate biopsy among men undergoing evaluation for prostate cancer (Karakiewicz *et al.*, 2005). However, these models to provide prostate cancer probability have come from the advanced countries. Furthermore, prostate cancer is thought to differ epidemiologically and biologically between Western, American, African-American and Asian populations. Therefore, nomograms developed for other populations cannot be directly applied to the Ghanaian population and evaluation of prostate cancer risk should be tailored along racial lines (Tang *et al.*, 2012; Yoon *et al.*, 2012; Zhu *et al.*, 2012). Consequently, the development and use of a localized nomogram for given population is particularly pertinent. To our knowledge, no nomogram to evaluate the risk of prostate cancer in a Ghanaian population setting has been studied and published to date.

### 1.3 AIMS/OBJECTIVES

This study sought to evaluate the indicators for the assessment of prostate disorders and to develop a prostate nomogram for predicting prostate biopsy outcome among Ghanaian adults visiting the urology unit at Komfo Anokye Teaching Hospital (KATH).

### 1.3.1 Specific Objectives

The specific objectives of the study were to

1. Evaluate the individual and combined performances of specific prostate diagnostic tools in the detection of prostate cancer.
2. Develop and validate a prostate nomogram to predict positive prostate biopsy outcome.
3. Determine the predictors of symptoms score on the IPSS score for patients with lower urinary tract symptoms.

## 1.4 RATIONALE OF THE STUDY

Increasing prostate disorders awareness motivates patients to seek the most objective information regarding the probability of being diagnosed with lower urinary tract symptoms, prostatitis, benign prostatic hyperplasia and prostate cancer respectively (Graefen *et al.*, 2002; Lopez-Corona *et al.*, 2003). Discriminating prostate cancer from benign prostatic disease is difficult; therefore, the number of unnecessary prostate biopsies has increased with the increase in PSA screening (Suzuki *et al.*, 2006).

Most previous studies have focused on the use of individual diagnostic tools in the diagnosis of prostate cancer but much attention have not given to the different combinations of the specific prostate diagnostic tools among Ghanaians. Several risk factors for prostate cancer have been identified, their combined, multivariate and most bias-free contribution may be difficult to quantify. Nomograms have been introduced to circumvent this difficulty (Djavan *et al.*, 2002b). Nomograms quantify the combined contribution of several risk factors and provide a predicted probability of the event of interest. Their prediction applies to an individual instead of situating this individual within a risk group (Graefen *et al.*, 2002; Garzotto *et al.*, 2003). Most published studies on

nomograms have been conducted among population in the western and Asian part of the word using retrospective data. This current study was a crosssectional prospective study which recruited new patients visiting the urology unit for the first time with symptoms of prostate disorders.



## 1.5 HYPOTHESES

1. The use of appropriate prostate disorder indicators provide a more reliable clinico-pathological outcome in the assessment of prostate diseases at the Komfo Anokye Teaching Hospital

2. Combination of prostate specific diagnostic tools give a better accuracy than the individual diagnostic tools in the detection of prostate cancer

3. The accuracy of a nomogram for predicting a positive initial prostate biopsy is better than the diagnostic performances of individual and combined diagnostic tools in the diagnosis of prostate cancer

# CHAPTER 2

# 2.0 LITERATURE REVIEW

## 2.1 THE PROSTATE (ANATOMY AND PHYSIOLOGY)

The prostate is an accessory genital gland with the size and shape of a chestnut. The gland is located in the pelvis, inferior to the bladder, where it surrounds the prostatic part of the urethra. It consists of 30 to 50 tubuloalveolar glands arranged in three concentric layers: aninner mucosal layer, an intermediate sub mucosal layer, and a peripheral layer containing the main prostatic glands (McNeal, 1972; McNeal, 1988; Dixon *et al.*, 1999). The glands of the mucosal layer secrete directly into the urethra; the other two layers have ducts that open into the prostatic

sinuses, located on either side of the urethral crest on the posterior wall of the urethra (Dixon *et al.*, 1999). The average weight of a healthy prostate is approximately 11grams, ranging between 7 and 16grams (Leissner and Tisell, 1979).

In men, the urethra serves two purposes; urination and ejaculation. It runs from the bladder through the prostate and to the tip of the penis. The section of the urethra running through the prostate is known as the *prostatic urethra*. After being produced in the testicles, sperm moves into a coiled mass, known as the *epididymis* for maturation. It then goes into two muscular tubes known as the *vas deferens*, which coil around the bladder and seminal vesicles. The seminal vesicle can house the sperm for several days until ejaculation. During ejaculation, the prostate muscles contract and expel the sperm into the prostatic urethra towards the tip of the penis (Blandy and Lytton, 1986).

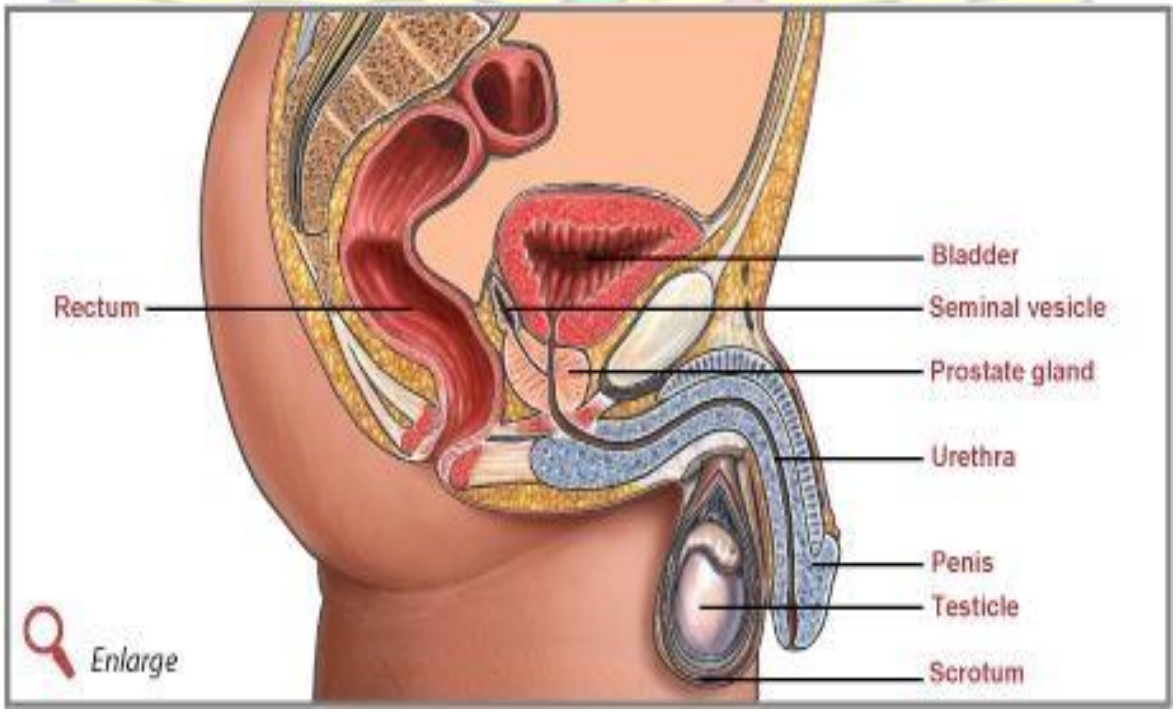



**Figure 2.1 Diagram showing the prostate gland** Source: **www.vantasimplant.com**

## 2.2 PROSTATE FUNCTION

The main function of the prostate gland is to store part of seminal fluid and assist ejaculation during sexual activity. During ejaculation, the smooth muscles in the prostate help the semen. The slightly alkaline fluid produced by the prostate makes up 25% of seminal fluid and allows sperm motility and viability. The vaginal tract is acidic therefore the alkalinity of the semen neutralizes the environment to allow the sperm to stay viable. A major constituent of prostatic secretion is prostate specific antigen (PSA), along with citrate (18.7 mg/ml), zinc (488 μg/ml), spermine (243 mg/ml) and cholesterol (78 mg/ml) (Blandy and Lytton, 1986).

## 2.3 THE STRUCTURE OF THE PROSTATE GLAND

The adult prostate gland is divided into four anatomical systems; zones and lobes. The zonal classification is used more in pathology; classifying the prostate into four different regions (McNeal, 1981; Cohen *et al.*, 2008).

### 2.3.1 The peripheral zone (PZ)

The PZ is located predominantly in the posterior and lateral aspects of the gland, extends to the apex variably and anteriorly, and surrounds the central zone towards the base. Its ducts open into the distal prostatic urethra. The PZ contains the majority (70%) of the glandular tissue in the normal prostate, and represents the most frequent site of prostate cancer (PCa) origin. It is also the predominant site for the occurrence of the PCa precursor lesion, prostatic intraepithelial neoplasia (PIN); including high grade PIN (HGPIN). This zone is the one most susceptible to inflammation (Difuccia *et al.*, 2005; Cohen *et al.*, 2008).

### 2.3.2 The central zone (CZ)

The CZ contains about 25% of the glandular tissue and is resistant to both carcinoma and inflammation. In comparison with the other zones, cells in the central zone have distinctive morphologic features: more prominent and slightly

basophilic cytoplasm and larger nuclei displaced at different levels in adjacent cells. Recent findings suggest that, this one originates embryologically from the inclusion of mesonephric duct cells into the developing prostate (Cohen *et al.*, 2008).

### 2.3.3 The transitional zone (TZ)

The TZ contains the mucosal glands. It is composed of lobules of glands with shorter ducts compared to those reaching out to the PZ and is often separated from the PZ by an indistinct band of collagenous tissue, which becomes more pronounced as the TZ is expanded by benign prostatic hyperplasia (BPH). Architectural and histologic differences in the glands of the TZ and the PZ are not well defined in the young, post-pubertal adult. The TZ is the exclusively site of BPH in the human prostate. In older individuals, the parenchymal cells of this zone frequently undergo extensive division and form nodular masses of epithelial cells. Since this zone is in close proximity to the proximity to the prostatic urethra, causing difficulty in urination. This condition is known as BPH.

### 2.3.4 The periurethral zone

It contains mucosal and sub-mucosal glands. In later stages of BPH this zone may undergo pathological growth, mainly from the stromal components. Together with the glandular nodules of the transitional zone, this growth causes increased urethral compression and further retention of urine in the bladder. The lobe classification system also divides the prostate into four different regions, the anterior lobe (roughly the same as the TZ), posterior lobe (comparable to the PZ), lateral lobes (spans all zones) and the median or middle lobe (CZ). This classification is usually used when describing the anatomy of the prostate (Cohen *et al.*, 2008).

## 2.4 HISTOLOGY

The prostate consists of approximately 70% glandular elements, while the

remaining 30% is a fibromuscular stroma. There are three distinct cell types in a normal prostatic gland: secretory (luminal) cells, basal cells, and neuroendocrine cells. The secretory cells line the glandular ducts and have a polarized intracellular organization, which is lost during carcinogenesis. The predominant secretory cells are characterized by the expression of androgen receptor (AR), cytokeratins 8 and 18, CD57, and prostate-specific antigen (PSA). The basal cells adjacent to the basal membrane contain a small number of cells considered the stem cells for the prostate gland. They express cytokeratins 5 and 14, CD44, and low levels of AR (Brawer *et al.*, 1985; Verhagen *et al.*, 1988; Sherwood *et al.*, 1990) Neuroendocrine (NE) cells of the prostate are spread among the epithelial cells and are of neurogeic origin. NE cells are androgen-independent and express chromogranin A and a variety of peptide hormones. NE cells have a role in both prostatic growth and differentiation as well as in the exocrine secretory process and pathogenesis of both prostatic cancer and hyperplasia (Bostwick and Brawer, 1987; Bostwick, 1996). The stromal cells in the prostate gland are composed of both smooth muscle cells and fibroblasts. The entire duct-acinar system, with the exception of the main lateral ejaculatory ducts, is lined by columnar secretory cells, separated from the prostatic stroma by a layer of basal cells belonging to the basement membrane (McNeal, 1981; Dixon *et al.*, 1999).

**2.5 SECRETIONS**

A slightly acid (pH 6.5) serous fluid in which several major secretory products can be identified, notably acid phosphatase, citrate, zinc, soluble fraction proteins, carbohydrates, electrolytes, polyamines, hormones, lipids and growth factors are contained in the ejaculate from the human prostate (Fair and Cordonnier, 1978; Zaichick *et al.*, 1996).

There are up to 57 major protein groups, of which 27 non-serum proteins (i.e. presumably excluded by the epithelial cells) have been identified. Major prostatic-

specific proteins are prostatic acid phosphatase (PAP), PSA, and prostate binding protein (PBP), which are expressed at pubertal and adult ages. Proteolysis is the major function of prostate secretion, being rich in exopeptidase and endopeptidase. The most extensively studied protease is PSA, also known as seminin, seminal protease or chymotrypsin-like protease (Neal *et al.*, 1992; Dixon *et al.*, 1999).



## 2.6 PROSTATE PATHOPHYSIOLOGY

There are a number of pathological conditions affecting the human prostate gland which ranges from prostatitis (acute and chronic), prostatic abscesses, benign nodular enlargement, prostatic infarct, prostate calculi and prostatic tuberculosis and tumors which are either benign or malignant (Djavan *et al.*, 2002a).

## 2.7 PROSTATITIS

Prostatitis is defined in its strictest sense to histological inflammation of the tissue of the prostate gland, although historically the term has been used loosely to describe a set of widely differing conditions (Collins *et al.*, 1998).

### 2.7.1 Incidence and Prevalence of Prostatitis

Men of any age can be affected by prostatitis, and it is estimated that 50% of men experience this disorder during their lifetime. Prostatitis is the most common urological disorder in men over the age of 50 and the third most common disorder in men younger than 50. The National Institutes of Health (NIH) reported that prostatitis accounts for 25% of all office visits involving the genitourinary system by young and middle-aged men (Collins *et al.*, 1998). The most common diagnoses are nonbacterial prostatitis and prostatodynia. Bacterial prostatitis (acute and chronic) accounts for less than 5-10% of cases. Acute bacterial prostatitis occurs most often in men under age 35, while chronic bacterial prostatitis primarily affects men between the ages of 40 and 70.(Collins *et al.*, 1998). Moreover, quality

of life for patients with chronic abacterial prostatitis (the most common type) is comparable to that of patients with
myocardial infarction, angina, or active Crohn disease(Krieger *et al.*, 2000).

### 2.7.2 Risk Factors and Causes of Prostatitis

The risk factors of prostatitis include bladder outlet obstruction, (e.g., stone, tumour), diabetes mellitus, a suppressed immune system, and urethral catheterization (Doble, 2000). Some sexually transmitted diseases (STDs) increase the risk of developing bacterial prostatitis. Bacterial prostatitis is caused by the growth of bacteria normally found in prostatic fluid, such as *Escherichia coli* and *Klebsiella* (Persson and Ronquist, 1996).Urine reflux entering the prostate can also cause the condition. There is no known cause of nonbacterial prostatitis or prostatodynia, but atypical organisms (e.g., viruses, chlamydial organisms) have been suggested.

## 2.8 LOWER URINARY TRACT SYMPTOMS (LUTS)

Lower urinary tract symptoms (LUTS) are term used to describe a range of symptoms related to problems of the lower urinary tract (bladder, prostate and urethra). LUTS are broadly grouped into voiding (obstructive) symptoms or storage (irritative) symptoms. It affects 15 – 60% of patients greater than 40 years which poses public health burden (Skolarikos *et al.*, 2004; Parsons, 2010).

### 2.8.1 Causes of Lower Urinary Tract Symptoms

LUTS, especially if pain on urination (dysuria) is also present, may be caused by an acute problem such as a urinary tract infection, inflammation of the prostate gland (prostatitis) or less commonly, bladder stones.

Storage symptoms or overactive bladder (OAB) – defined as urgency, with or without urge incontinence, usually with frequency and nocturia may indicate an underlying chronic medical condition such as obesity, diabetes (high glucose levels in the blood), high blood pressure or obstructive sleep apnoea, or be due to

the effects of smoking (Su *et al.*, 1996; Kuritzky, 2004; Kuo, 2007). Voiding symptoms are usually due to a blockage of the outlet of the bladder making it more difficult to pass urine. The blockage may be caused by an enlarged prostate gland or a urethral stricture (scarring of the urethra (Su *et al.*, 1996; Kuritzky, 2004; Kuo, 2007)



### 2.8.2 Prevalence of Lower Urinary Tract Symptoms

Globally, various studies have been conducted reporting racial difference in LUTS prevalence (Cotran *et al.*, 1999; Engström *et al.*, 2003). Prevalence of 41.0% of moderate-severe LUTS among African-American men in Michigan was significantly higher than that of Caucasian-American men in Minnesota (34.0%) (Sarma *et al.*, 2003). A hospital-based study among Nigerians reported a prevalence of 88% which is compatible to 84.4% in another hospital-based study in Ethiopia but is higher than 40% reported in India (Rao *et al.*, 2004; Berhanu, 2008; Adegun and Popoola, 2011). Recent data from a population-based study in the capital of Ghana reported a prevalence of 19.9%, 62.3% and 13.3% using the international prostate symptom score (IPSS), PSA and an enlarged prostate on DRE respectively which is higher than the Triumph project in the Netherlands as well as a population-based study in Nsukka, south-eastern Nigeria and UK (Verhamme *et al.*, 2002; Ezeanyika *et al.*, 2006; Chokkalingam *et al.*, 2012).

### 2.8.3 Treatment of Lower Urinary Tract Symptoms

When deciding on the best treatment, factors such as the type of LUTS, the cause of the LUTS and other factors such is the degree of bother caused by the LUTS and lifestyle factors are taken into account. Lifestyle changes or managing other health conditions such as diabetes or hypertension may be the first option. If symptoms are not very bothersome, the best approach may be to monitor the LUTS through regular checks with the physician. If the LUTS are bothersome, oral medicines such as alpha-blockers, anticholinergics, phosphodiesterase inhibitors and 5-

alpha reductase inhibitors are used. The medicine suggested by the doctor will depend on the type and cause of LUTS. Surgery is the most effective treatment for relieving symptoms caused by an enlarged prostate but it has potential side-effects (Madersbacher *et al.*, 2004; Gacci *et al.*, 2012; Oelke *et al.*, 2013).

## 2.9 BENIGN PROSTATIC HYPERPLASIA (BPH)

Benign prostatic hyperplasia is used to indicate that a patient has an enlarged prostate or that the patient has urinary symptoms that are believed to be the result of bladder outlet obstruction by the prostate. This can lead to a host of many complications such as urinary retention, urinary hesitancy, and frequent urination as well as increased risk of urinary tract infections (Djavan *et al.*, 2002a). Peak urinary flow rate (Qmax) has also been used by many investigators to help define the presence of BPH (Barry *et al.*, 1993; Barry, 2001).

There is a poor correlation between histologic changes within the gland, the size of the prostate, and the severity of urinary symptoms (Barry *et al.*, 1993). These confounding relationships may be attributed in part to physiologic changes in the aging bladder, alterations in the volume and pattern of urine production, and/or other unspecified factors (Jacobsen *et al.*, 2001).

### 2.9.1 Etiology of Benign Prostatic Hyperplasia

Androgens (testosterone and its related hormones) are considered to play a permissive role in BPH (Schultheiss *et al.*, 2004). Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator of prostatic growth and also of BPH. The use of 5-reductase inhibitor as therapy markedly reduces the DHT content of the prostate and in turn reduces prostate volume. There is growing evidence that both estrogens and inflammation play roles in the etiology of BPH (Di Silverio *et al.*, 2003; Kramer *et al.*, 2007). Environmental factors, lifestyles, racial, cellular and genetic factors, were scrutinized for the possibility of causeeffect relationships with BPH. Numerous lifestyle factors have been studied, such as

physical exercise, cigarette smoking, alcohol consumption, and coffee consumption. Family history, hypertension, racial differences, sexual activity, obesity, and metabolic syndrome were other factors being studied (Meigs *et al.*, 2001; Dahle *et al.*, 2002; Kang *et al.*, 2004).

### 2.9.2 Histopathology of Benign Prostatic Hyperplasia

The nodularity attributed to glandular proliferation and to fibrous or muscular perforation of the stroma serves as hallmark of BPH. These elements vary from nodule to nodule in different proportions, ranging from purely stromal fibromuscular nodules to fibro epithelial nodules with glandular predominance. Glandular proliferation takes the form of aggregations of small to large to cystically dilated glands, lined with two layers, an inner columnar and an outer cuboidal or flattened epithelium, based on an intact basement membrane. The diagnosis of BPH cannot usually be made on needle biopsy, as the histology of glandular or mixed glandular-stromal nodules of BPH cannot be appreciated on this limited sampling. Two other histological changes are associated with BPH, namely foci of squamous metaplasia and small areas of infarction (Scattoni *et al.*, 1999; Milord *et al.*, 2000).

### 2.9.3 Prevalence of Benign Prostatic Hyperplasia

The reported prevalence of microscopic, macroscopic and clinical BPH differs significantly. Autopsy studies conducted in Western countries indicate that 40% of men in their 50s and up to 90% of men in their 80s have histological evidence of BPH (Berry *et al.*, 1984). It is estimated that about half of these men will have detectable prostatic enlargement and that half of those will seek medical attention because of LUTS (McConnell, 1994). Most American studies of BPH prevalence have been concentrated on white men but there does not appear to be an increased risk of BPH in African Americans (Platz *et al.*, 2000). Researchers in other countries have studied the prevalence of BPH using symptom

questionnaires and have found similar results (Bosch *et al.*, 1995; ChicharroMolero *et al.*, 1998; Madersbacher *et al.*, 1998).

In a population-based study of West African men, the observed age-standardized prevalence of prostate enlargement by DRE was 62.3%, that of selfreported moderate-to-severe LUTS was 19.9% and those estimated from PSA values alone and a regression model based on age, PSA and DRE were 35.3 and 29.0%, respectively. The prevalence of BPH and/or LUTS increased with age for all case definitions except for DRE-detected BPH (Chokkalingam *et al.*, 2012).

### 2.9.4 Risk Factors of Benign Prostatic Hyperplasia

Majority of men around the world once experienced BPH as they age, predominantly in men over the age of 70 years. The occurrence of histologically diagnosed prostatic hyperplasia rises from 8 percent in men ages 31% to 40%, to 40% to 50% in men ages 51%to 60%, to over 80% in men older than 80 years (Djavan *et al.*, 2002a). A variety of other factors have been explored in men with BPH in addition to aging. Platz *et al*. studied the role of racial or ethnic origin in the prevalence of BPH among American male health professionals (Platz *et al.*, 2000). The role of a variety of lifestyle factors in the development of BPH has also been investigated. Three studies have addressed the effect of cigarette smoking on prostate size and BPH (Nukui, 1997; Signorello *et al.*, 1999; Meigs *et al.*, 2001).

### 2.9.5 Diagnosis of Benign Prostatic Hyperplasia

History should be performed in men with bothersome lower urinary tract symptoms, to establish the severity of symptoms, evaluate for causes other than BPH, and identify contraindications to potential therapies. The American Urological Association (AUA) Symptom Index is a validated seven-question instrument that can be used to objectively assess the severity of BPH(American Urological Association, 2007). Symptomatic men have a digital rectal

examination to assess the size and contour of the prostate (American Urological Association, 2007). A palpable nodule suggests prostate cancer and requires biopsy. The AUA recommends urinalysis for all men presenting with lower urinary tract symptoms (American Urological Association, 2007).

### 2.9.6 Treatment of Benign Prostatic Hyperplasia

The size or growth of the prostate is not a core problem in BPH, but the bothersome clinical symptoms and related complications. There is a wide range of treatment preferences for BPH. Depending on the severity of the disease, recommendations for therapy are given by various guidelines, and ranges from watchful waiting to open prostatectomy (Berges *et al.*, 2003; Committee, 2003; Madersbacher *et al.*, 2004). Traditionally, medical therapy with $\alpha$1-adrenergic antagonists has been regarded as the first line therapy due to their rapid onset of action and mild and infrequent adverse events (Lepor *et al.*, 1996).

The alternative treatment options for patients with large prostate volumes (>3040ml).are 5$\alpha$-reductase inhibitors (5ARI) (Boyle *et al.*, 1996; Roehrborn *et al.*, 2005). Finasteride treatment has been recommended to reduce the relative risk of needing surgery or developing AUR by 43% to 60%, compared to placebo (Roehrborn *et al.*, 2005). A dual inhibitor of 5$\alpha$-reductase types 1 and 2, Dutasteride gives the same risk reduction benefit.

Both $\alpha$1-adrenergic antagonists and 5ARIs are now recommended first line therapies, as single modalities or in combination (Coffey and Isaacs, 1981; Madersbacher *et al.*, 2004). Surgical techniques such as transurethral resection of the prostate are still appropriate for some patients (Brown and Das, 2002).

## 2.10 CANCER OF THE PROSTATE (PCa)

Cancers are defined as uncontrolled growth and consequent spread of cells to other parts of the body (Gabriel, 2007). All kinds of cells can go through such malignant changes and become cancers, nonetheless only epithelial cells can

become carcinomas. The normal cycle of the cell is disrupted and the new "tumour" cells overgrow in a confined region at first, then spread to nearby tissue and lastly to other parts of the body via the lymphatic system and vascular system (Corner and Bailey, 2001; Ayala and Ro, 2007). Prostate cancer is an adenocarcinoma that may be slow growing, aggressively evolving and metastising predominantly in the bones and lymph nodes (Grover and Martin, 2002). Prostate Cancer is progressively becoming a significant health problem among men in the world (Ferlay *et al.*, 2010; Lozano *et al.*, 2013). About 0.9 million prostate cancer cases and 0.26 million deaths from prostate cancer result yearly in the world (Ferlay *et al.*, 2010).

There is high incidence in Europe and North America, which ranges from around 50 to 135 cases per 100.000 person-years, against less than 5 per 100.000 in the low-incidence regions of south-eastern Asia (Hsing and Devesa, 2001). Majority of men with pathologic evidence of cancer of the prostate are not mostly clinically diagnosed with the disease. However men die with prostate cancer than as a direct result of the disease due to the indolent nature of most prostate (Hsing and Devesa, 2001).

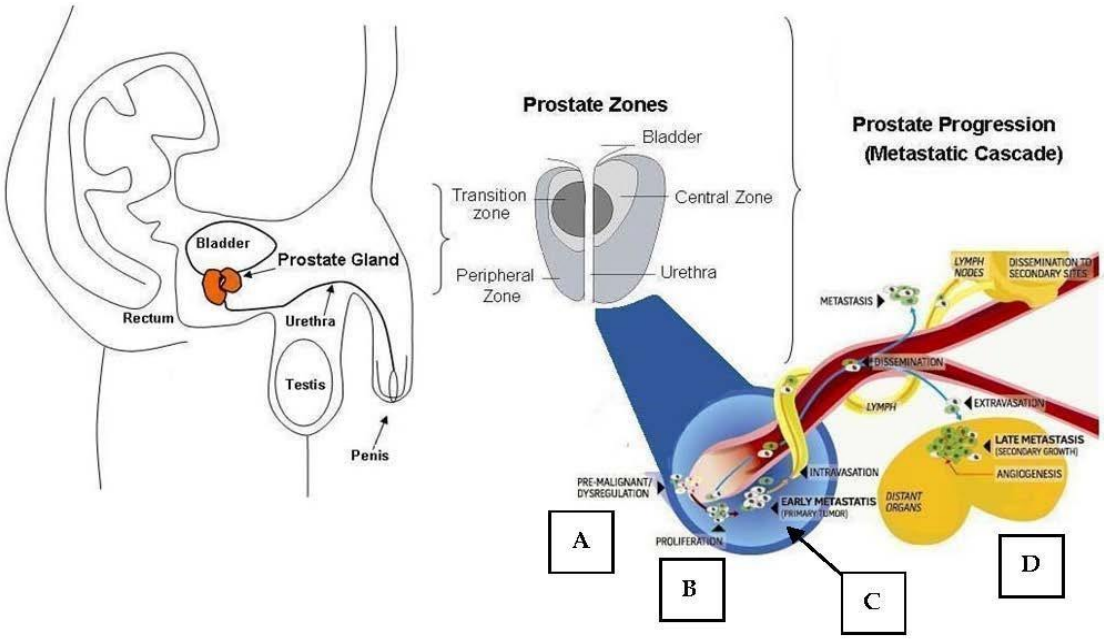


**Figure 2.2 Diagram showing prostate cancer occurrence in the various zones and it progression**
**Source: prostate-cancer-ribbon.blogspot.com**

### 2.10.1 Prostate Cancer- World Health Nuisance

Prostate malignancy is the second most commonly diagnosed cancer in men in the world (899,000 cases or 13.6% of male cancers) and the fifth most frequent cancer (Ferlay *et al.*, 2010). The rate of incidence of prostate cancer differ by region and continent, largely due to changes in the uptake of the prostate cancer screening practice and subsequent biopsy that are common in Europe and North America (Ferlay *et al.*, 2010; Lozano *et al.*, 2013).

There are high mortality rates predominantly among black populations (SubSaharan Africa, 18-19/100,000 and Caribbean, 26.3/100,000 ), very low in Asia, and intermediate in Europe and Oceania (Ferlay *et al.*, 2010; Lozano *et al.*, 2013). Recent data reported show more rapid increasing incidence of PCa in Asia than high-risk countries such as in Japan, Singapore, and even in some Chinese cities, such as Beijing, Shanghai, and Hong Kong (Pu *et al.*, 2004). In Singapore Chinese, the age-adjusted incidence rate has increased from 6.6 to 14.4 per 100,000 personyears from 1978 to 1997 (Pu *et al.*, 2004).

### 2.10.2 Global Incidence of incidence of prostate cancer

In 2008, according to the International Agency for research on Cancer (IARC), prostate cancer was the leading male cancer after lung cancer with an age standardized rate of 28.5/100 000 worldwide (Ferlay *et al.*, 2010). However GLOBOCAN estimations have relevant limits related mostly to the facts that the data collected in the developing countries were often derived from registries covering Hospitals, small subnational areas or only major cities (Jedy-Agba *et al.*, 2012). These estimates were mostly deduced from results of Ibadan (Nigeria) and Kampala (Uganda). Only 26% of the world population was covered by

tumor registries in 2006 and this figure was even lesser in Africa (11%) and Asia (8%) (Parkin, 2006). Prostate cancer incidence of 93.8/100000 was reported in Cameroon by Angwafo *et al* (Angwafo *et al.*, 1993) while in Lagos, Nigeria Osegbe *et al* reported an incidence of 127/100000. These findings are inconsistent with data presenting a higher incidence of prostate cancer in black male in Jamaica where the reported incidence was 304/100000 (Glover *et al.*, 1998) and in the US (Howlader *et al.*, 2011). A recent review shows that in low and middle income countries facing a high prevalence on non-communicable diseases – including cancers (Lachat *et al.*, 2013).

### 2.10.3 Staging and Classification of Prostate Cancer

The stage of a cancer is a description of the extent the cancer has spread. The stage often takes into account the size of a tumour, how deeply it has penetrated, whether it has invaded adjacent organs, the number of lymph nodes it has possibly metastasized to, and whether it has spread to distant organs. There is a uniform system for classifying prostate cancer based on its stage (Meyer and Bootz, 2003). The Tumor, Nodes, Metastases (TNM)classification describes the anatomic extent of cancer and is based on the premise that the choice of treatment and the chance of survival are related to the extent of the tumour at the primary site (T), the presence or absence of tumour in regional lymph nodes (N), and the presence or absence of metastasis beyond the regional lymph nodes (M). Tumours must be classified before treatment (ie, clinical staging [cTNM]) and after surgical intervention (ie, pathologic staging [pTNM]). T is usually divided into 4 major parts (T1 to T4), expressing increasing size or spread of the primary tumour. N and M comprise at least 2 categories each (0 and 1— absence or presence of tumour respectively). A number of sites have subcategories, with up to 4 subdivisions of T1 and T4 and 6 subdivisions of pN1 in breast carcinoma and 3 subdivisions of M in prostate carcinoma (Samowitz *et al.*, 2001).

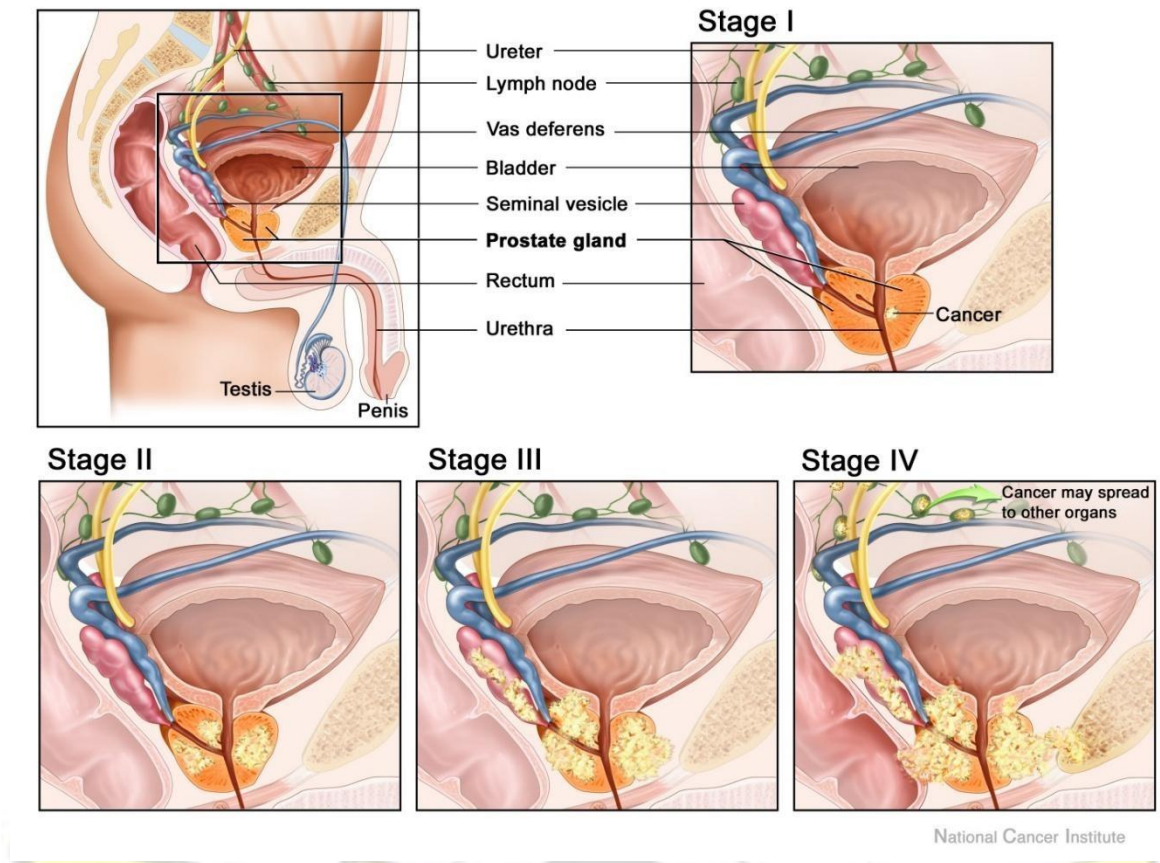



**Figure 2.3 Diagram showing the different stages of prostate cancer Source: www.cancer.gov**

## 2.11 RISK FACTORS OF PROSTATE CANCER

### 2.11.1 Age and Ethnicity

Prostate cancer has been known as a disease of elderly men. Diagnosis is rare before the age of 50 years, but after this age incidence and mortality rates both increase almost exponentially. The Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence rates in 1990 were 45.2 per 100,000 men age 50 to 55 years, 337.5 per 100,000 for those age 60 to 64 years, and more than 1,000 per 100,000 for men older than 65 years. The lifetime probability at birth of being diagnosed with prostate cancer in the United States has been estimated to be 8% (Haas and Sakr, 1997).

The results of autopsy studies, however, suggest that the probability of developing histologic evidence of prostate cancer is even higher. Moreover, for the period from 1992 to 1999, the mortality rate for African Americans was 2.3

times higher than for whites, 3.3 times higher than for Hispanics, and 5 times higher than for Asians/Pacific Islanders. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program indicate that a higher percentage of African Americans present with metastatic disease, but they are not more likely than whites to present with high-grade lesions (Clegg *et al.*, 2002). For the last 3 decades, 5-year survival rates have improved significantly for African Americans, but they remain lower than for whites (93% vs. 98% for cases diagnosed from 1992 to 1998), although the gap between the 2 races appears to have narrowed (Bianco *et al.*, 2002; Ward *et al.*, 2004)

### 2.11.2 Family History and Genetic Susceptibility

The risk of developing prostate cancer has been identified to double for men who have a father or brother affected by prostate cancer, and the risk increases further when multiple first-degree relatives are affected (Steinberg *et al.*, 1990; Carter *et al.*, 1992) Epidemiologic studies indicate that men with a positive family history are diagnosed at an earlier age—on average 6 to 7 years earlier—than those without affected first-degree relatives (Bratt, 2002). These studies estimate that 5% to 10% of all prostate cancer cases and up to 40% of those occurring at <55 years of age may have a hereditary basis (Bratt, 2002). Other than being diagnosed at an earlier age, hereditary prostate cancer does not differ clinically from disease that arises sporadically. The familial clustering of prostate cancer may be caused by inheritance of a susceptibility gene, but it may also be caused by exposure to common environmental factors or simply from chance alone because of the high incidence of this malignancy. There have been 7

susceptibility loci for prostate cancer identified, but demonstrating linkage of currently known candidate genes has proved to be quite difficult (Simard *et al.*, 2002). Using linkage analysis based on a genome-wide search, Smith *et al.* (2005) first mapped prostate cancer susceptibility to the hereditary prostate cancer HPC1 locus on the long arm of chromosome 1 in high-risk families from Sweden and the

United States. In these families, prostate cancer developed at an early age, affected ≥5 family members, and spanned 2 generations. However, strong evidence of linkage was found in a subset of 8 families; in 2 of these families, a gene within the HPC1 locus—the 2′, 5′- oligoisoadenylate synthetase–dependent ribonuclease L 27 (RNASEL) gene—showed deleterious germ line mutations (Carpten *et al.*, 2002). The RNASEL gene is believed to be a tumor suppressor gene that regulates cellular proliferation and apoptosis (Simard *et al.*, 2002).

### 2.11.3 Diet

Several studies have identified diet as an important risk factor for prostate cancer. An influence of diet and environment on prostate cancer risk is suggested by studies of Japanese men who relocated to the United States (Shimizu *et al.*, 1991; Whittemore *et al.*, 1995; Cook *et al.*, 1999). The Western lifestyle, particularly the higher intake of fat, meat, and dairy products, may be responsible for conveying the higher prostate cancer risk. In a multicenter study of dietary factors, prostate cancer risk was associated with total fat intake in whites, African Americans, and Asian Americans About 10% to 15% of the difference in prostate cancer incidence among these ethnicities was attributed to differences in saturated fat intake (Shimizu *et al.*, 1991; Cook *et al.*, 1999). Beef and dairy products for instance are major sources of dietary branched fatty acids. An enzyme that plays a key role in the peroxisomal oxidation of these fatty acids (α-methyl-coenzyme-M-reductase) is upregulated in prostate cancer but not in the healthy prostate (Shirai *et al.*, 2002). The lower incidence of prostate cancer in Japan than in the United States may be related to the difference in intake of soybean products that are rich in isoflavones, such as genistin and daidzin (Shirai et al., 2002).

### 2.11.4 Hormonal and other factors

The growth and differentiation of the prostate is controlled by androgen. Men

who underwent castration before puberty and those with congenital abnormalities in androgen metabolism do not develop prostate cancer(Haas and Sakr, 1997). Moreover, androgen blockade with 5$\alpha$-reductase inhibitors is also effective in causing involution of benign prostatic hyperplasia (BPH), whereas androgen ablation either surgically or with luteinizing hormone–releasing hormone agonists is an effective strategy in the treatment of advanced prostate cancer (Hsing *et al.*, 2003). Recent results from epidemiologic studies suggest that a high body mass index (BMI) and bone mass may be associated with prostate cancer (Clegg *et al.*, 2002; Calle *et al.*, 2003).

### 2.11.5 Protective factors

According Miller *et al.* (2002) epidemiologic and case-control studies suggest that consumption of tomatoes and its products is associated with a lower risk of prostate cancer. It has also been pointed out that lycopene, an antioxidant in raw and processed tomato products, may be responsible for the lower risk, although other carotenoids and phytochemicals in these products may also contribute to the benefit. A report from Giovannucci *et al.* (2002) indicates that in a study of 2,481 men, high levels of lycopene consumption were associated with a 16% lower risk of prostate cancer as compared with consumption of its small amounts. Studies by Vogt *et al.* (2003) and (Wintherington *et al.*, 1998) have suggested that selenium offers some level of protection against prostate cancer.

Selenium is an essential trace element found mainly in fish, grains and meat.

## 2.12 DIAGNOSIS OF PROSTATE CANCER

The main diagnostic tools that are currently used to obtain evidence of PCa include direct rectal examination (DRE), serum concentration of prostate specific antigen (PSA) and trans rectal ultrasonography (TRUS). Its definite diagnosis however, depends on the presence of adenocarcinomas in prostate biopsy cores

or operative specimens. Histopathological examination also allows grading and determination of the extent of the tumour (Carvalhal *et al.*, 1999).

### 2.12.1 Digital Rectal Examination (DRE)

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is large. A suspect DRE is an absolute indication for prostate biopsy. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (Richie *et al.*, 1993). A suspect DRE in patients with a PSA level of up to 2ngmL-1 has a positive predictive value of 5-30% (Carvalhal *et al.*, 1999).

### 2.12.2 Prostate-Specific Antigen (PSA)

The measurement of PSA level has revolutionized the diagnosis of PCa (Stamey *et al.*, 1993). Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. However, the level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (Catalona *et al.*, 1994). The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa (Table 2.1). This means there is no universally accepted cut-off or upper limit. The finding that many men may harbour PCa, despite low levels of serum PSA, has been underscored by the findings from a US prevention study (Thompson *et al.*, 2004).

**Table 2.1 Gives the rate of PCa in relation to serum PSA for 2,950 men in the placebo arm and with normal PSA values.**

| PSA Level (ngml) | Risk of PCa |
|---|---|
| 0 - 0.5 | 6.60% |
| 0.6 - 1.0 | 10.10% |

| | |
|---|---|
| 1.1 - 2.0 | 17.00% |
| 2.1 -3.0 | 23.90% |
| 3.1 - 4.0 | 26.90% |

### 2.12.3 Free/Total PSA ratio (F/TPSA)

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to discriminate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels between 4 and 10ngmL-1 and a negative DRE. In a prospective multi-centre trial, PCa was found on biopsy in 56% of men with an f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25 (Catalona *et al.*, 1994). Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA. In addition, assay characteristics may vary and concomitant BPH in

large prostates may result in a dilution effect' (Stephan *et al.*, 2006).

## 2.13 PROSTATE BIOPSY

### 2.13. 1 Baseline biopsy

The need for prostate biopsies is usually determined on the basis of the PSA level and/or a suspicious DRE. The patient's biological age, potential comorbidities and the therapeutic consequences are also vital considerations. It is now considered the standard of care to perform prostate biopsies guided by ultrasound. Although a trans-rectal approach is used for most prostate biopsies, some urologists prefer to use a perineal approach. The cancer detection rates of perineal prostate biopsies are comparable to those obtained of trans rectal

biopsies (Hara *et al.*, 2008; Takenaka *et al.*, 2008).

### 2.13.2 Repeat biopsy

The indications that usually call for repeat biopsy include: rising and/or persistent PSA, suspicious DRE; atypical small acinar proliferation (ASAP). The optimal

timing of a repeat biopsy is uncertain. It depends on the histological outcome of the baseline ASAP biopsy and the index of a persistent suspicion of PCa (high or dramatically rising PSA, suspect DRE, family history). The later the repeat biopsy is done, the higher the detection rate (Epstein and Herawi, 2006). High-grade prostatic intraepithelial neoplasia (PIN) as an isolated finding is no longer considered an indication for re-biopsy (Moore *et al.*, 2005). A repeat biopsy should therefore be prompted by other clinical features, such as DRE findings and PSA level. It has however been known that if PIN is extensive (i.e. in multiple biopsy sites), it could be a reason for early re-biopsy as the risk of subsequent prostate cancer is slightly increased (Merrimen *et al.*, 2009). Meanwhile, it has been suggested that if clinical suspicion for prostate cancer persists in spite of negative prostate biopsies, MRI may be used to investigate the possibility of an anterior located prostate cancer, followed by TRUS or magnetic resonance imaging (MRI)-guided biopsies of the suspicious area (Merrimen *et al.*, 2009).

### 2.13.3 Sampling sites and number of cores

On baseline biopsies, the sample sites should be as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. These should be chosen on an individual basis.

Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive (Moran *et al.*, 2006). The British Prostate Testing for Cancer and Treatment Study has also recommended 10-core biopsies (Donovan *et al.*, 2003).

### 2.13.4 Seminal vesicle biopsy

Indications for seminal vesicle biopsies are poorly defined. At PSA levels > 15-20 ng/mL, a biopsy is only useful if the outcome will have a decisive impact on treatment, i.e. if the biopsy result rules out radical removal for tumour

involvement or radiotherapy with intent to cure. At PSA levels > 15-20 ngmL-1, the odds of tumour involvement are 20-25% (Linzer *et al.*, 1996).

### 2.13.5 Transition zone biopsy

Transition zone (TZ) sampling during baseline biopsies has been linked to the provision of a very low detection rate. TZ sampling has therefore been suggested to be confined to repeat biopsies (Pelzer *et al.*, 2005).

### 2.13.6 Diagnostic Transurethral Resection of the Prostate (TURP)

The use of diagnostic TURP instead of repeat biopsies is of minor importance. Its detection rate is no better than 8% and makes it a poor tool for cancer detection (Zigeuner *et al.*, 2003).

## 2.14 NOMOGRAM

Nomograms are visual and mathematical tools that allow clinicians, researchers, patients, and members of a population to give relative context and probabilities related to developing clinical outcomes. Nomograms can predict for the probability of a clinical outcome based upon the presence of pertinent risk factors, confounders, and predictor variables (Iasonos *et al.*, 2008). All nomograms are based on regression models that are used to predict for outcomes. The type of regression model used for a nomogram depends upon the scale of measurement of the outcome. Logistic regression, multinomial logistic regression, and proportional odds regression are used to build nomograms for categorical and ordinal outcomes (Iasonos *et al.*, 2008). Nomograms use continuous scales to calculate the continuous probability of a particular outcome. This obviates the effect of spectrum bias that might be operational when predictors are stratified. Spectrum bias consists of a forced central effect applied to the entire range of observations that decrease within the limits of a given category (Shariat *et al.*, 2008; Kuo *et al.*, 2013).

Nomograms provide superior individualized disease-related risk estimations that facilitate patient management-related decisions (Iasonos *et al.*, 2008). Nomograms are the most accurate and have the best discriminating

characteristics currently available tools for predicting outcomes in patients with prostate cancer (Iasonos *et al.*, 2008; Shariat *et al.*, 2008).Several models—nomograms, risk groupings, artificial neural networks, probability tables, and logistic regression analysis—have been developed to help predict a positive prostate biopsy in men being evaluated for prostate cancer (Chun *et al.*, 2007; Benecchi *et al.*, 2008; Lughezzani *et al.*, 2012). The first nomogram developed by Partin and Oesterling to predict the risks of nomogram confined disease and involvement of seminal vesicles and iliac lymph nodes in patients that underwent radical retropubic prostatectomy, included the biopsy Gleason score, clinical stage and serum PSA levels (Partin and Oesterling, 1994).

# CHAPTER 3

## 3.0 MATERIAL AND METHODOLOGY

### 3.1 Study Design/Setting

The study was prospective hospital-based cross-sectional one which was conducted from December 2014 to March, 2016 at the Surgery Department (Urology Unit) of the Komfo Anokye Teaching Hospital (KATH) in the Ashanti Region of Ghana, which has an average population of 4,780,380 (Ghana Statistical Service, 2012). Komfo Anokye Teaching Hospital is the second largest tertiary hospital in Ghana with a thousand bed capacity and is a major referral centre that provides health services to five regions namely Ashanti, BrongAhafo, Northern, Upper East and Upper West of Ghana. The hospital also

receives referrals from other regions such as Central, Eastern, Western and some parts of the Volta region of Ghana and this gives fair representation of the Ghanaians population.

### 3.2 Selection of Study Participants

Non-probability convenience sampling technique was used to recruit 241 patients visiting the urology unit at Department of Surgery, KATH. Indications for TRUS biopsy were an elevated total PSA, defined as > 4.0ng/ml or a digital rectal examination, abnormal or suspicion of cancer, defined as the presence of a nodule, areas of induration or asymmetry in the size lateral lobes.

#### 3.2.1 Data Collection

Structured questionnaire was used to elicit socio-demographics such as age, educational status, marital status and religion. Furthermore, various identified risk factors including smoking, family history of prostate cancer, number of sexual partners, alcohol, marriage duration, hypertension, diabetes, age of first sexual intercourse, heart attack as well as rheumatoid arthritis was noted.

Trained interviewers used the International Prostate Symptoms Scores (IPSS), which adds a quality of life question to the American Urology Association symptom index to determine the extent to which patients are troubled by their symptoms. This validated tool contains eight questions. Seven falls under the LUTS categories and one pertains to quality of life (Kupelian *et al.*, 2006; Cruz and Desgrandchamps, 2010). It has sound internal consistency, as measured by a Cronbach's alpha coefficient of 0.89. The seven questions of the IPSS comprise one on post-micturition symptoms, three on voiding symptoms and three on bladder storage symptoms. The sum of the IPSS was obtained by combining the sum of the answers for questions 1 to 7. This symptom category allows the physician to understand the degree of inconvenience that patients perceive their symptoms to have caused. Significant LUTS is usually defined as a total IPSS of at least 8 (moderate or severe) (Kupelian *et al.*, 2006).

### 3.3 Inclusion Criteria

Recruited patients were male patients aged 40 years and above who presented to the urology clinic KATH for the first time with suspected prostate disease. Patients who had PSA-based indications for prostate biopsy (elevated serum total PSA levels) and gave consent were included

### 3.4 Exclusion Criteria

Male patients who were below 40 years of age who presented with LUTS were excluded. Patients taking Finasteride, Dutasteride or any drugs used in the treatment of prostate disease and had past history of prior biopsy, PSA or equivocal biopsy results with no confirmatory immuno-histopathologic staining were excluded. Patients who failed to give consent were excluded from the study.

### 3.5 Sample Size Justification

The estimated sample size for the cross-sectional prospectively was calculated to be 241 as described by Kish-Leslie formula to detect a 5% statistical difference with α-error of 5%, acceptable β-error of 20%, and a statistical power of 80%.

The sample size (n) was determined using the Kish-Leslie formula;

$n = [T^2 \times p\ (1-p)]/m^2$;

Where, T is the confidence level (CI) at 95%, p is the average proportional rate of prostate disorders in Ghana (Hsing *et al.*,

2014 Laryea *et a.,l* 2014, Chokkalingam *et al*, 2012 m

is the margin of error.

Therefore Average p = 0.190 t = 1.96 at 95% CI, m= 0.05 (5%)

Thus, $n = [1.96^2 \times 0.196(1- 0.196] \div 0.05^2$

$= (3.842 \times 0.196 \times 0.804) \div 0.0025$

$= 242$

### 3.6 Ethical Consideration

Ethical Approval (CHRPE/AP/243/15) for the study was obtained from the Committee on Human Research, Publication and Ethics of the School of Medical Sciences (SMS), Kwame Nkrumah University of Science and Technology (KNUST) as well as ethical review board of the Komfo Anokye Teaching Hospital (KATH). Participation was voluntary and written informed consent was obtained from each participant according to Helsinki declaration. Respondents were assured that the information gathered was to be used strictly for research and academic purpose only. In addition, respondents were given the freedom to opt out any time they thought they could not continue with the study

### 3.7 Digital Rectal Examination

Physical examination of the patients was carried out by an experience Urologist who performed a DRE to evaluate prostate shape, size, consistency, induration, nodularity, symmetry, edge, tenderness, or the presence of a rectal mass. An enlarged, firm, mobile rectal mucosa, smooth surface, well defined margins and symmetrical prostate was indicative of benign prostatic hyperplasia. An enlarged, hard masses or indurated nodular masses were suggestive of prostate cancer.

### 3.8 Prostate Volume

Prior to prostate, biopsy trans rectal ultrasonography was performed using an endocavitary convex probe with a 6.5MHz transducer. Measures of the triaxial distances of the prostate were taken in its larger diameter and total volume was calculated using the formula; volume 0.52 x transverse diameter x anterior posterior diameter x longitudinal diameter.

#### 3.8.1 Collection of Samples

Prior to ultrasonography, 5ml of venous blood specimen was collected from the study participants between under aseptic conditions, at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. About 5 mL of blood was drawn from every

study participant and was dispensed into vacutainer serum separator tube. The collected blood sample was then transported to the Chemical Pathology laboratory at Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. The blood samples were centrifuged at 4000 r.p.m for 10 minutes. Sera obtained were separated and total PSA assayed using the electrochemiluminiscence method (Cobas e411 Analyzer, Roche Diagnostics, Germany) as illustrated by figure 3.1

### 3.8.2 Test Principle

The Cobas e411 analyzer uses the sandwich principle for the measurement of total PSA with the duration of 18 minutes for the assay

**1st incubation**: 20 μL of sample, a biotinylated monoclonal PSA-specific antibody, and a monoclonal PSA-specific antibody labeled with a ruthenium complexa) reacted to form a sandwich complex.

**2nd incubation:** After addition of streptavidin-coated micro particles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin

The reaction mixture is aspirated into the measuring cell where the micro particles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent barcode

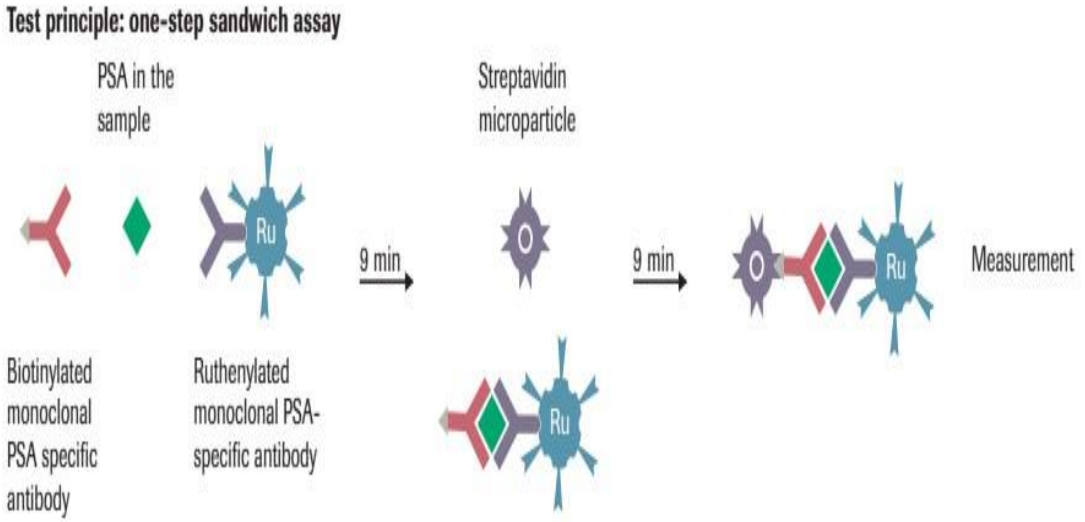



**Figure 3.1 A diagram showing the principle of PSA measurement by Cobas e411 (Roche diagnostics, Germany).**

### 3.9 Prostate Specific Antigen Density (PSAD)

The prostate specific antigen density was calculated as PSA (ng/ml) divided by the prostate volume (ml) and expressed as ng/ml/ml. Value of PSAD taken to be indicative of cancer was >0.15 ng/ml/ml

### 3.10 Prostate Biopsy

Prostate biopsy was performed when PSA was more than 4.0ng/mL or when abnormal digital rectal examination (DRE) or mass lesions on imaging studies of prostate were detected. Trans rectal biopsies of the prostate were also performed by an experienced urologist with an 18-gauge automatic Tru-cut biopsy needle (Sonocare, Shanghai P.R.C) trans rectal ultrasonography. Ultrasound-guided trans-rectal 6-12 core prostate biopsy was performed according to prostate volumes. The technique was performed systematically to cover lateral and medial aspects of the apex, mid gland, and base of the right and left prostate lobes. They were all examined by a board-certified pathologist at the department of Pathology, Komfo Anokye Teaching Hospital. The two pathologists were blinded from the clinical indicators of the patients.

### 3.11 Statistical Analysis

Descriptive statistics were performed for demographic variables, expressed as mean ± standard deviation (SD) in the case of continuous variables with normal distribution. In case of asymmetrical distribution, the median and inter quartile (IQR) values were used, whereas categorical variables were expressed as Figure and proportion.. Comparisons of variables (age, prostate volume, PSA and PSAD) between the patients with and without prostate cancer were done with ttest, Mann-Whitney u-test, chi ($\chi$ 2) tests, or Fisher exact test was used to compare non-parametric values. The positive predictive value, negative

predictive value, sensitivity and specificity for the test were calculated for total PSA, PSAD, DRE and test combinations. Chi Squared was used to test the differences in frequency. For evaluation of PSA, PSAD and DRE, we used the receiver operating characteristics curve analysis and areas under the curve (AUC). To determine whether the combination of these four biomarkers into a single score could improve the diagnostic performance, individual data were scored as 0 or 1 whether they were below or above the threshold previously determined with the ROC curves. This constituted the bioscore, which therefore ranged between 0 (all four markers below their respective thresholds) and 4 (all four markers above threshold). Multiple logistic-regression analysis was used to select independent predictors. P-values less than 0.05 were also considered

significant.

#### 3.11.1 Logistic Regression

Logistic regression is useful when we are trying to model a categorical dependent variable (DV) as a function of one or more independent variable. Logistic regression deals with these issues by transforming the DV. Rather than using the categorical responses, it uses the log of the odds ratio of being in a particular category for each combination of values of the independent variables (IVs) (Hosmer Jr and Lemeshow, 2004)..

### 3.11.2 Bootstrapping

Bootstrapping can refer to any test or metric that relies on random sampling with replacement. Bootstrapping allows assigning measures of accuracy (defined in terms of bias, variance, confidence intervals, prediction error or some other such measure) to sample estimates (Efron and Tibshirani, 1994; Efron, 2003). This technique allows estimation of the sampling distribution of almost any statistic using random sampling methods(Mammen, 1993; Varian, 2005).

### 3.12 Development of the Nomogram

A prediction model was conducted based on the data collected. Nomograms can predict for the probability of a clinical outcome based upon the presence of pertinent risk factors, confounders, and predictor variables. Both univariate and multivariate logistic regression analysis were used to examine the association between predictive variables and biopsy outcomes. Crude or adjusted odds ratios and 95% confidence intervals (CI) were calculated.

Univariate logistic regression analysis indicated that age, total PSA, DRE, PSAD, history of smoking and alcohol consumption were the six significant predictors for a positive prostate biopsy. A stepwise multivariate logistic regression analysis showed that the most significant of the six risk factors for detecting prostate cancer are total PSA, DRE PSAD and history of alcohol consumption. Based on the final model, the estimated probability of a positive biopsy could be calculated, a nomogram was accordingly developed to use as a clinical tool. The development method was that the regression coefficients representing the

strengths of correlation were proportionately transferred to the distances on the graph, on which they can be linked to corresponding points and summed to a total. The estimated probability of a positive biopsy thus can thus be determined. Model fitness and interpretability were assessed using the Hosmer– Lemeshow. Receiver-operating characteristic curve was used to assess the model's ability to discriminate. The model was also internally validated using a

500 bootstrapped re-samples as described above.

**Equation 1Logistic regression model for nomogram I equation**

$$\ln\left(\frac{p}{1-p}\right) = -4.51 - 0.19 * Agegroups - 0.45 * HxofSmoking - 1.51 * HxofAlcohol - 1.67 * DRE - 0.84 * PSAD - 0.84 * PSA$$

**Equation 2Logistic regression model for nomogram II equation**

$$\ln\left(\frac{p}{1-p}\right) = -4.39 - 1.71 * DRE - 0.81 * PSAD - 0.69 * PSA$$

IBM Statistical Package for the Social Sciences (SPSS) version 20.00, GraphPad Prism version 6.00 for windows, Stata, version 12.00 were used for statistical analysis where appropriate (SPSS Inc, Chicago, USA; www.spss.com; GraphPad software, San Diego California USA, www.graphpad.com; Stata Corp. LP, Texas, USA, www.stata.com)

## CHAPTER 4

## 4.0 RESULTS

**Socio-demographic characteristics of study participants**

Two hundred and forty-one (241) men participated in the study with a mean age of 70.27 years. Majority (43.2%) of the subjects were between the ages of 70–79 years. The study population was predominantly made up of married men (88.8%). There were more Christians (88.0%) than Muslims (12.0%). Higher proportions of the participant were educated to the tertiary level (54.8%) (**Table 4.1**).

**Table 4.1 Socio-demographic characteristics of Study participants**

| Variables | Frequency (n) | Percentage (%) |
|---|---|---|
| **Age (years, mean ±SD)** | 70.3±8.3 | |
| **Age Groups (years)** | | |
| 50 -59 | 23 | 9.5% |
| 60 – 69 | 82 | 34.0% |
| 70 – 79 | 104 | 43.2% |
| 80+ | 32 | 13.3% |
| **Marital Status** | | |
| Single | 15 | 6.2% |
| Married | 214 | 88.8% |
| Widower | 8 | 3.3% |
| Divorced | 4 | 1.7% |
| **Religion** | | |
| Christian | 212 | 88.0% |
| Muslim | 29 | 12.0% |
| **Occupational Status** | | |
| Unemployed | 20 | 8.30% |
| Pensioner | 132 | 54.8% |
| Formal | 13 | 5.0% |
| Informal | 76 | 31.5% |
| **Educational Status** | | |
| Primary | 45 | 18.7% |
| Secondary | 64 | 26.6% |
| Tertiary | 132 | 54.8% |
| **Age of Sexual First Contact (mean ±SD)** | 20.5±2.2 | |

**SD=Standard Deviation**

**Comparison of clinical, prostate related characteristics and diagnostic parameters of participants, PCa and without PCa patients**

Prostate cancer was found in 63 (26.1%) and 178 (73.9%) did not have cancer. Thirty (30) patients (12.5%) had PSA < 4.0ng/ml. The positive DREs detected among subjects were 57.7%. Higher proportion (53.9%) of all participants had PSAD >0.15ng/ml/ml. Greater proportion (46.0%) of cancer subjects were in the PSA range 20.1–50.0ng/ml. Higher proportion of cancer participants (84.3%) had

PSAD ≥ 0.15ng/ml/ml**.** Total serum PSA and PSA Density were significantly higher (**p<0.0001)** in subjects with PCa than subjects without PCA. There was no significant difference in the mean age and prostate volume between subjects with and without prostate cancer (p > 0.05). There was a significant difference in age groups, DRE findings, PSA category and PSAD categories between subjects with and without cancer (**p<0.0001**) (**Table 4.2**).



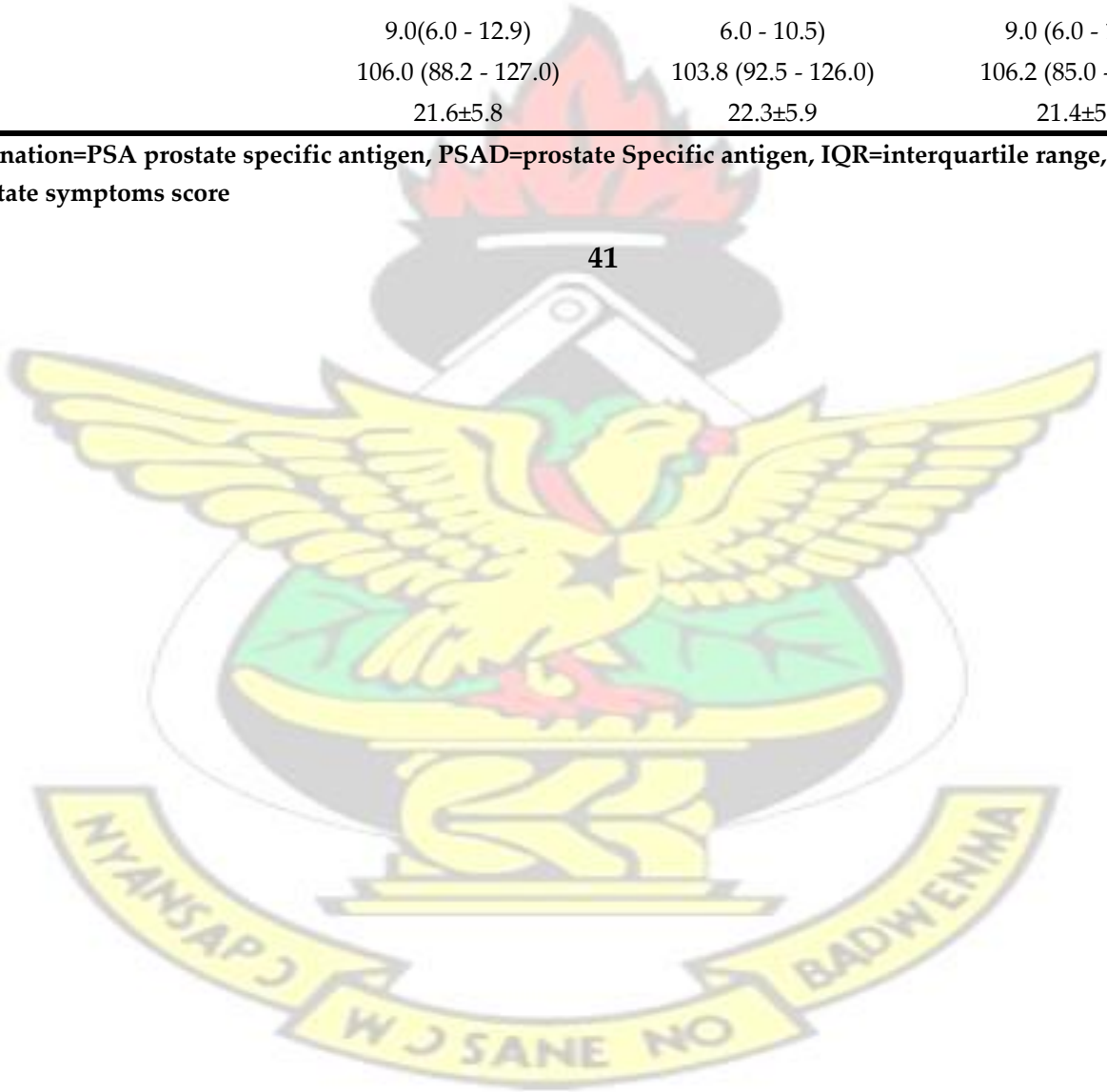
**Table 4. 2 Comparison of clinical, prostate related characteristics and diagnostic parameters of all participants, PCa and without PCa patients**

| Variables | All Participants (n=241) | PCa (n=63) | Without PCa (n=178) | P-value |
|---|---|---|---|---|
| **Age (years, mean ±SD)** | 70.3±8.3 | 71.8±6.8 | 69.7±8.8 | 0.094 |
| **Age Groups** | | | | |
| 50 -59 | 23(9.5%) | 2(3.2%) | 21(11.8%) | **0.036** |
| 60 – 69 | 82 (34.0%) | 18(28.6%) | 64(36.0%) | |
| 70 – 79 | 104(43.2% | 36(57.1%) | 68(38.2%) | |
| 80+ | 32 (13.3%) | 7(11.1%) | 25 (14.0%) | |
| **PSA (ng/ml, Median IQR)** | 18.6 (6.9 - 28.0) | 29.6(21.0 - 91.3) | 12.9 (5.6 - 23.6) | **<0.0001** |
| **PSA Category (ng/ml)** | | | | **<0.0001** |
| ≤ 4.0 | 30 (12.5%) | 1 (1.6%) | 29(16.3%) | |
| 4.1 – 10 | 56 (23.2%) | 4 (6.3%) | 52 (29.2%) | |
| 10.1 -20 | 39 (16.2%) | 7 (11.1%) | 32 (18.0%) | |
| 20.1 50 | 81 (33.6%) | 29 (46.0%) | 52 (29.2%) | |
| > 50 | 35 (14.5%) | 22 (34.9%) | 13 (7.3%) | |
| **DRE Findings** | | | | **<0.0001** |
| Positive (Abnormal) | 102 (42.3%) | 44 (69.8%) | 58 (32.58%) | |
| Negative | 139 (57.7%) | 19 (30.2%) | 120 (67.41%) | |
| **PSAD (ng/ml/ml, Median IQR )** | 0.17 (0.08 - 0.41) | 0.40 (0.18 - 0.77) | 0.12 (0.007 - 0.33) | **<0.0001** |
| **PSAD Category** | | | | **<0.0001** |
| < 0.15 | 121 (46.1%) | 10(15.87%) | 101 (56.7%) | |
| ≥ 0.15 | (130 (53.9%) | 53 (84.3%) | 77 (43.3%) | |
| **Prostate Volume (ml, Median IQR )** | 83.1 (60.9 - 124.5) | 86.9 (61.0 - 124.5) | 80.65 (60.7 - 124.6) | 0.600 |
| **Prostate Volume Category** | | | | 0.385 |

| | | | | |
|---|---|---|---|---|
| < 40 | 24(10.0%0 | 6(9.5%) | 18 (10.1%) | |
| 40 -80 | 89(36.9%) | 19(30.2%) | 70 (39.3%) | |
| > 80 | 128(53.1%) | 90(60.3%) | 90(50.6%) | |
| **Qmax** | 9.0(6.0 - 12.9) | 6.0 - 10.5) | 9.0 (6.0 - 14.0) | 0.262 |
| **Vcomp** | 106.0 (88.2 - 127.0) | 103.8 (92.5 - 126.0) | 106.2 (85.0 - 136.8) | 0.569 |
| **I-PSS Score** | 21.6±5.8 | 22.3±5.9 | 21.4±5.7 | 0.121 |

**DRE digital rectal examination=PSA prostate specific antigen, PSAD=prostate Specific antigen, IQR=interquartile range, SD=standard deviation, IPSS=International prostate symptoms score**





**Association of risk factors of prostate cancer and the outcome of prostate biopsy**

Sixty patients (24.9%) had a family history of prostate cancer. Sixty-seven (27.8%) had history of smoking, 30.3% had history of alcohol consumption and 39.0% had hypertension respectively as shown in Table 4.3. There was a significant association of history of smoking (**p=0.033**) and history of alcohol consumption (**p=0.0004**) with prostate biopsy outcome. There was no significant association of family history of PCa, hypertension, diabetes and rheumatoid arthritis with prostate biopsy outcome ($p > 0.05$) (**Table 4.3**).

**Table 4.3 Distribution and association of family history, social history and medical history with prostate biopsy outcome**

| Variables | All Participants (n=241) | PCa (n=63) | Without PCa (n=178) | $X^2$, df | P-Value |
|---|---|---|---|---|---|
| **Family History** | | | | 1.4,1 | 0.232 |
| No | 181 (75.1%) | 51 (80.9%) | 131 (73.6%) | | |
| Yes | 60 (24.9%) | 12 (19.1%) | 48 (26.4%) | | |
| **History of Smoking** | | | | 4.5, 1 | **0.033** |
| No | 174 (72.2%) | 52 (82.5%) | 122 (69.5%) | | |
| Yes | 67 (27.8%) | 11 (17.5%) | 56 (31.5%) | | |
| **History of Alcohol** | | | | 12.5, 1 | **0.0004** |
| No | 168 (69.7%) | 55 (32.7%) | 113 (63.5%) | | |
| Yes | 73 (30.3%) | 8 (11.0%) | 65 (36.5%) | | |
| **Hypertension** | | | | 1.9, 1 | 0.169 |
| No | 147 (62.0%) | 43 (71.7%) | 104 (58.4%) | | |
| Yes | 94 (39.0%) | 20 (28.3%) | 74 (41.6%) | | |
| **Diabetes** | | | | 2.0, 1 | 0.155 |
| No | 214 (88.8%) | 59 (93.7%) | 155 (87.1%) | | |
| Yes | 27 (11.2%) | 4 (6.3%) | 23 (12.9%) | | |
| **Rheumatoid Arthritis** | | | | 0.4, 1 | 0.539 |
| No | 230 (95.4%) | 61 (96.8%) | 169 (94.9%) | | |
| Yes | 11 (4.6%) | 2 (3.2%) | 9 (5.1%) | | |

**PCa = prostate cancer, $X^2$ = Chi square, df = degree of freedom**

**Distribution and association of developed symptoms of prostate disorder with prostate biopsy outcome**

Higher proportion of the participants had experience incontinence (63.1%), straining (66.6%) weakness (63.5%) and dribbling (51.9%) respectively. There was a significant association of incontinence (**p=0.019**) with prostate biopsy outcome. There was no significant association of waist pain, straining, weight loss, dribbling weakness and pain upon urination with prostate biopsy outcome (**p > 0.05** (Table 4.4).

**Table 4:4 Distribution and association of developed symptoms of prostate disorders with prostate biopsy outcome**

| Variables | All Participants (n=241) | PCa (n=63) | Without PCa (n=178) | $X^2$, df | P-Value |
|---|---|---|---|---|---|
| **Incontinence** | | | | 5.4, 1 | **0.019** |
| No | 89 (36.9%) | 27 (42.9%) | 62 (34.8%) | | |
| Yes | 152 (63.1%) | 36 (57.1%) | 116 (65.2%) | | |
| **Waist Pain** | | | | 0.2, 1 | 0.635 |
| No | 140 (58.1%) | 35 (55.6%) | 105 (59.0%) | | |
| Yes | 101 (41.9%) | 28 (44.4%) | 73 (41.0%) | | |
| **Pain Upon Urination** | | | | 0.6, 1 | 0.448 |
| No | 155 (64.3%) | 43 (68.3%) | 112 (62.9%) | | |
| Yes | 86 (35.7%) | 20 (31.7%) | 66 (37.1%) | | |
| **Straining** | | | | 1.5,1 | 0.222 |
| No | 82 (34.0%) | 21 (33.3%) | 61 (34.3%) | | |
| Yes | 159 (66.0%) | 42 (66.7%) | 117 (65.7%) | | |
| **Weight Loss** | | | | 1.3, 1 | 0.258 |
| No | 163 (67.6%) | 39 (61.9%) | 124 (69.7%) | | |
| Yes | 78 (32.4%) | 24 (38.1%) | 54 (30.3%) | | |
| **Dribbling** | | | | 0.5, 1 | 0.495 |
| No | 88 (36.5%) | 26 (41.3%) | 62 (34.8%) | | |
| Yes | 153 (63.5%) | 37 (58.7%) | 116 (65.2%) | | |
| **Weakness** | | | | 0.8, 1 | 0.362 |
| No | 116 (48.1%) | 28 (44.4%) | 88 (49.4%) | | |
| Yes | 125 (51.9%) | 35 (55.6%) | 90 (50.6%) | | |

**PCa = prostate cancer, $X^2$ = Chi square, df = degree of freedom**

**Diagnostic yields of PSA based parameters, DRE and prostate volume using prostate biopsy as gold standard**

Using a cut-off value of 4.0ng/ml PSA had a sensitivity of 98.4% and specificity of 16.3% with negative predictive value of 96.7% and positive predictive value 29.4%. With PSAD, a cut-off value of 0.15ng/ml/ml was used; this yielded a sensitivity of 84.1% and specificity of 56.7% for detection of prostate cancer with positive predictive value of 40.8% and negative predictive value of 91.0%. Digital rectal examination had a sensitivity of 69.8% and specificity of 67.4%. Prostate volume had a sensitivity of 90.5% and specificity of 10.11% with a cut off value of 40.0ml (**Table 4.5**).

**Table 4.5 Diagnostic yields for PSA based parameters, digital rectal examination (DRE) and prostate volume**

| Variable | Sensitivity (95% CI) | Specificity (95%CI) | PPV | NPV | TP | TN | FP | FN |
|---|---|---|---|---|---|---|---|---|
| PSA (ng/ml) | 98.4(90.5 -100) | 16.23 (11.6 -22.5) | 29.4% | 96.7% | 62 | 29 | 149 | 1 |
| DRE findings | 69.8 (57.6 -79.8) | 67.42 (60.2 - 73.9) | 43.1% | 86.3% | 44 | 120 | 58 | 19 |
| PSAD (ng/ml/ml) | 84.1 (72.9 - 91.3) | 56.7 (49.3 - 63.8) | 40.8% | 90.9% | 53 | 101 | 77 | 10 |
| Prostate Volume (ml) | 90.5 (80.3 - 95.8) | 10.1 (6.5 - 15.5) | 26.3% | 75% | 57 | 18 | 160 | 6 |

**PPV=Positive Predictive Value, NPV=Negative Predictive Value, CI = Confidence Interval, TP=true positive, TN=true negative FP=false positive, FN= false negative**

**Diagnostic performance of bioscore in diagnosis of prostate cancer**

The four combined parameters (PSA+PSAD+DRE+ PV) had the highest specificity 100% but the lowest sensitivity 0.1% in the diagnosis of sepsis. Also a bioscore of 2 recorded sensitivity of 90.5% and specificity of 48.3% respectively. Bioscore of 2 for three combinations DRE+PSAD+PSA) recorded sensitivity of 57.2% and specificity of 89.3% respectively. Bioscore of 2 for two combinations of PSA+DRE, PSAD+PSA and PSAD+DRE had the highest specificity of 100% and lowest specificity 0.1% respectively (Table 4.6).

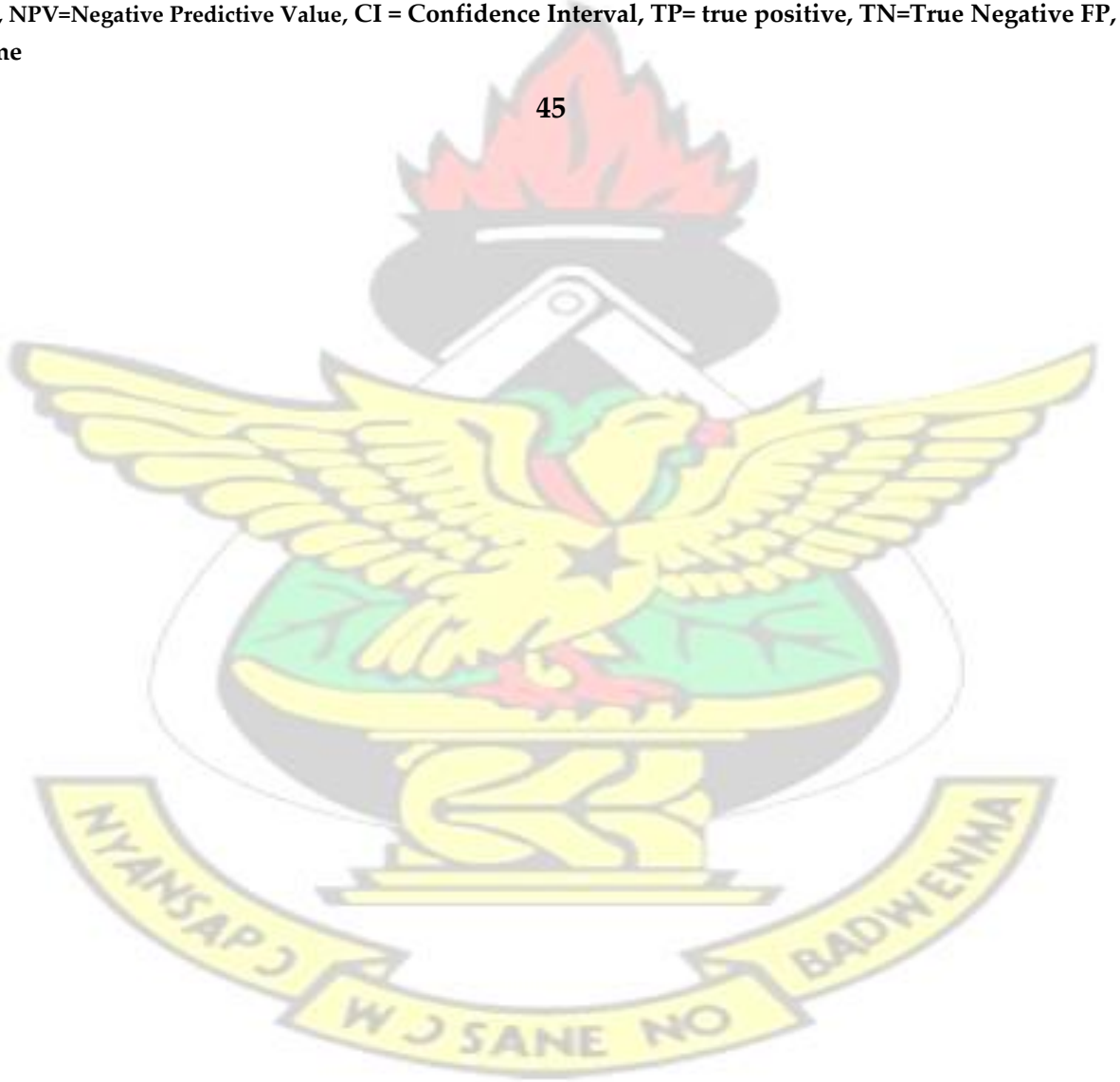
**Table 4.6 Diagnostic performance of bioscore combination of diagnostic tool in diagnosis of prostate cancer**

| Variable | Sensitivity (95% CI) | PPV | NPV | TP | TN | FP | FN |
|---|---|---|---|---|---|---|---|
| **Specificity (95%CI)** | | | | | | | |
| **Bioscore (DRE+PSAD+PSA+PV** | | | | | | | |
| 1 | 100 (90.6 -100) | 11.8 (7.8 - 17.5) | 28.3 | 95.5 | 62 | 21 | 157 | 1 |
| **2** | **90.5 (80.3 - 95.3)** | **48.3 (41.1 - 55.6)** | **38.3** | **93.5** | **57** | **86** | **92** | **6** |
| 3 | 49.2 (37.3 - 61.2) | 87.6 (81.9 -91.7) | 58.5 | 82.9 | 31 | 156 | 22 | 32 |
| 4 | 0.1 (0 - 7.1) | 100 (97.4 - 100) | 0 | 73.9 | 0 | 178 | 0 | 63 |
| **Bioscore (DRE+PSAD+PSA)** | | | | | | | | |
| 1 | 95.2 (86.2 -98.8) | 45.2 (38.1 - 52.6) | 38.2 | 96.4 | 60 | 80 | 97 | 3 |
| **2** | **57.2 (44.9 - 68.6)** | **89.3 (83.7 - 93.1)** | **65.5** | **85.4** | **36** | **158** | **19** | **27** |
| 3 | 0.2 (0 - 7.1) | 100 (97.4 - 100) | 0 | 73.4 | 0 | 177 | 0 | 63 |
| **Bioscore (PSA+DRE)** | | | | | | | | |
| **1** | **65.1 (52.7 - 75.7)** | **76.4 (69.6 - 82.0)** | **49.4** | **86.1** | **41** | **136** | **42** | **22** |
| 2 | 0.1 (0 - 7.1) | 100 (97.4 - 100) | 0 | 74.9 | 0 | 179 | 0 | 63 |
| **Bioscore (PSAD+PSAD)** | | | | | | | | |
| **1** | **(84.1 (46.4 - 70.0)** | **57.3 (49.9 - 64.3)** | **41.1** | **91.1** | **53** | **102** | **76** | **10** |
| 2 | 0.1 (0 - 7.1) | 100 (97.4 - 100) | 0 | 74.9 | 0 | 179 | 0 | 63 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Bioscore (PSAD + DRE)** | | | | | | | | |
| **1** | **58.7 (46.4 - 70.0)** | **86.5 (80.6 - 90.8)** | **60.7** | **85.6** | **37** | **154** | **24** | **26** |
| 2 | 0.1 (0 - 7.1) | 100 (97.4 - 100) | 0 | 74.9 | 0 | 179 | 0 | 63 |

**PPV=Positive Predictive Value, NPV=Negative Predictive Value, CI = Confidence Interval, TP= true positive, TN=True Negative FP, False positive, FN=False Negative PV=prostate volume**





**Binary logistic regression of parameters used in differentiating between patients with and without prostate cancer.**

Bioscore for the combination of PSA+DRE+PSA+ PV showed increasing odds ratios with a score of 4 recoding the highest significant odds of 24.4 (95% CI, 3.15 – 204.3). Bioscore of 3 of three combination (PSA+PSAD+DRE) recorded the highest significant odds of 24.6 followed by a bioscore of 2 (OR = 4.0). The bioscore of 2 for combination of PSAD+DRE recorded significant of odds of 33.40 followed by PSA+PSAD at 19.52 and PSA+DRE at 13.67 (**Table 4.7**)

**Table 4.7 Binary logistic regression of parameters used in differentiating between patients with and without prostate cancer**

| Variable | Odd Ratio | 95% CI | P-value |
|---|---|---|---|
| **Model 1** | | | |
| PSA | 1.01 | 1.0 -1.1 | 0.545 |
| PSAD | 2.15 | 0.9 – 5.4 | 0.104 |
| DRE | 4.85 | 2.52 – 9.3 | **<0.001** |
| **Model 2** | | | |
| Bioscore (DRE+PSAD+PSA+PV | | | |
| 1 | **1 (referent)** | | |
| 2 | 1.40 | 0.2 - 12.6 | 0.773 |
| 3 | 6.70 | 0.9 - 52.6 | 0.071 |
| 4 | 25.40 | 3.2 - 204.3 | **0.002** |
| **Bioscore (DRE+PSAD+PSA)** | | | |
| 0 | **1 (referent)** | | |
| 1 | 0.40 | 0.03 -4.6 | 0.453 |
| **2** | 4.10 | 0.5 -32.2 | 0.192 |
| 3 | 24.60 | 3.0 - 202.9 | **0.003** |
| **Bioscore (PSA+DRE)** | | | |
| **0** | **1 (referent)** | | |
| **1** | 2.40 | 0.3 -19.3 | 0.407 |
| 2 | 13.70 | 1.7 - 108.7 | **0.013** |
| **Bioscore (PSAD+PSAD)** | | | |
| 0 | **1 (referent)** | | |
| **1** | 3.40 | 0.4 - 28.1 | 0.255 |
| 2 | 19.50 | 2.6 - 147.8 | **0.004** |
| **Bioscore (PSAD + DRE)** | | | |

| | | | |
|---|---|---|---|
| 0 | **1 (referent)** | | |
| **1** | 5.60 | 1.6 - 19.4 | **0.001** |
| 2 | 33.40 | 9.4 - 118.5 | **<0.0001** |

**CI=confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD= prostate Specific antigen density**

**Univariate analysis of diagnostic tools and identified risk factors for evaluating the risk of positive prostate biopsy outcome**

Univariate logistic regression analysis showed that age, prostate specific antigen (PSA), digital rectal examination (DRE), PSA Density (PSAD), history of smoking and history of alcohol consumption were all significantly($p < 0.05$). PSA level of > 50.0ng/ml recorded the highest odds of 49.1 (95% CI, 5.9 – 204.1), followed by PSA range of 20.1 – 50.0 ng/ml at 16.2, PSAD levels of ≥ 0.15ng/ml/ml at 6.9 and age range of 70 – 79 years at 5.7 respectively (**Table 4.8**).

**Table 4.8 Univariate logistic regression analyses of diagnostic tools and identified risk factors for evaluating the risk of positive prostate biopsy outcome**

| Variable | Patients | Positive Biopsy | Odd Ratio | 95% CI | P-Value |
|---|---|---|---|---|---|
| **Age Groups** | | | | | |
| 50 -59 | 23 | 2 (8.7%) | 1(referent) | | |
| 60 – 69 | 82 | 18 (22.0%) | 2.9 | 0.6 -13.8 | 0.169 |
| 70 – 79 | 104 | 36(33.3%) | 5.7 | 1.2 -25.1 | **0.026** |
| 80+ | 32 | 7 (21.9%) | 2.9 | 0.6 - 15.7 | 0.201 |
| **PSA Category (ng/ml)** | | | | | |
| ≤ 4.0 | 30 | 1 (3.3%) | 1(referent) | | |
| 4.1 – 10 | 56 | 4 (7.1%) | 2.2 | 0.2 -20.9 | 0.482 |
| 10.1 -20 | 39 | 7 (17.9%) | 6.3 | 0.7 - 54.7 | 0.093 |
| 20.1 50 | 81 | 29 (35.8%) | 16.2 | 2.1 - 124.9 | **0.008** |
| > 50 | 35 | 22 (45.9%) | 49.1 | 5.9 - 204.1 | **<0.0001** |
| **DRE Findings** | | | | | |
| Negative | 102 | 44 (43.1%) | 1(referent) | | |
| Positive | 139 | 19 (13.7%) | 4.8 | 2.6 - 8.9 | **<0.0001** |
| **PSAD Category** | | | | | |
| < 0.15 | 111 | 10 (9.0%) | 1(referent) | | |
| ≥ 0.15 | 130 | 53 (40.8%) | 6.9 | 3.3 - 14.5 | **<0.0001** |

| | | | | | |
|---|---|---|---|---|---|
| **History of Smoking** | | | | | |
| No | 174 | 52 (29.9%) | 1(referent | | |
| Yes | 67 | 11(16.4%) | 0.5 | 0.2 - 1.0 | **<0.036** |
| **History of Alcohol** | | | | | |
| No | 168 | 55 (32.7%) | 1(referent | | |
| Yes | 73 | 8(11.0%) | 0.3 | 0.1 - 0.6 | **0.001** |

**CI=confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD,=prostate Specific antigen**

**Multivariate logistic regression analysis of diagnostic tools and identified risk factors for evaluating the risk of positive prostate biopsy outcome**

Multivariate logistic regression analysis showed that age, prostate specific antigen (PSA) and history of alcohol consumption in men with initial positive prostate biopsy were all significantly different from those in men with negative biopsy (p <0.05). PSA level of > 50.0ng/ml recorded the highest odds ratios at 30.0, followed by PSA range of 20.1 – 50.0 ng/ml at 8.7, PSA range of 10.1 -20.0 ng/ml at 7.7 and age range of 70 – 79 years at 6.2 respectively. The HosmerLemeshow good of fit test showed that the model was well calibrated P equal to 0.366 (**Table 4.9**).

**Table 4.9 Multivariate analyses of diagnostic tools and identified risk factors for evaluating the risk of positive prostate biopsy outcome (Nomogram I)**

| Variables | Odd Ratio | 95% CI | P-Value | Beta |
|---|---|---|---|---|
| **Age Groups** | | | | |
| 50 -59 | 1(referent) | | | |
| 60 – 69 | 3.90 | 0.6 - 26.0 | 0.158 | 1.36 |
| 70 – 79 | 6.20 | 1.0 - 39.9 | 0.053 | 1.83 |
| 80+ | 3.10 | 0.4 - 23.7 | 0.278 | 1.13 |
| **PSA Category (ng/ml)** | | | | |
| ≤ 4.0 | 1(referent) | | | |
| 4.1 – 10 | 2.24 | 0.2 - 22.4 | 0.492 | 0.81 |
| 10.1 -20 | 7.70 | 0.8 - 75.9 | 0.080 | 2.04 |
| 20.1 50 | 8.70 | 0.9 - 84. 64 | 0.062 | 2.16 |
| > 50 | 30.0 | 2.7 - 333.1 | **0.006** | 3.4 |

| | | | | |
|---|---|---|---|---|
| **DRE Findings** | | | | |
| Negative | 1(referent) | | | |
| Positive | 5.80 | 2.7 - 12.43 | **<0.0001** | 1.76 |
| **PSAD Category** | | | | |
| < 0.15 | 1(referent) | | | |
| ≥ 0.15 | 2.40 | 0.8 - 7.3 | **0.019** | 0.88 |
| **History of Smoking** | | | | |
| No | 1(referent) | | | |
| Yes | 1.70 | 0.6 - 4.6 | 0.325 | 0.51 |
| **History of Alcohol** | | | | |
| No | 1(referent) | | | |
| Yes | 0.20 | 0.08 - 0.63 | **0.005** | -1.5 |
| Constant | 0.0003 | 0.0002 - 0.049 | **<0.0001** | -7.55 |

**CI=confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD= prostate Specific antigen density**

**Validation of nomogram I on 500 bootstrapped re-samples**

The parametric standard error for the PSA range of 10.1 -20.0ng/ml was large (8.64) and a significance value **of 0.002** was reported by the bootstrap results. The age range 50 -59 years had a high standard error of 6.75 but was not significant. Significance values were observed for PSA ranges 20.1–50.0ng/ml, >50.0 ng/ml, positive DRE and history of alcohol consumption respectively in the bootstrap output. This shows that the observed difference between significant variables in non-bootstrapped and non-significant variables in the bootstrapped is not due to chance (Table 9 vs. Table 10). The Hosmer-Lemeshow good of fit test showed that the model was well calibrated P equal to 0.683 (**Table 4.10**).

**Table 4.10 Validation of Nomogram I on 500 bootstrapped re-samples**

| Variable | Beta | Bias | Std Error | P-Value | BCa 95%CI |
|---|---|---|---|---|---|
| **Age Groups** | | | | | |
| 50 -59 | 1(referent) | | | | |
| 60 – 69 | -0.75 | -2.51 | 6.75 | 0.441 | -20.0 - 1.30 |
| 70 – 79 | 0.33 | -0.11 | 1.46 | 0.655 | -1.28 - 2.87 |
| 80+ | 0.75 | 1.26 | 1.43 | 0.250 | -0.92 - 20.0 |

| | | | | | |
|---|---|---|---|---|---|
| **PSA Category (ng/ml)** | | | | | |
| ≤ 4.0 | 1(referent) | | | | |
| 4.1 – 10 | -2.7 | -0.63 | 2.92 | **0.002** | -4.48 - 1.61 |
| 10.1 -20 | -3.59 | -5.82 | 8.64 | **0.002** | -22.03 - -2.22 |
| 20.1 50 | -1.43 | -0.24 | 1.08 | **0.022** | -2.37 - -0.85 |
| > 50 | -1.25 | -0.81 | 0.58 | **0.016** | -2.38 - - 0.31 |
| **DRE Findings** | | | | | |
| Negative | 1(referent) | | | | |
| Positive | -1.82 | -0.09 | 0.45 | **0.002** | -2.60 - -1.20 |
| **PSAD Category** | | | | | |
| < 0.15 | 1(referent) | | | | |
| ≥ 0.15 | -0.79 | -0.62 | 0.62 | 0.138 | -1.87 - 0.33 |
| **History of Smoking** | | | | | |
| No | 1(referent) | | | | |
| Yes | -0.46 | -0.03 | 0.61 | 0.363 | -1.75 - 0.70 |
| **History of Alcohol** | | | | | |
| No | 1(referent) | | | | |
| Yes | -1.46 | 0.17 | 0.6 | **0.006** | 0.32 - 3.51 |

**CI=confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD= prostate Specific antigen density, BCa=Biased Corrected accelerated**

**Multivariate logistic regression analysis of diagnostic tools for evaluating the risk of positive prostate biopsy outcome**

Prostate specific antigen (PSA) and DRE were found to be significant independent predictors of initial positive prostate biopsy (p **< 0.05**). A PSA level of > 50.0ng/ml recorded the highest odds ratios at 32.2 (95% CI, 2.9 – 352.5), followed by PSA range of 20.1 – 50.0 ng/ml at 10.8 (95% CI, 1.1 – 104.9), PSA range of 10.1 -20.0 ng/ml at 7.7 (95% CI, 0.78 – 75.9) and positive DRE at 5.8 (95% CI, 2.8 – 11.9) respectively The Hosmer-Lemeshow good of fit test showed that the model was well calibrated P equal to 0.287 (**Table 4.11**). **risk of positive prostate biopsy outcome (Nomogram II)**

**Table 4.11: Multivariate analyses of diagnostic tools factors for evaluating the**

| Variable | Odd Ratio | 95% CI | P-value | Beta |
|---|---|---|---|---|
| **PSA Category (ng/ml)** | | | | |
| ≤ 4.0 | 1(referent) | | | |

| | | | | |
|---|---|---|---|---|
| 4.1 – 10 | 2.70 | 0.3 - 25.8 | 0.398 | 0.98 |
| 10.1 -20 | 7.70 | 0.8 - 74.4 | 0.078 | 2.04 |
| 20.1 50 | 10.80 | 1.1 - 104.9 | **0.040** | 2.38 |
| > 50 | 32.20 | 2.9 - 352.5 | **0.004** | 3.47 |
| **DRE Findings** | | | | |
| Negative | 1(referent) | | | |
| Positive | 5.80 | 2.8 - 11.9 | **<0.0001** | 1.75 |
| **PSAD Category** | | | | |
| < 0.15 | 1(referent) | | | |
| ≥ 0.15 | 2.20 | 0.74 - 6.5 | 0.158 | 0.78 |
| **Constant** | 0.01 | 0.001 - 0.08 | **<0.0001** | -4.59 |

**CI=confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD= prostate Specific antigen density**

**Validation of nomogram II on 500 bootstrapped re-samples**

The parametric standard error for the PSA range of 10.1 -20.0ng/ml was large (9.03) and a significance value of 0.008 was reported by the bootstrap results.

Significance values were observed for PSA ranges ≤4.0ng/ml, 20.1 – 50.0ng/ml, > 50.0 ng/ml, positive DRE and respectively in the bootstrap output. This shows that the observed difference between significant variables in non-bootstrapped and non-significant variables in the bootstrapped is not due to chance. (Table 4.11 vs. Table 4.12)The Hosmer-Lemeshow good of fit test showed that the model was well calibrated P equal to 0.653 (**Table 4.12)**

**Table 4.12: Validation of Nomogram II on 500 bootstrapped re-samples**

| Variable | Beta | Bias | Std Error | P-Value | BCa 95%CI |
|---|---|---|---|---|---|
| **PSA Category (ng/ml)** | | | | | |
| ≤ 4.0 | 1(referent) | | | | |
| 4.1 – 10 | -2.49 | -0.4 | 2.38 | **0.006** | - 4.37 - -1.21 |
| 10.1 -20 | -3.47 | -7.04 | 9.03 | **0.008** | -21.98 - -2.02 |
| 20.1 50 | -1.43 | -0.1 | 0.68 | **0.020** | -2.70 - -0.41 |

| | | | | | |
|---|---|---|---|---|---|
| > 50 | -1.09 | -0.47 | 0.51 | **0.014** | -2.11 - -0.30 |
| **DRE Findings** | | | | | |
| Negative | 1(referent) | | | | |
| Positive | -1.76 | 0.83 | 0.41 | **0.020** | -2.48 - -1.18 |
| **PSAD Category** | | | | | |
| < 0.15 | 1(referent) | | | | |
| ≥ 0.15 | 0.78 | -0.32 | 0.66 | 0.172 | - 2.17 - 0.44 |

**CI= confidence interval, DRE=digital rectal examination, PSA=prostate specific antigen, PSAD=prostate Specific antigen, BCa,=Biased Corrected accelerated**

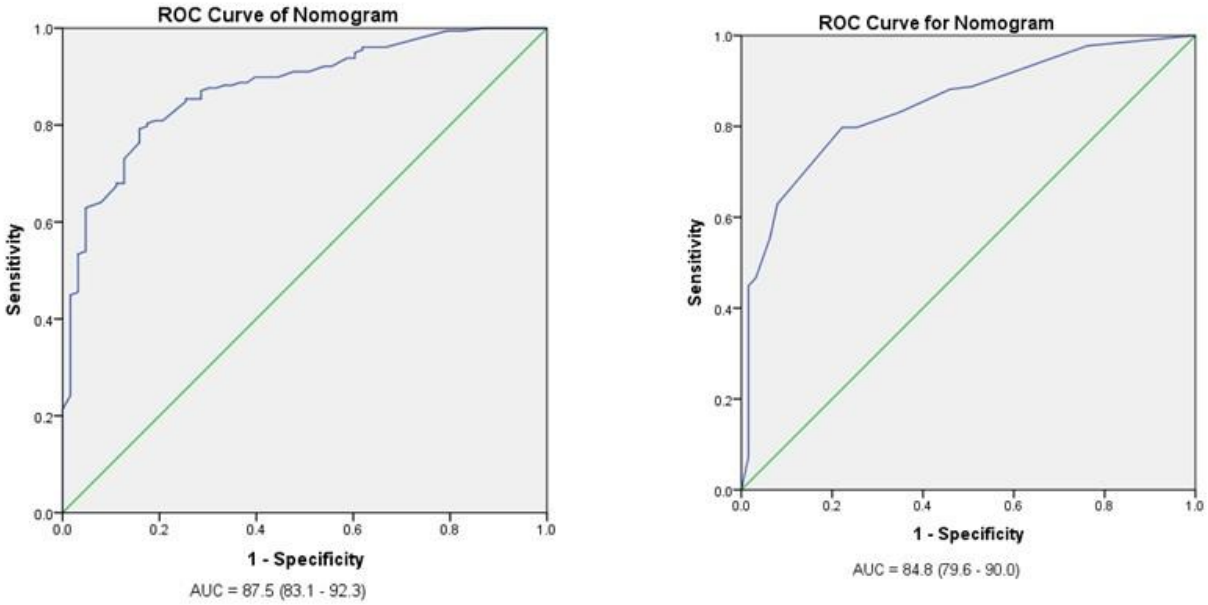



**Figure 4.1: Receiver-operating characteristic curve (AUC) for depicting the accuracy of nomogram I and nomogram II for predicting a positive initial prostate biopsy**

**Figure 4.1** shows the area under the receiver-operating characteristic curve (AUC) for depicting the accuracy of nomogram I and nomogram II for predicting a positive initial prostate biopsy. AUC was 87.5 (83.1 -92.3) for nomogram I and 84.8 (79.6 – 90.0) with significant asymptomatic p-value (<0.0001)

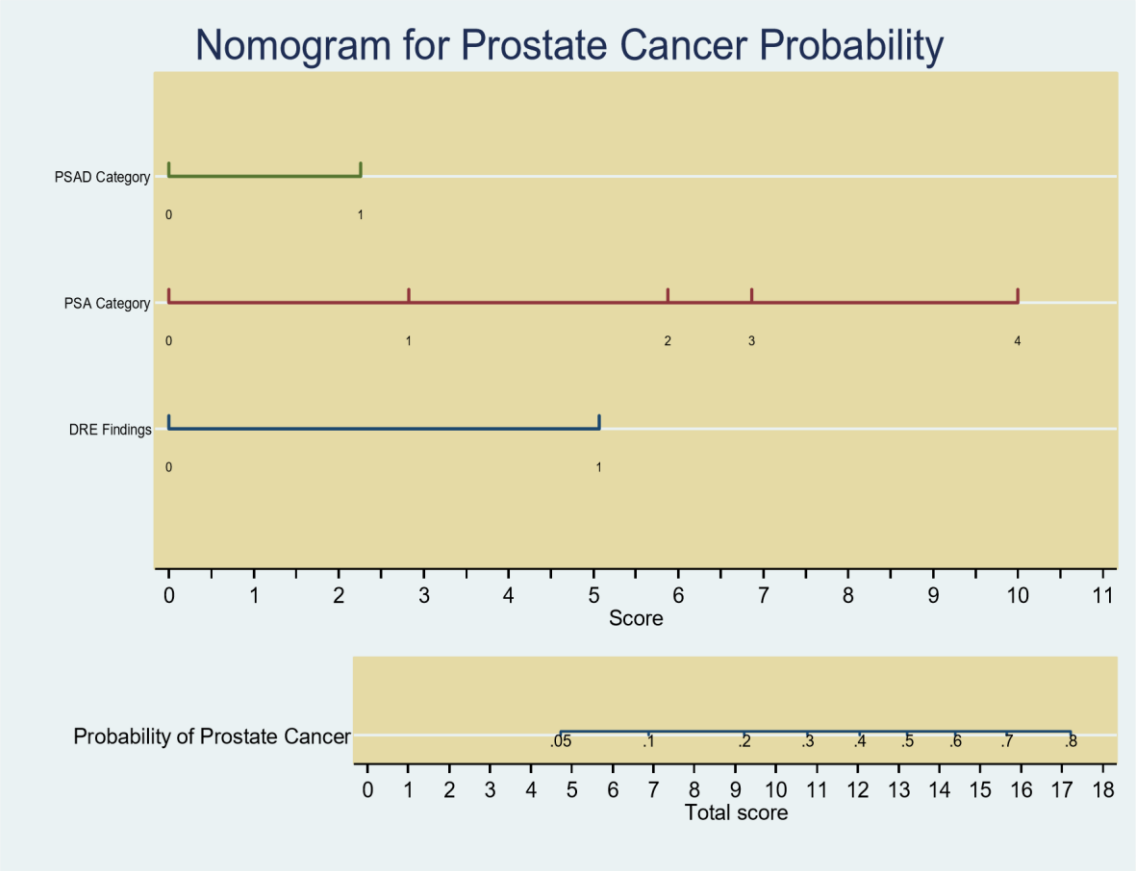



**Figure 4.2: Nomogram II for predicting the probability of prostate cancer on needle biopsy using PSA category, PSAD category and DRE findings.**

**Figure 4.2** shows nomogram I for predicting the probability of prostate cancer on needle biopsy using PSA category, PSAD category and DRE findings. To determine the predicted probability of prostate cancer on initial biopsy, locate patient values on each axis. Draw a vertical line to the '**Score**' axis to determine how many points are attributed to each variable. After summation of the points for all variables, locate the sum on the '**Total Scores**' line to determine the individual probability of prostate cancer on initial prostate biopsy on the 'Probability of Prostate Cancer' line.

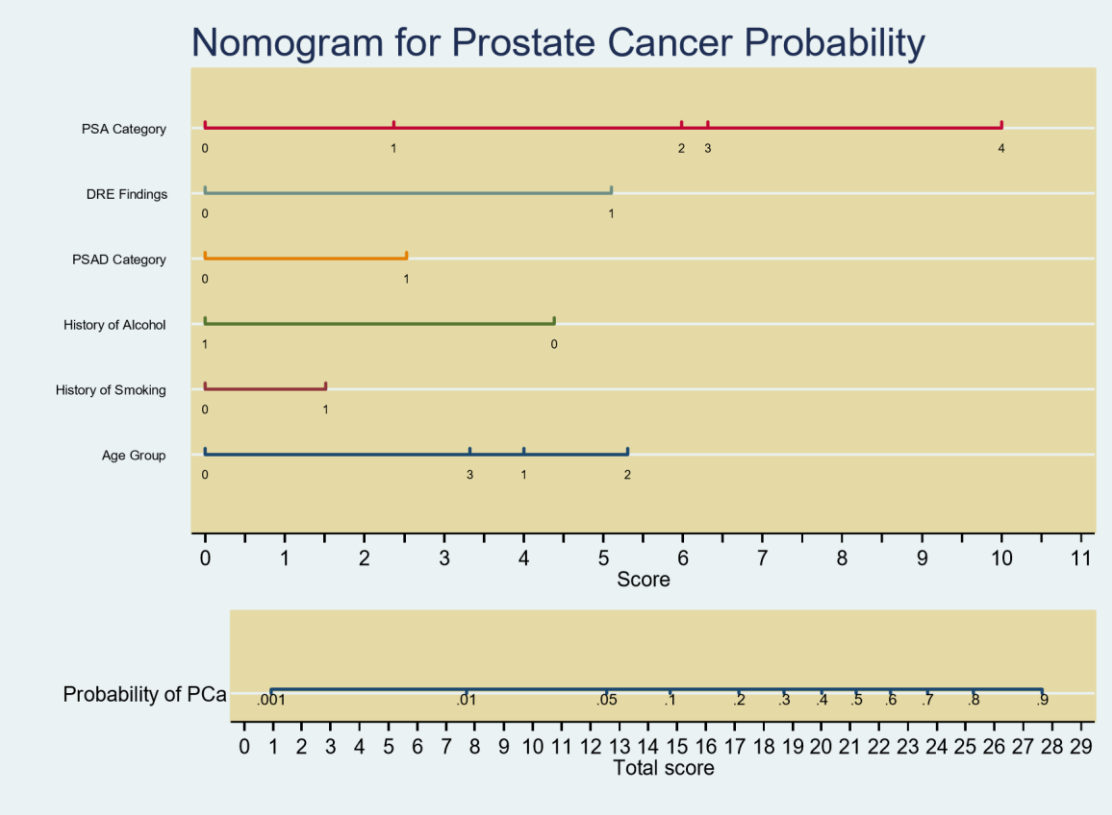



**Figure 4.3: Nomogram I for predicting the probability of prostate cancer on needle biopsy using age, PSA category, PSAD category, history of smoking, history of alcohol consumption, and DRE findings.**

**Figure 4.3** shows **n**omogram I for predicting the probability of prostate cancer on needle biopsy using age, PSA category, PSAD category, history of smoking, history of alcohol consumption, and DRE findings. To determine the predicted probability of prostate cancer on initial biopsy, locate patient values on each axis. Draw a vertical line to the '**Score**' axis to determine how many points are attributed to each variable. After summation of the points for all variables, locate the sum on the '**Total Scores**' line to determine the individual probability of prostate cancer on initial prostate biopsy on the 'Probability of Prostate Cancer' line. For instance given a patient with age between 70-79, falls into 20.1 -50ng/ml PSA category, has history of smoking, no history of alcohol consumption, abnormal DRE and PSAD >0.15ng/ml/ml, the total point is 22.5 read from the above nomogram, and the corresponding probability of having the event is about 0.6.

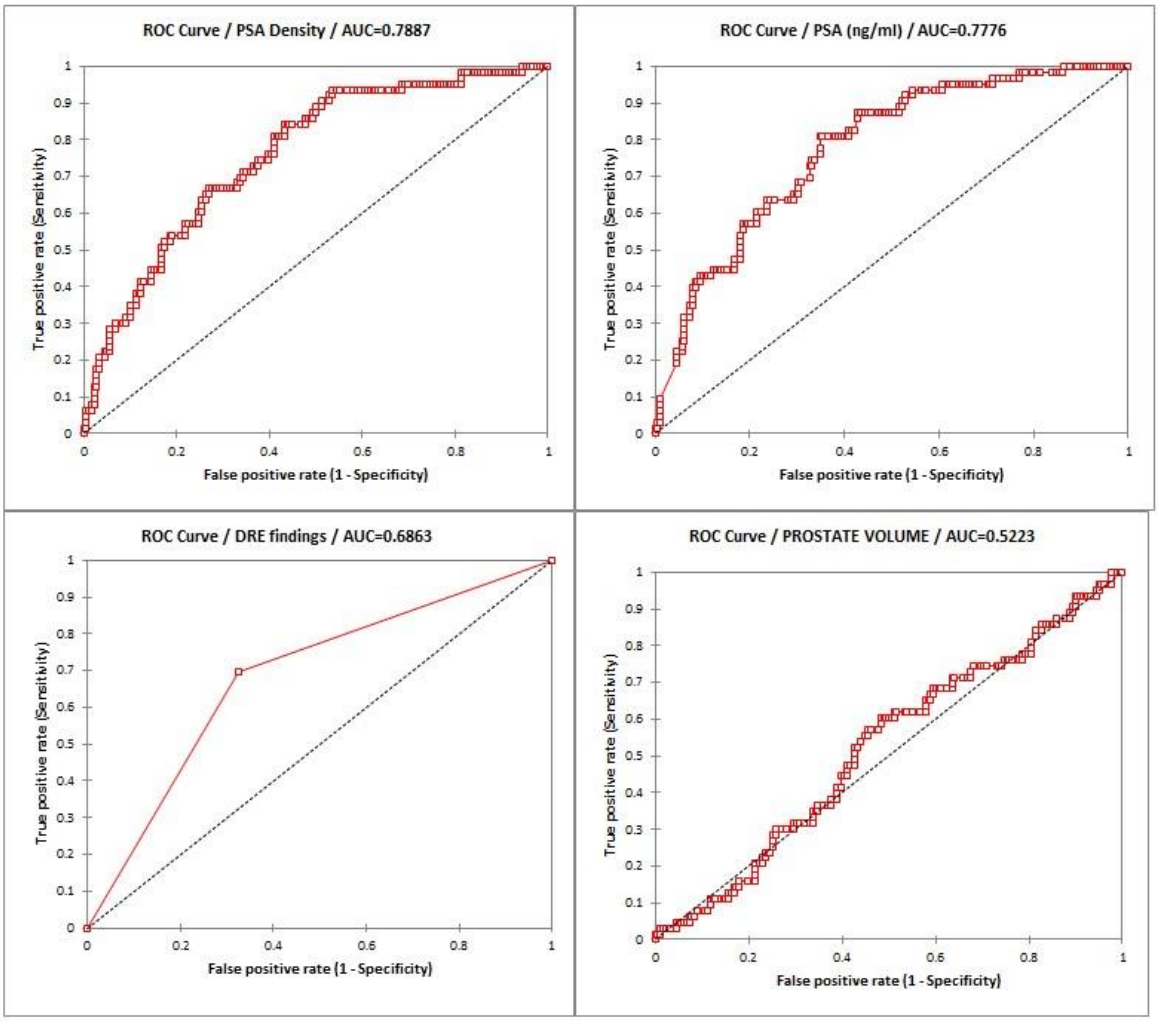



**Figure 4.4 Receiver operating characteristics (ROC) curve analyses for depicting the accuracy of Prostate Specific Antigen (PSA) Digital Rectal Examination (DRE) and PSA Density (PSAD ROC curve.**

**Figure 4.4** shows receiver operating characteristics (ROC) curve analyses for depicting the accuracy of Prostate Specific Antigen (PSA) Digital Rectal Examination (DRE) and PSA Density (PSAD ROC curve. Area under curve (AUC) was 78.9(69.3 – 82.4) for PSAD, 77.8 (71.6 – 83.96) for PSA, 68.6 for DRE and 52.2 for prostate volume (44.1 – 60.4) respectively.

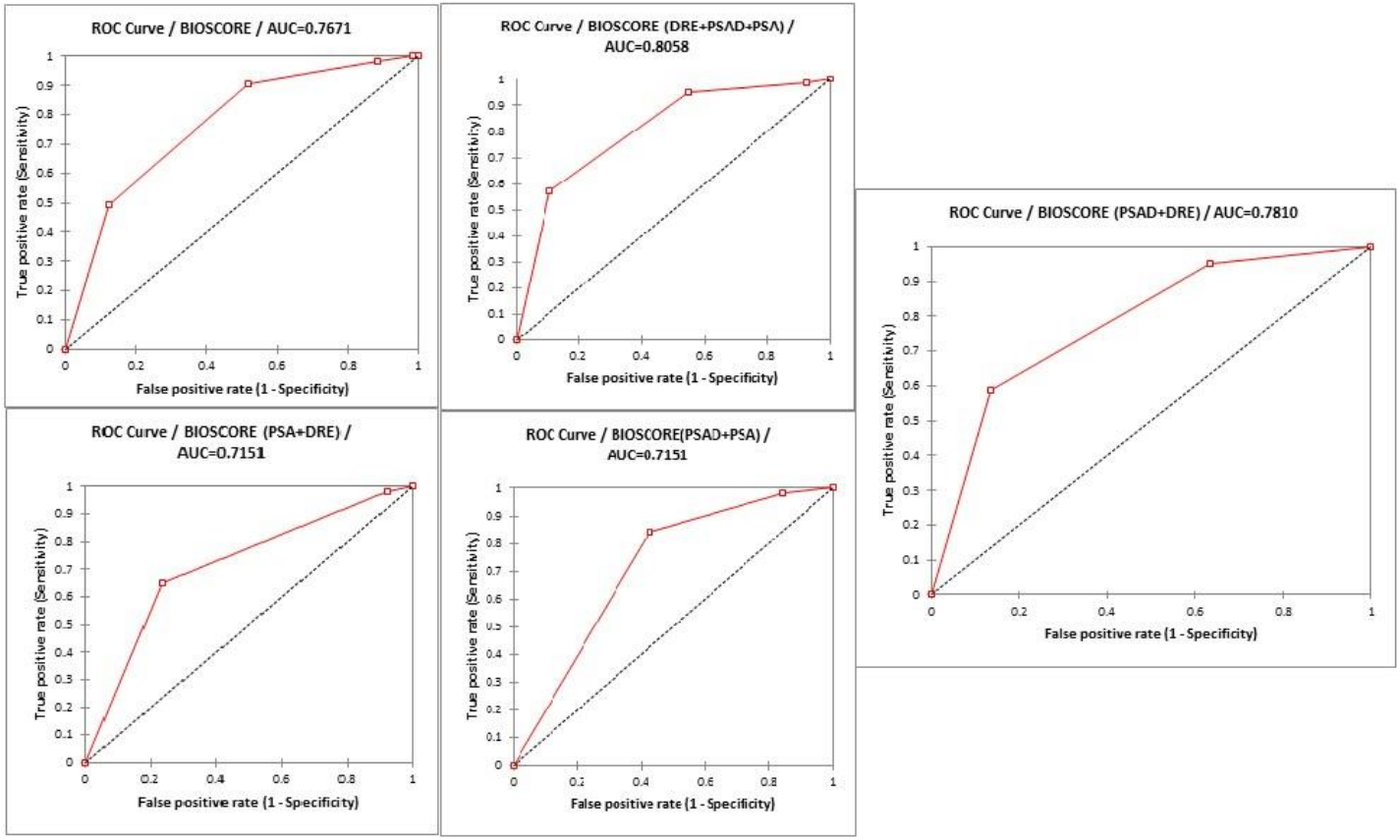



**Figure 4.5: Receiver operating characteristics (ROC) curve analyses for showing the accuracy the bioscore for the various combinations of the diagnostic tools AUC= Area under Curve**

ROC curve for combinations of the various diagnostic tools showing AUC are shown in **Figure 4.5**. AUC was 76.7 for the bioscore combinaion of PSA+PSAD+DRE+ Prostate Volume, 80.6 for DRE+PSAD+PSA, 71.5 for PSA+DRE, 71.5 for PSAD+PSA and 78.1 PSAD+DRE respectively

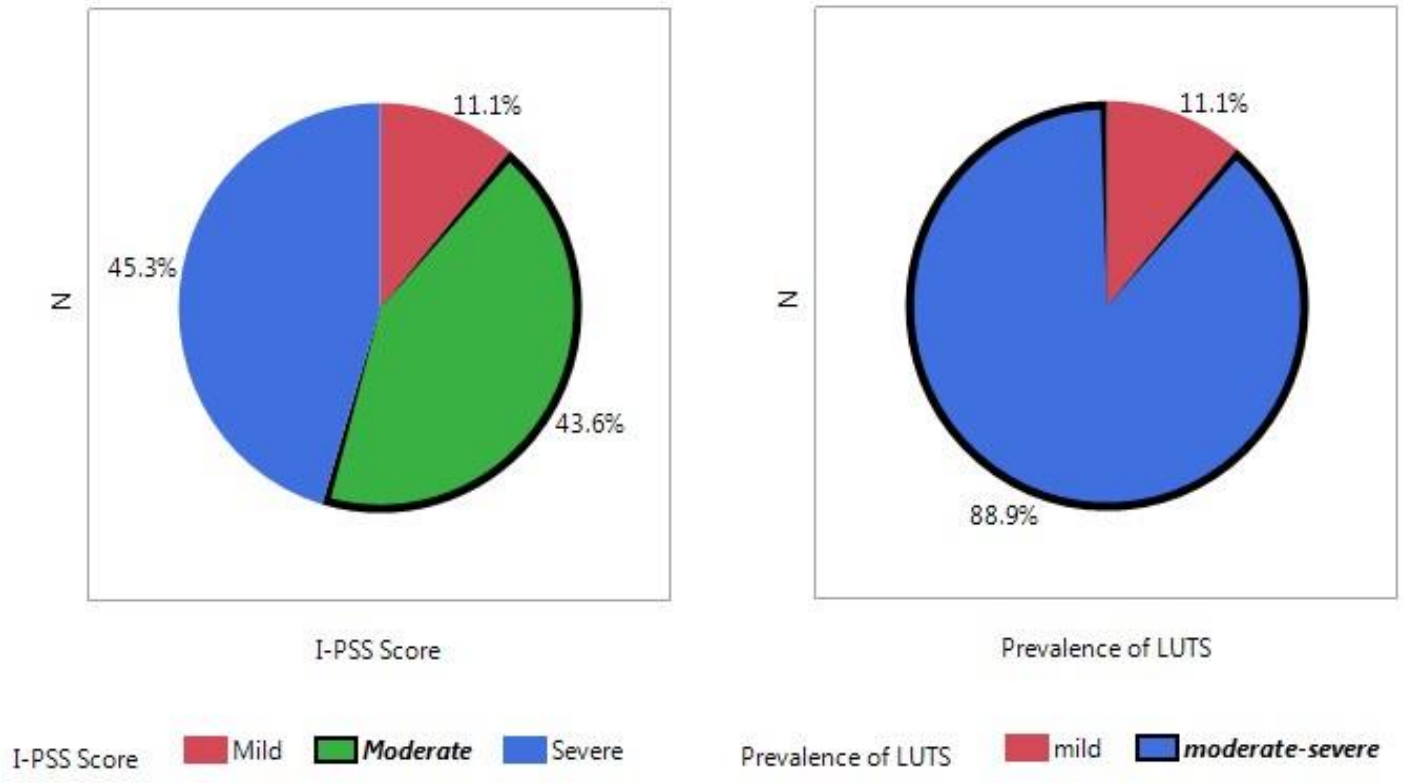



**Figure 4.6 Prevalence of LUTS using IPSS score**

Figure 4.6 shows the prevalence of LUTS. Higher proportion (45.3%) of participants had severe symptoms. Majority of participants had moderate to severe symptoms (88.9%)

**Distribution pattern of Lower urinary tract symptoms of the participants**

One hundred and ninety-one of the participants (84.89%) experienced a sense of incomplete emptying which denotes individuals with post-micturition symptoms. Participants with weak stream, intermittency and hesitancy represented 86.67%, 84.44% and 87.11% respectively with a mean of 86.00% having voiding symptoms. The proportion of participants who experienced frequency, nocturia and urgency were 80.89%, 91.56% and 93.33%. An average of 88.59% experienced bladder storage symptoms (**Table 4.13**).

**Table 4.13: Distribution of the pattern of the lower urinary tract symptoms suggestive of BPH**

| Symptoms score Frequency (%) | 0 | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|---|
| Incomplete Emptying | 36(15.11%) | 17(7.11%) | 25(10.67%) | 53(22.22%) | 82(34.22%) | 28(11.11%) | 205(84.89%) |
| Frequency | 46(19.11%) | 2(0.89%) | 42 (17.33%) | 66(27.56%) | 53(22.22%) | 31(12.89%) | 195(80.89%) |
| Intermittency | 31(12.89%) | 17(7.11%) | 57(23.56%) | 60(24.89%) | 57(23.56%) | 21(8.89%) | 210(87.11%) |
| Urgency | 16(6.67%) | 14(5.78%) | 37(15.56%) | 73(30.22%) | 64(26.67%) | 36(15.11%) | 225(93.33%) |
| Weak stream | 32(17.33%) | 7(3.11%) | 48(20.00%) | 62(25.78%) | 58(24.00%) | 22(9.78%) | 209(86.67%) |
| Hesitancy | 37(13.33%) | 11(4.44%) | 45(18.67%) | 61(26.67%) | 57(25.33%) | 28(11.55%) | 204(84.44%) |
| Nocturia | 20(8.44%) | 17(7.11%) | 34(14.22%) | 26(10.22%) | 86(35.56%) | 56(24.44%) | 221(91.56%) |

**Distributions of lower urinary tract symptoms by bother score**

None of the participants with severe LUTS were pleased with their symptoms while 1 (0.96%) with severe LUTS was most satisfied with the symptoms. None of the participants with moderate LUTS was pleased or most satisfied with their symptoms. In addition, no participants felt terrible with mild LUTS while 68 (65.39%) with severe LUTS felt terrible in relation to their symptoms. One hundred and eighty-two (75.5%) had a mixture of most satisfied and dissatisfied, most dissatisfied, unhappy and terrible which suggest that 75.5% had bothersome LUTS **[Table 4.14).**

**Table 4.14: Distribution of Lower Urinary Tract Symptoms by Bother Score**

| Variables | IPSS symptom grade | | | |
|---|---|---|---|---|
| | Mild (%) | Moderate (%) | Severe (%) | Total |
| Bother Score | | | | |
| Pleased | 39(65.45%) | 0 (0) | 0 (0) | 39 (16.00%) |
| Mostly Satisfied | 12(20.00%) | 0 (0) | 1 (0.96%) | 13(5.33%) |
| Mixed | 5(7.27%) | 10(13.64%) | 4 (3.85%) | 19(7.56%) |
| Mostly Dissatisfied | 2(3.64%) | 4(6.06%) | 12 (10.58%) | 18 (7.56%) |
| Unhappy | 1(1.82%) | 18(25.76%) | 21(19.23%) | 40(16.89%) |
| Terrible | 0 (0) | 39(54.54%) | 73(65.39%) | 112(46.22%) |
| Total | 59(24.44%) | 71(29.33%) | 111(46.22%) | 241(100%) |

**Factors associated with moderate-to-severe LUTS suggestive of BPH**

The age ranges 50–54 years and 65 – 69 years respectively were not statistically significant (**p>0.05**) in the univariate logistic model but were statistically significant in the multivariate logistic model (p**<0.05**).There was no significant difference between the various PSA levels ranges in the univariate logistic model but the PSA range 20.1-50ng/ml was statistically significant (**p=0.006**) in the multivariate logistic model in comparison to mild LUTS. There was no statistical significant difference was observed in the univariate and multivariate logistic models with grade IV recording the highest odds (OR=4.05: 95% CI = 0.166 – 7.28) (**Table 4.15**).

**Table 4.15: Factors associated with moderate-to-severe lower urinary tract symptoms**

| | IPSS symptoms grade | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | **Moderate-Severe (%)** | **Mild (%)** | **Crude OR (95%)** | **P -Value** | **Adjusted OR (95%)** | **P -Value** |
| Age (Groups) | | | | | | |
| 40 – 44 | 4 (36.36%) | 7(63.63%) | **1 (referent)** | **1 (referent** | **1 (referent)** | **1 (referent)** |
| 45 – 49 | 7 (36.80%) | 12(63.20%) | 1.02 (0.22 - 4.77) | 0.999 | 1.26 (0.05 – 18.90) | 0.860 |
| 50 – 54 | 11 (55.0%) | 9 (45.0%) | 2.14 (0.47 -9.70) | 0.458 | 3.43 (0.32 – 99.40) | **0.002** |
| 55 – 59 | 17 (72.27%) | 5 (22.73%) | 5.95(1.22 - 6.82) | **0.052** | 4.33 (0.57 – 60.21) | **<0.0001** |
| 60 – 64 | 23 (100%) | 0 | 18.33 (3.76 - 163.1) | **<0.0001** | 5.97 (0.40 -250.27) | **<0.0001** |
| 65 – 69 | 24 (96.0%) | 1 (4.0%) | 22.00 (2.21 - 114.3) | **0.0003** | 13.85 (0.83 – 120.62) | **<0.0001** |
| 70 – 74 | 27 (96.43%) | 1 (3.57%) | 3.50 (0.24 - 51.93) | 0.539 | 9.08 (0.50 -53.23) | **<0.0001** |
| 75+ | 75 (97.4%) | 2 (2.60%) | 27.63 (10.15 - 174.3) | **<0.0001** | 18.72 (1.15 – 99.78) | **<0.0001** |
| PSA value (ng/ml) | | | | | | |
| 0 – 4 | 34 (82.93%) | 7 (17.07%) | **1 (referent)** | **1 (referent)** | **1 (referent)** | **1 (referent)** |
| 4.1 – 10 | 29 (78.38%) | 8 (21.62%) | 0.99 (0.31 - 3.27) | 0.890 | 4.24 (0.48 – 46.77) | 0.195 |
| 10.1 – 20 | 34 (85.0%) | 6 (15.0%) | 1.43 (0.46 - 4.45) | 0.526 | 2.81 (0.37 – 28.78) | 0.329 |
| 20.1 – 50 | 50 (71.43%) | 20(28.57%) | 1.49 (0.59 - 3.98) | 0.252 | 17.37 (2.19 – 223.45) | **0.006** |
| >50 | 28 (51.35%) | 18 (48.65%) | 1.33 (0.45- 3.97) | 0.610 | 6.23 (0.65 – 87.67) | 0.116 |
| Prostate Volume (ml) | | | | | | |
| Grade I | 13 (61.91%) | 8 (38.09%) | **1 (referent)** | **1 (referent)** | **1 (referent)** | **1 (referent)** |
| Grade II | 32 (74.42%) | 11 (25.58%) | 1.79 (0.58 - 5.47) | 0.385 | 3.91 (0.46 -41.98) | 0.217 |
| Grade III | 40(76.92%) | 12 ((23.08%) | 2.05 (0.69 - 6.11) | 0.248 | 1.18 (0.13 – 10.20) | 0.878 |
| Grade IV | 75 (75.76%) | 24 (24.24%) | 1.92 (0.71 - 5.20) | 0.280 | 4.05 (0.166 – 7.28) | 0.206 |

**OR= odds ratio, CI=Confidence Interval IPSS=International Prostate Symptoms Score**

**Association between demographic life and medical history characteristics and moderate-to-severe LUTS**

There was a significant difference between moderate-to-severe LUTS in reference to being a widowed in both univariate (**p=0.041**) and multivariate logistic models (**p = 0.10**). No significant difference was observed between moderate-to-severe and mild LUTS in reference to smoking in the univariate

logistic analysis but was statistically significant upon multivariate logistic model (**p=0.038**). Subject who smoked were at increased odds of having moderate-tosevere LUTS in comparison with those who did not smoke (OR =1.29; 95%CI = 0.56-3.18) (**Table 4.16**).

**Table 4.16: Association between demographic, life and medical history characteristics and moderate-to-severe LUTS**

| Variables | Moderate-to-severe | Mild | Crude OR (95% CI) | P-value | Adjusted OR(95%CI) | P-value |
|---|---|---|---|---|---|---|
| **IPSS Symptom Grading** | | | | | | |
| **Alcohol Consumption** | | | | | | |
| No | 136 (75.14%) | 45 (24.86%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 31 (75.61%) | 10 (24.39%) | 1.03 (0.47 - 2.26) | 0.990 | 1.29 (0.56 - 3.18) | 0.551 |
| **Smoking Cigarette** | | | | | | |
| No | 157 (76.96%) | 47 (23.03%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 11 (57.89%) | 8 (42.11%) | 0.41 (0.19 - 1.26) | 0.916 | 0.32 (0.11 – 0.94) | **0.038** |
| **Marital Status** | | | | | | |
| Single | 10 (90.91%) | 1 (9.09%) | **1 (referent)** | | **1 (referent)** | |
| Married | 147 (75.0%) | 49 (25.0%) | 0.30 (0.04 - 2.40) | 0.303 | 0.37 (0.02 -2.08) | 0.294 |
| Widowed | 3 (37.50%) | 5 (62.50%) | 0.06 (0.004 - 0.74 | **0.041** | 0.05 (0.002 -0.52) | **0.010** |
| Divorced | 8 (3.56%) | 0 (0%) | 0.80 (0.04 - 14.90 | 0.992 | 0.68 (0.06 – 18.94) | 0.356 |
| **Educational Status** | | | | | | |
| No education | 7 (87.50%) | 1 (12.50%) | **1 (referent)** | | **1 (referent)** | |
| Basic | 48 (76.19%) | 15 (23.81%) | 0.46 (0.05 -4.02) | 0.673 | 0.34 (0.09 -6.02) | 0.673 |
| Secondary | 15(68.18%) | 7 (31.82%) | 0.36 (0.03 - 2.99) | 0.391 | 0.29(0.10 – 3.96) | 0.391 |
| Tertiary | 98 (74.24%) | 34 (25.76%) | 0.41 (0.05 - 3.47) | 0.697 | 0.19 (0.02 - 4.56) | 0.697 |
| **Diabetes** | | | | | | |
| No | 149 (77.20%) | 44 (22.80%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 19 (63.33%) | 11 (36.67%) | 0.51 (0.23 - 1.15) | 0.113 | 1.19 (0.41 – 3.78) | 0.750 |
| **Hypertension** | | | | | | |
| No | 92 (78.63%) | 25 (21.36%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 76 (71.70%) | 30 (28.30%) | 0.69 (0.37 - 1.27) | 0.217 | 0.96 (0.48 – 1.91) | 0.896 |
| **Family History** | | | | | | |
| No | 149 (75.5%) | 48 (24.36%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 19 (73.08%) | 7 (26.92%) | 0.87 (0.35 - 2.21) | 0.870 | 0.75 (0.29 – 3.47) | 0.870 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Heart disease** | | | | | | |
| No | 166 (75.11%) | 55 (24.89%) | **1 (referent)** | | **1 (referent)** | |
| Yes | 2 (0.89%) | 0 (0%) | 1.67 (0.07 - 35.27) | 0.990 | 1.02 (0.47 – 38.26) | 0.137 |

**OR= odds ratio, CI=Confidence Interval IPSS=International Prostate Symptoms Score 63**

**A**

**B**

**C**

**D**

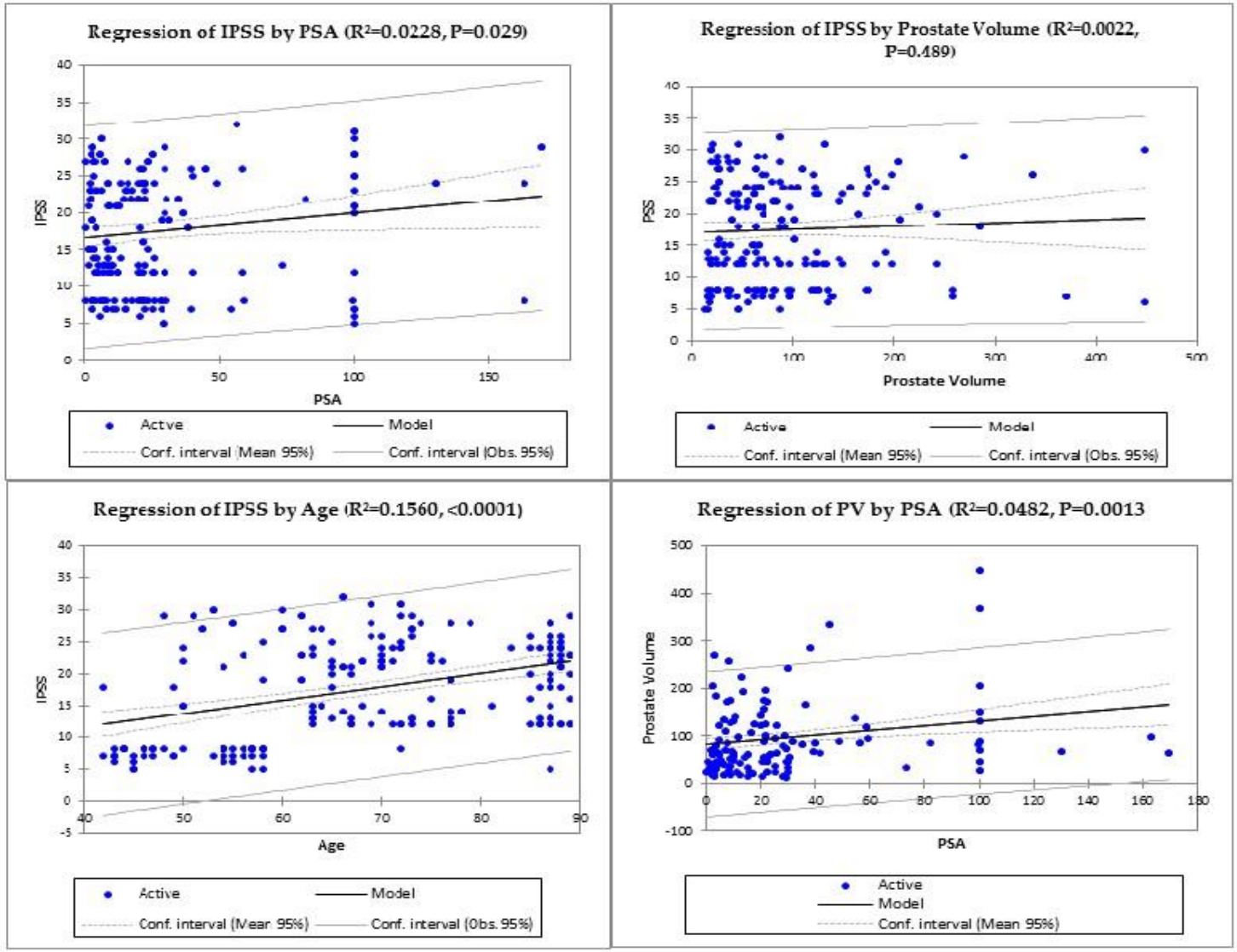



**Figure 4.7: Regression graphs between IPSS and Prostate Specific Antigen, Age, Prostate Volume (PV)**

**Regression graphs between IPSS and Prostate Specific Antigen, Age, Prostate Volume (PV) as shown in the above figure.**

The regression plot of the individual patient data points for IPSS in relation to the age (**B**), PSA (**D**), showed a mild statistically significant positive relationship ($p < 0.05$). However, the coefficients of determination ($R^2$ value) were 0.156 and 0.022 respectively. This means that, each unit increase of age and PSA only influences 15.6% and 2.3% of the change in the symptom score. Prostate volume was statistically significant positive relationship with prostate specific antigen(**C**) (**p=0.0013**). The coefficients of determination ($R^2$ value) was 0.0482 which means that, each unit increase of PSA influences 4.8% of the change in the prostate volume.

# CHAPTER 5

## 5.0 DISCUSSION

This study evaluated the indicators for the assessment of prostate disorders at the Komfo Anokye Teaching Hospital (KATH) and the development of a novel prostate nomogram for predicting the outcome of prostate biopsy among Ghanaian men. In all, total of 241 participants were recruited into the study were referred to KATH for initial prostate biopsy. Among the eligible patients 172(71.4%) had benign prostatic hyperplasia, 6 (2.5%) had chronic inflammation and the remaining 63 (26.1%) had prostate adenocarcinoma (Table 4.2). Prostate disorders were assessed using prostate specific antigen (PSA), digital rectal examination (DRE) prostate volume and prostate specific antigen density (PSAD) as individual diagnostic tools and a bioscore for their combinations. PSAD showed a better accuracy than PSA, DRE and prostate volume in detecting prostate cancer respectively. Combination of three tests (DRE+PSAD+PSA) yielded a higher better accuracy than combination of two tests (PSAD+DRE) and four tests combinations respectively. Bioscore for the combination of the diagnostic tools were significantly associated with increasing odds of prostate cancer detection upon logistic regression analysis (Table 4.7). In this study, two prostate nomograms were developed and internally validated using 500 bootstrapped re-samples with nomogram I composed of only the diagnostic tools and identified risk factors and nomogram II composed of diagnostic tools. Nomogram I showed a better diagnostic accuracy than nomogram II in predicting prostate biopsy outcome.

### 5.1 PREVALENCE OF PROSTATE CANCER, BENIGN PROSTATIC HYPERPLASIA, AND LOWER URINATION TRACT SYMPTOMS (LUTS)

Prostate cancer was diagnosed in 63 (26.1%) patients. This finding consistent with a prospective study by Murray *et al.* (2014) among Chilean men

respectively. In a related screen-based study conducted among 660 men aged 5070 years using PSA assays and digital rectal examination in South Africa, Heyns *et al.* (2003) reported a high detection rate of 43%. Furthermore, recent study in Senegal screened 572 men using a PSA cut-off 4.0ng/ml and DRE findings also reported a higher detection rate of 30.6% (Naing *et al.*, 2006). However, Hsing *et al* (2014), reported a high prostate cancer prevalence of 7.0% in a populationbased study among a relatively unscreened population in Africa (Hsing *et al.*, 2014) which is lower than the prevalence reported in this study. It is evident that prostate cancer is a much more common disease in Ghanaian than implied by reported registry incidence data although direct comparison of rates between population and hospital-based studies is challenging due to sample size and study design (Chu *et al.*, 2011; Rebbeck *et al.*, 2013). Majority (57.1%) of the prostate cancer subjects were between the ages of 70 – 79 years (Table 4.2). This finding is in line with a prospective study by Hudson *et al.* (1994) who reported that cancer detection rate among Americans increased in men aged 50 years to 80 years or older.

Benign prostatic hyperplasia (BPH) was histologically diagnosed in 172 (71.4%) patients in this current study (Table 4.2). This is higher than cross-sectional prospective study among Filipino men by Chua et al, 2015 who reported a prevalence of 29.9%. This is supported by reports from several studies showing low incidence rate of prostate disorder among Asian and Pacific landers (Clegg *et al.*, 2002). Furthermore, findings from this current study agrees with a previous cross-sectional study among Ghanaians (Obu, 2014). Majority of participant diagnosed with BPH were in the age range 70 -79 years. This is supported by previous studies which reported that BPH is uncommon before age 40; roughly 50% of men develop BPH-related symptoms at 50 year of age. The incidence of BPH increases by 10% per decade and reaches 80% at approximately 80 year of age (Girman, 1998; Briganti *et al.*, 2009). However, only 2.64% of the participants were diagnosed of having chronic inflammation which is lower than estimates reported in previous studies(Nickel *et al.*, 2001; Chua *et*

*al.*, 2015).

Lower urinary tract symptoms are common symptomatic presentation in the elderly men. The study indicated that, the using of the IPSS score, prevalence of LUTS was 88.9%. Figure (4.7) This was far higher than a population-based study that was carried out among Ghanaian men in the Greater Accra region in which a prevalence of 19.9% was reported (Chokkalingam *et al.*, 2012). Furthermore, the frequency of occurrence of LUTS in the present study was higher than the 12% reported in France and other white population from Netherland (10.3%), Germany (14%) and Canada (21%) (Norman *et al.*, 1994; Sagnier *et al.*, 1994; Braun *et al.*, 2003; Chokkalingam *et al.*, 2012). It should also be mentioned here that, our observed prevalence was also higher than results obtained elsewhere in which IPSS tool was employed (Sarma *et al.*, 2003; Kupelian *et al.*, 2006; Markland *et al.*, 2007) This observed inconsistencies are due to the different study designs and sample sizes between hospital and population-based studies. However, the prevalence in this present study was comparable to reports from hospital-based studies in south-western Nigeria (88.0%), Ethiopia (84.4%) and Port Harcourt, Nigeria (72.2%) (Berhanu, 2008; Adegun and Popoola, 2011; BockOruma *et al.*, 2013). These observations tend to indicate that prevalence of LUTS in hospital-based studies is comparatively higher than that reported in population-based studies.

As age advanced, it is expectant that the prevalence of LUTS seen in men would increase. In this current study, it was found that the prevalence of LUTS increased with age with higher proportion of the subjects being older than 70 years of age (Table 4.14). These findings are consistent with a population-based study among Swedish men and Austrian men (Haidinger *et al.*, 2000; Andersson *et al.*, 2004). The presentation patterns of LUTS in this present study have shown that bladder storage symptoms were the most experienced symptoms (88.59%).

Urgency was the most predominant reported LUTS (93.3%) observed in this study consistent with a study in India (Braun *et al.*, 2003). It is of interest to note that, perhaps exclusion of urgency score from the IPSS tool would significantly change the LUTS score and reduce the prevalence of LUTS.

In contrast to the results for IPSS, the prevalence of prostate enlargement based on DRE among the subjects was 42.3% which is lesser compared to reports from population-based study among Ghanaian and a hospital-based study among Nigerians, but substantially higher than that reported for predominantly Caucasian in the United States (Naslund *et al.*, 2007; Chokkalingam *et al.*, 2012; Bock-Oruma *et al.*, 2013) (Table 4.2). However DRE assessment may vary depending on the experience of the health care provider preforming the evaluation.

PSA levels less than or equal to 4.0ng/ml is an optimal cut off acceptable for most populations. PSA elevated level gave a prevalence of 87.60% in this present study. Recent data have also shown that PSA ≥1.5ng/ml indicates a prostate volume of ≥30ml which is the volume range with the risk for BPH progression increases (Roehrborn *et al.*, 1997; Bosch *et al.*, 2004). In our study, 205 subjects had PSA ≥1.5ng/ml and out of these, 85.23% had prostate volume ≥30ml. This study also showed that 75.5% of the subjects had troublesome LUTS which is comparable to a hospital-based study among Nigerians (Bock-Oruma *et al.*, 2013) but inconsistent with a hospital-based study among Indians which is due to the large size of men recruited for the study (Rao *et al.*, 2004). The occurrence of bothersome LUTS in this study showed that LUTS suggestive of BPH impacted negatively on the lives of the subjects. It is therefore necessary for clinicians to be knowledgeable of the management of the condition if the quality of life of patients and members of the society are to be improved.

## 5.2 PERFORMANCES OF INDIVIDUAL AND COMBINATION OF DIAGNOSTIC TOOLS IN DETECTING PROSTATE CANCER

Although PSA is the routinely used marker in assessing PCa and other prostate related conditions, various studies (Bozeman *et al.*, 2002; Punglia *et al.*, 2006) have indicated that, this marker lacks adequate specificity and sensitivity for a clinical decision to be made in a suspected prostate disorder. This study therefore assessed the performance of individual and combination of specific diagnostic tool used in the detection of prostate cancer among Ghanaian men.

Results from the present study shows that, 42.3% of patients diagnosed with prostate cancer had abnormal DRE (Table 4.2).This agrees with a prospective study by Catalona et al., (Catalona *et al.*, 1994) among Americans. Among the patients with prostate cancer in our study, 69.8% had both abnormal DRE and PSA> 4.0ng/ml which is comparable to a prospective study done by Hudson et al.,(Hudson *et al.*, 1994). The result of this present study showed that majority of patients diagnosed with prostate cancer had an abnormal DRE which is comparable to a retrospective study among Turkish by Akdas et al., (Akdas *et al.*, 1995). This means that DRE should routinely be on the clinical examination panel as it remains a key tool of PCa diagnosis.

This current study observed that higher proportion of the diagnosed prostate cancer patients were within the PSA range 20.1ng/ml to 50ng/ml (Table 4.2) which corroborate with a retrospective study by Gerstenbluth et al., (Gerstenbluth *et al.*, 2002). A similar trend was also reported in a population study among Iranians by Ghafoori and colleagues (2009). Our study showed that, higher proportion of prostate cancer patients had PSAD > 0.15ng/ml/ml which is the traditionally accepted cut-off point (Ghafoori *et al.*, 2009). This implies that, the possibility of identifying patients with PCa is higher when PSAD is greater than 0.15ng/ml/ml. Several authors have stated that PSAD could be a useful marker to distinguish

patients with PCa from BPH more accurately (Deliveliotis *et al.*, 1998; Murray *et al.*, 2014).

The findings of this study indicates that PSA and PSAD were significantly higher ($p<0.0001$) in comparison between patients with and without prostate cancer. This is consistent with previous reports from some studies (Polascik *et al.*, 1999; Brawer, 2000; Ghafoori *et al.*, 2009). Age has been identified as a significant risk factor for prostate cancer, therefore no significant difference in age was observed between the patients with and without prostate cancer which agrees with a cross-sectional study by Sheik et al., (Sheikh *et al.*, 2005) among Arab men. However, Stephen and colleagues (2005) did find a significant difference in a retrospective study among Germans (Stephan *et al.*, 2005). A serum PSA threshold of 4ng/ml is usually an indication for prostate biopsy and PSA level between 4 and 10ng/ml which is considered a gray zone are shown to have low sensitivity but values above 10ng/ml have a high sensitivity for PCa. The sensitivity even reaches 100% if values higher than 15ng/ml are considered (Morgan *et al.*, 1996; Sheikh *et al.*, 2005). In our study the lower cut-off point of 4ng/ml for PSA had a higher sensitivity and lower specificity which is in line with a study among Iranian population (Ghafoori *et al.*, 2009).

The result of this current study showed that, among the individual diagnostic tools, PSAD had better accuracy than PSA, DRE and prostate volume respectively. PSAD was introduced to correct the PSA levels associated with prostate volume on the basis that prostate cancer releases more PSA per unit volume into circulation than BPH. Previous studies by Deliveliotis *et al.* (1998) have shown that PSAD is a useful marker in detecting prostate cancer which agrees with finding in our present study and that of a cross-sectional study among a Japanese population by Sasaki et al., (Sasaki *et al.*, 2000). To make this study

more credible and very successful, bioscores were developed combining different tests (DRE, ultrasound, PSA assay and PSAD) in the diagnosis of

prostate cancer.

The combination of three tests (DRE+PSAD+PSA) yielded a higher better accuracy (AUC =80.6) followed by combination of two test (PSAD+DRE) with AUC of 78.1 and an AUC of 76.7 for fours combinations respectively. These trends of accuracies have shown that combinations of diagnostic tools have high rate of detection of prostate tumors better than the use of a single diagnostic test that can evoke a low detection rate. Similar findings were reported in descriptive retrospective study conducted among Algerians by Kandouci (2014). Likewise,
In Japan, Shimizu et al. conducted mass screening for PCa using PSA and DRE as indices without age limit and reported that the high detection rate for PCa when these parameters were combined**.** However, they indicated that the
detection rate was low % when PSA alone was examined (Shimizu *et al.*, 1995). Based on data from advanced countries (Benson *et al.*, 1992; Benson and Olsson, 1994) , PSA density of 0.15ng/ml/ml has been widely used as a cut-off point value. Results from our study shows that PSAD had sensitivity of 84.1% and specificity of 56.7% which is comparable to findings from previous studies (Lee
*et al.*, 2004; Murray *et al.*, 2014).

Positive predictive value is another parameter in the assessment for cancer detection. It gives vital clinical information. Higher values imply less redundant biopsies (Catalona *et al.*, 1994). In our study, the positive predictive values for PSAD+DRE+PSA and PSAD+DRE were in the increasing order respectively (Table 4.6). Similar findings pertaining to positive predictive values have also been reported by some previous studies (Catalona *et al.*, 1994) (Ghafoori *et al.*, 2009; Murray *et al.*, 2014). In the study, sensitivity and specificity were done for the various combinations of the test methods which are common in clinical

practice with combination of all four diagnostic tools having sensitivity of 90.5%. However, combinations of PSAD+DRE had the highest specificity. These findings obtained from these two different combinations agree with a retrospective study among Turkish population by Akdas et al., (Akdas *et al.*, 1995). Indeed for the first time, we have shown that, the combination of diagnostic tools have a better diagnostic performance for detecting prostate
cancer among Ghanaian men. The bioscore's calculation implies the measurement of three biomarkers; it clearly provides relevant information likely to strengthen the physician's decision in addition to clinical work-up.

### 5.3 FACTORS ASSOCIATED WITH PROSTATE CANCER

Results from our study have clearly confirm that bioscores for the combination of the diagnostic tools were significantly associated with increasing odds of prostate cancer detection upon logistic regression analysis [Table 7] this is in line with a retrospective study among Chinese population by Teoh et al., (Teoh *et al.*, 2015). Another cross-sectional prospective study among Filipino males by Chua et al., (Chua *et al.*, 2015) reported that increased PSA level, abnormal DRE were statistically ($p < 0.001$) associated with prostate cancer with lower odd ratios in comparison to findings in our study. These low odd ratios are likely to be due to the lower incidence of prostate cancer among Asians compared to that of Africans, African Americans and European Caucasians (Kimura, 2012).

Previous studies by Key (Key, 1994), Gann (Gann *et al.*, 1996), Patel and Klein (Patel and Klein, 2009) and Gong et al., (Gong *et al.*, 2006) also reported family history, age, race/ethnicity and smoking as associated risk factors of prostate cancer. Result from our present study shows a significant association of age, history of alcohol consumption and history of smoking with prostate cancer diagnosis upon regression analysis which is consistent with the findings of

Honda *et al.* (1988). Moreover, there was a significant association of history of smoking and alcohol consumption with positive prostate biopsy outcome ($p < 0.05$) upon chi square analysis.

## 5.4 NOMOGRAM FOR PREDICTING PROBABILITY OF POSITIVE PROSTATE BIOPSY OUTCOME AMONG GHANAIAN MEN

Prostate biopsy is performed with caution, yet various procedure-associated complications after prostate biopsy may occur (Loeb *et al.*, 2011; Loeb *et al.*, 2012). Recent studies have reported an increase in the occurrence of infections and other complications after trans-rectal prostrate biopsy (Nam *et al.*, 2010; Loeb *et al.*, 2012). It is therefore imperative that, prostate biopsy be carefully performed to avoid associated risk of procedure-related complications. Although nomograms have been developed as a guideline to reduce these mistakes in some parts of the world, this study provides a novel predictive model that incorporates clinical and laboratory data from general practice and examines the accuracy of a nomogram for the prediction of the prostate cancer risk in a Ghanaian population

Reliable nomogram that can accurately predict and differentiate the presence of aggressive prostate cancer from benign conditions would be useful for urologist and patients to make decisions (Chua *et al.*, 2015). In the current dataset for nomogram development, it was found that age, DRE PSA, PSAD, history of smoking, and history of alcohol consumption were significantly independent predictors ($p<0.05$) of prostate cancer and were used for the nomogram predictor variables. These findings are consistent with those in previous reports from systematic review and the prevention trial and European randomized study (Schröder and Kattan, 2008; Cavadas *et al.*, 2010). Furthermore, in some studies, multiple variables were used as a predictor of PCa, such as age, PSA, percent free PSA, family history of PCA, abnormal DRE findings and races (Optenberg *et al.*, 1997; Karakiewicz *et al.*, 2005; Chua *et al.*, 2015). However, after multivariate analysis in this present study, it was observed that age and history of smoking

were not independent predictors of positive initial prostate biopsy (p>0.05) (Table 4.9). Nam *et al.* (2010) used 6 factors including age, PSA, percent free PSA, family history of PCa, abnormal DRE findings and race to develop a predicting model for PCA and the predictive value was up to 74%. Furthermore, Optenberg *et al.* (1997) developed a model to predict the risk of PCa on prostate biopsy using 633 patients and the total AUC of the model was 0.81. In this study we developed and internally validated 2 nomograms predicting the probability of PCa on needle biopsy in men referred for prostate biopsy. Using DRE, PSA and PSAD the prediction AUC was 84.8% (Figure 4.1). Adding more variable such as age, history of smoking, alcohol consumption enhances the AUC to 87.7%. Therefore, in 100 sets of randomly paired patients in which 1 has PCa on needle biopsy and the other does not, the nomograms would correctly predict which of the patients has PCa to about 84.8% and 87.7% accuracy respectively. These findings from our study appear higher compared to previously reported regressions based nomograms for patients with localized PCa (Garzotto *et al.*, 2003; Suzuki *et al.*, 2006; Thompson *et al.*, 2006; Hernandez *et al.*, 2009; Park *et al.*, 2011). The results from this study favorably relates to the nature of the predictor variables used in the employed nomograms; namely age, DRE, PSA, history of smoking, history of alcohol consumption and PSAD. Indeed these predictors in combination have been shown to be more informative and reliable in the diagnosis of prostate cancer.

In the Ghanaian setting, there is a widespread use of the PSA, DRE and PSAD tests, thus Ghanaian men are more frequently referred for biopsy under these conditions. However, in the present study, we found that the accuracy of nomogram I and II for predicting a positive initial prostate biopsy was better than using PSA levels alone (AUCs were 87.7%, 84.9 vs. 79.7%, respectively). Similar trends were also shown between the PSAD, DRE, prostate volume and the two nomograms respectively (AUC were 78.9%, 68.6% 52.2% vs. 87.5%, 84.8%). While

these results are similar with those reported from previous studies from developed countries (Kuo *et al.*, 2013; Tang *et al.*, 2013; Ahn *et al.*, 2014; Chua *et al.*, 2015), this is the first report to do so in a Ghanaian population, using a Ghanaian cohort. Compared to other reports from literature, previous studies have not included PSAD in most prostate nomogram, although PSAD has been shown in several studies and this study to have better accuracy than PSA and DRE (Deliveliotis *et al.*, 1998; Chun *et al.*, 2007). The median PSAD value in our study cohort was high because PSAD testing is still not routinely used for early detection of prostate cancer in Ghana; thus, the majority of prostate cancers are diagnosed at a later disease stage. PSAD, which was included in our predictive model, may also be a key factor in improving the accuracy of the nomogram.

This stresses fact that regression-based model needs to be calibrated and validated in patients with similar disease characteristics before usage, because patient characteristics may vary. It should be emphasized here that, the characteristics of prostate cancer might not be the same in Europe, United States and Africa (Steuber *et al.*, 2006).. In this study, the two nomograms developed were well calibrated by the Hosmer-Lemeshow good-of-fit test (P=0.683 and P=0.287) and validated internally with 500 bootstrapped re-samples Most of the predictors used in the development of the two nomograms were significant in the bootstrapped output. This means that, the observed difference between significant variable in non-bootstrapped analysis is not due to chance. These internal validated estimates demonstrated less pronounced differences between developed and internally validated data than were observed for the prostate biopsy nomograms. These findings are similar to previous studies on internally validated regression-based nomograms by Tang *et al.* (2013), Garzotto *et al.* (2003) and Thompson *et al.* (2006) in the Chinese and Western population. Nomogram in these studies demonstrated minimal decrease in predictive

accuracy relative to the current nomograms developed in this study. It should be pointed out that this present cross-sectional prospective study has some level of limitation due to the sample size. However, nomograms uses for predicting a positive initial prostate biopsy are not new. It is likely that, nomograms generated in Asian and Western countries may not be directly applicable to a Ghanaian population.



## 5.5 PREDICTORS OF SYMPTOMS SCORE ON THE IPSS FOR PATIENTS WITH LOWER URINARY TRACT SYMPTOMS

As age advanced, it is expected that the prevalence of LUTS seen in men would increase. In this current study, it was found that the prevalence of LUTS increased with age with higher proportion of the subjects with age being greater than 70 years of age (Table 4.14) This increase in age was statistically significant ($p < 0.0001$). In parallel and according to logistic model results from the study, an advanced age greater than 70 years was significant risk factor for LUTS (OR = 27.63; $P < 0.0001$), followed by subjects in the 60 – 69 age range (OR = 22.0; $P = 0.0003$). These findings are in line with previous reported studies (Haidinger *et al.*, 2000; Andersson *et al.*, 2004).

Several studies have reported that PSA levels correlate positively with prostate size and has been used as a surrogate marker for prostate volume as well for the estimation of patient's risk of progression to BPH. Traditionally, it has been thought that an increase in prostate volume precipitates the development of lower urinary tract symptoms (LUTS), due to the bladder outlet obstruction caused by the prostate exerting pressure on the urethra. Some studies have reported that prostate size and PSA levels do not always correlate well with symptom severity (Roehrborn *et al.*, 1999; Bosch *et al.*, 2004). Regression analysis in this study showed that IPSS was linearly and positively related to PSA ($R^2 = 0.023$; $p = 0.029$) and age ($R^2 = 0.156$; $p < 0.0001$) (Figure 4.6). These findings are consistent with reports from

the Tsukamoto *et al.* (2007) study. However, the clinical application of this finding is minimal, as it is only able to influence 2.3%
and 15.6% of the symptoms reported by patients, thus making it a poor predictor. Moreover, according to logistic regression model results, an elevated PSA levels in the range of 20.1 -10ng/ml was an important risk factor but statistically not significant for LUTS suggestive of BPH (OR = 1.49; p = 0.252). The fact still remains that prostate size is associated with PSA levels and the symptoms severity.

Furthermore, it has been reported in previous studies educational level plays an important role in making the individual aware of LUTS. This allows them to seek and comply with treatment performed to them. In a parallel study, Signorello et al (1999) reported that as education levels increased, LUTS risk decreases. This positive relation may related to the fact that, those whose educational level are high reach to health services easily (Signorello *et al.*, 1999; Badia *et al.*, 2001). According to the outcome of the logistic model used in this study, advancement in education was found to be associated with reducing risk for LUTS but was not statistically significant; basic education level (OR =0.46; p = 0.673), secondary education level (OR =0.36; 0.391) and tertiary education level (OR = 0.41; 0.679) respectively (Table 4.15).

Most studies that examined the role of alcohol consumption as a risk factor among surgically treated BPH patients showed an inverse association (Gann *et al.*, 1995; Platz *et al.*, 1999) or no association (Sidney *et al.*, 1991; Meigs *et al.*, 2001) with alcohol consumption. In this present study, we observed higher proportion (75.61%) of men with moderate to severe symptoms scores who consumed alcohol (Table 4.15). In addition, we did not find any significant association between alcohol consumption and moderate to severe symptoms but with increased odds (OR = 1.026; p =0.990) according to logistic model results. Indeed, it has been shown that, nicotine increase sympathetic nerve system activity and

might contribute to LUTS via an increase in the tone of the prostate and bladdersmooth muscle. Some previous studies have indicated that, those who smoke cigarettes had more prevalence of LUTS(Platz *et al.*, 1999; Orsini *et al.*, 2006). Similarly, the present study revealed that higher proportion (57.9%) of subjects who smoke had moderate to severe symptoms scores (Table 4.15). Platz *et al.* (1999) noted that, obstructive symptoms were strong associated with smoking, we however did not observe any significant association between history of smoking and moderate to severe symptoms score upon univariate logistic regression although there was a significant association (AOR = 0.32: p = 0.038) in the multivariate logistic model controlling for age.

Concurrently with LUTS, cardiovascular disease, hypertension and diabetes mellitus are common condition in the elderly men (Hammarsten and Högstedt, 2001; Hammarsten and Högstedt, 2004). However, we did not observe significant association with stroke, hypertension and diabetes mellitus in men with moderate to severe LUTS (Table 4.15). In this current study, the prevalence of LUTS was higher in married men in comparison to single males. This finding is in line with other studies showing similar results (Glynn *et al.*, 1985; Safarinejad, 2008). Moreover, the logistic model results in this present study showed that married men were more likely to experience LUTS suggestive of BPH (OR = 2.89; p =0.303). There was also a significant association (p =0.041) between widowed men and moderate to severe symptoms with reduced odds for LUTS (OR = 0.06 (0.004 – 0.740) (Table 4.15). Until to now, no acceptable reason has been given to explain why married men have more LUTS than single men; therefore there is the need to assess the impact of being single and or married on prevalence of LUTS in individuals. The reports of this study were hospital-based and this may not be representative of what occurs in the general community. Therefore, extrapolations should be made with restraint.

# CHAPTER 6

# 6.0 CONCLUSION & RECOMMENDATION

## 6.1 CONCLUSION

Serum total PSA and PSAD were confined as sensitivity biomarkers however; the study clearly showed that they lack the clinical specificity for the definitive diagnosis of prostate cancer. On the other hand, DRE as a diagnostic tool did not show adequate specificity and sensitivity in reaching a clinical decision of suspected case of prostate cancer. However, combining, the diagnostic performance of DRE+PSAD+PSA provides a better diagnostic accuracy. Bioscores for the combination of the diagnostic tools were significantly associated with increasing odds of prostate cancer detection upon logistic regression analysis.

Furthermore, the study has established that, bladder storage symptoms are the most experienced LUTS and may be associated with troublesome symptoms. This study has also showed that the prevalence estimates of LUTS in older men are progressively higher and therefore there is the need to increase effort to detect and treat LUTS in men over 50 years as early as possible. This study has been able to develop and validate a novel nomogram useful for Ghanaian men with elevated serum total PSA level or abnormal DRE. The nomograms based on routinely available clinical parameters and PSA derivatives provided high predictive accuracy with good performance characteristics in predicting the prostate biopsy outcome such as presence of prostate cancer and benign prostatic hyperplasia. The prediction rate of PCa of employing this nomogram was higher than that of other existing nomograms.

## 6.2 STUDY LIMITATION

The inability to conduct a longitudinal cohort study among larger population which could have assessed the changes of these diagnostics tools over time and the use elevated total PSA or abnormal digital rectal examination as indicators for selections of participants. The data in our study were obtained from a single, tertiary hospital, which may lead to some degree of biased results, besides our nomograms have not been validated externally whether it can be universally applied to Ghanaian populations must be confirmed. Furthermore, larger, prospective and randomized studies are necessary to corroborate our findings.

## 6.3 RECOMMENDATION

1. Combinations of specific prostate diagnostic tools (PSA, PSAD, DRE, and Prostate Volume) are required for early detection of prostate cancer

2. Incorporating the use of nomograms will improve the accuracy in the diagnosis of prostate cancer and prevent unnecessary biopsies.

3. This study reflected a center-based screening population and validated internally for its accuracy. It is therefore imperative for other centers to confirm and externally validate the present findings. A multi-institutional study is strongly recommended.

## PUBLICATION EMANATING FROM THE PROJECT

1. Kenneth, A., Francis, A.Y., Christian, G.S.K., Ferguson, L.E., **Emmanuel, A.**, Benjamin, T.F., George, A., Emmanuella, B.N. and Portia, A.A., 2016. Lower

urinary tract symptoms suggestive of benign prostatic hyperplasia among Ghanaian men: a hospital-based cross-sectional prospective study. *International Journal of Research in Medical Sciences*, *4*(9), pp.3905-3911. ***DOI: 10.9734/BJMMR/2016/27890***

**2.** Agyemang-Yeboah F., A.Y., Kenneth, A., Christian, G.S.K., Ferguson, L.E., **Emmanuel, A**., Benjamin, T.F., George, A., Emmanuella, B.N., Enoch O. A., Bright A., 2016. Assessment of the performance of specific prostate diagnostic Tools in the Detection of Prostate cancer among Ghanaian men, *British Journal of Medicine & Medical Research 17(2)*: 1-13, 2016. ***DOI: http://dx.doi.org/ 10.18203/2320-6012.ijrms20162906***

**UNDER REVIEW**

**3.** Francis, A.Y., Kenneth, A., Christian, G.S.K., Ferguson, L.E., **Emmanuel, A**., Benjamin, T.F., George, A., Emmanuella, B.N., Enoch O. A., Bright A., 2016. Nomogram for Predicting the Probability of the Positive Outcome of Prostate Biopsies among Ghanaian Men, ***BMC cancer, BCAN-D-16-01984***

**CONFERENCE PAPERS**

1. Kenneth, A., Francis, A.Y., Christian, G.S.K., Ferguson, L.E., **Emmanuel, A**., Benjamin, T.F., George, A., Emmanuella, B.N. and Portia, A.A., 2016. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia among Ghanaian men: a hospital-based cross-sectional prospective study, ***In the 4th Congress, European Federation Laboratory medicine***, Double Tree by Hilton Hotel and Conference Centre, Warsaw, Poland, 0011 September, 21-24, p.116. ***DOI:10.1515/cclm-2016-0657***

2. Agyemang-Yeboah F., Kenneth, A., Christian, G.S.K., Ferguson, L.E., **Emmanuel, A**., Benjamin, T.F., George, A., Emmanuella, B.N., Enoch O. A., Bright A., 2016. Assessment of the performance of specific prostate diagnostic Tools in the Detection of Prostate cancer among Ghanaian men, ***In the 4th Congress, European Federation Laboratory medicine***, Double Tree by Hilton Hotel and Conference Centre, Warsaw, Poland, 0020, September, 21-24, p.53, ***DOI:10.1515/cclm-2016-0657***

## REFERENCES


Adegun P. and Popoola A. (2011) A survey of benign prostatic hyperplasia (BPH) amongst patients with prostatic disorders in Ado-Ekiti, Nigeria. *Nig Med Pract* 60(3-6), 38-42.

Agyei-Frempong M., Frempong N., Aboah K. and Boateng K. (2008) Correlation of serum free/total prostate specific antigen ratio with histological features for differential diagnosis of prostate cancer. *J. Med Sci* 8(6), 540-546.

Ahn J.H., Lee J.Z., Chung M.K. and Ha H.K. (2014) Nomogram for prediction of prostate cancer with serum prostate specific antigen less than 10 ng/mL. *Journal of Korean medical science* 29(3), 338-342.

Akdas A., Tarcan T., Türkeri L., Cevik I., Biren T. and Gürmen N. (1995) The diagnostic accuracy of digital rectal examination, transrectal ultrasonography, prostatespecific antigen (PSA) and PSA density in prostate carcinoma. *British journal of urology* 76(s1), 54-56.

American Urological Association (1992) Executive committee report. *Baltimore: American Urological Association*.

American Urological Association (2007) Guideline on the management of benign prostatic hyperplasia (BPH). *Accessed September 19*.

Andersson S.O., Rashidkhani B., Karlberg L., Wolk A. and Johansson J.E. (2004) Prevalence of lower urinary tract symptoms in men aged 45–79 years: a population-based study of 40 000 Swedish men. *BJU international* 94(3), 327-331.

Angwafo F., Yomi J. and Mbakop A. (1993) Is cancer of the prostate rare in tropical (black) Africa? Case series from the Centre Hospitalier et Universitaire and the Hospital General de Yaounde from 1986 to 1990. *Bulletin du cancer. Radiotherapie: journal de la Societe francaise du cancer: organe de la societe francaise de radiotherapie oncologique* 81(2), 155-159.

Arthur F., Yeboah F., Adu-Frimpong M., Sedudzi E. and Boateng K. (2006) Prostate cancer screening in Ghana-a clinical benefit? *Journal of Science and Technology (Ghana)* 26(1), 1-7.

Aslan G., İrer B., Kefi A., Çelebi İ., Yörükoğlu K. and Esen A. (2005) The value of PSA, free-to-total PSA ratio and PSA density in the prediction of pathologic stage for clinically localized prostate cancer. *International urology and nephrology* 37(3), 511514.

Ayala A.G. and Ro J.Y. (2007) Prostatic intraepithelial neoplasia: recent advances. *Archives of pathology & laboratory medicine* 131(8), 1257.

Badia X., Rodriguez F., Carballido J., Losa M.G., Unda M., Dal-Ré R. and Roset M. (2001) Influence of sociodemographic and health status variables on the American Urological Association symptom scores in patients with lower urinary tract symptoms. *Urology* 57(1), 71-77.

Barry M., Cockett A., Holtgrewe H., McConnell J., Sihelnik S. and Winfield H. (1993) Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. *The Journal of urology* 150(2 Pt 1), 351-358.

Barry M.J. (2001) Evaluation of symptoms and quality of life in men with benign prostatic hyperplasia. *Urology* 58(6), 25-32.

Barry M.J. (2009) Screening for prostate cancer—the controversy that refuses to die. *New England Journal of Medicine* 360(13), 1351-1354.

Basler J.W. and Thompson I.M. (1998) Lest we abandon digital rectal examination as a screening test for prostate cancer. *Journal of the National Cancer Institute* 90(23), 1761-1763.

Benecchi L., Pieri A.M., Melissari M., Potenzoni M. and Pastizzaro C.D. (2008) A novel nomogram to predict the probability of prostate cancer on repeat biopsy. *The Journal of urology* 180(1), 146-149.

Benson M.C. and Olsson C.A. (1994) Prostate specific antigen and prostate specific antigen density. Roles in patient evaluation and management. *Cancer* 74(6), 16671673.

Benson M.C., Whang I., Pantuck A., Ring K., Kaplan S., Olsson C. and Cooner W. (1992) Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *The Journal of urology* 147(3 Pt 2), 815-816.

Berges R., Dreikorn K., Höfner K., Jonas U., Laval K., Madersbacher S., Michel M., Muschter R., Oelke M. and Pientka L. (2003) Guidelines of German urologists on therapy of benign prostate syndrome. *Der Urologe. Ausg. A* 42(5), 722.

Berhanu N. (2008) The safety and efficacy of trans-vesical prostatectomy done at a primary general hospital setting in Ethiopia.

Berry S.J., Coffey D.S., Walsh P.C. and Ewing L.L. (1984) The development of human benign prostatic hyperplasia with age. *The Journal of urology* 132(3), 474-479.

Bianco F.J., Wood D.P., Grignon D.J., Sakr W.A., Pontes J.E. and Powell I.J. (2002) Prostate cancer stage shift has eliminated the gap in disease-free survival in black and white American men after radical prostatectomy. *The Journal of urology* 168(2), 479-482.

Blandy J.P. and Lytton B. (1986) *The Prostate*. London:: Butterworths.

Bock-Oruma A.A., Dienye P.O. and Oghu I.S. (2013) Prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care, Port Harcourt, Nigeria. *South African Family Practice* 55(5), 467-472.

Bosch J., Bohnen A. and Groeneveld F. (2004) Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. *European urology* 46(6), 753-759.

Bosch J., Hop W., Kirkels W. and Schröder F. (1995) The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. *British journal of urology* 75(5), 622-630.

Bostwick D.G. (1996) Prospective origins of prostate carcinoma: prostatic intraepithelial neoplasia and atypical adenomatous hyperplasia. *Cancer* 78(2), 330-336.

Bostwick D.G. and Brawer M.K. (1987) Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. *Cancer* 59(4), 788-794.

Boyle P., Gould A.L. and Roehrborn C.G. (1996) Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 48(3), 398-405.

Bozeman C.B., Carver B.S., Eastham J.A. and Venable D.D. (2002) Treatment of chronic prostatitis lowers serum prostate specific antigen. *The Journal of urology* 167(4), 1723-1726.

Bratt O. (2002) Hereditary prostate cancer: clinical aspects. *The Journal of urology* 168(3), 906-913.

Braun M., Sommer F., Haupt G., Mathers M., Reifenrath B. and Engelmann U. (2003) Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "Aging Male" symptoms? Results of the "Cologne Male Survey". *European urology* 44(5), 588-594.

Brawer M.K. (2000) Screening for prostate cancer. *Seminars in surgical oncology* **18**, 29-36.

Brawer M.K., Peehl D.M., Stamey T.A. and Bostwick D.G. (1985) Keratin immunoreactivity in the benign and neoplastic human prostate. *Cancer research* 45(8), 3663-3667.

Briganti A., Capitanio U., Suardi N., Gallina A., Salonia A., Bianchi M., Tutolo M., Di Girolamo V., Guazzoni G. and Rigatti P. (2009) Benign prostatic hyperplasia and its aetiologies. *European Urology Supplements* 8(13), 865-871.

Brown C. and Das G. (2002) Assessment, diagnosis and management of lower urinary tract symptoms in men. *International journal of clinical practice* 56(8), 591-603.

Calle E.E., Rodriguez C., Walker-Thurmond K. and Thun M.J. (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine* 348(17), 1625-1638.

Carpten J., Nupponen N., Isaacs S., Sood R., Robbins C., Xu J., Faruque M., Moses T., Ewing C. and Gillanders E. (2002) Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. *Nature genetics* 30(2), 181-184.

Carter B.S., Beaty T.H., Steinberg G.D., Childs B. and Walsh P.C. (1992) Mendelian inheritance of familial prostate cancer. *Proceedings of the National Academy of Sciences* 89(8), 3367-3371.

Carvalhal G.F., SMITH D.S., MAGER D.E., RAMOS C. and CATALONA W.J. (1999) Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. *The Journal of urology* 161(3), 835-839.

Catalona W., Richie J., Ahmann F., Hudson M., Scardino P., Flanigan R., Dekernion J., Ratliff T., Kavoussi L. and Dalkin B. (1994) Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *The Journal of urology* 151(5), 1283-1290.

Cavadas V., Osório L., Sabell F., Teves F., Branco F. and Silva-Ramos M. (2010) Prostate cancer prevention trial and European randomized study of screening for prostate cancer risk calculators: a performance comparison in a contemporary screened cohort. *European urology* 58(4), 551-558.

Center M.M., Jemal A., Lortet-Tieulent J., Ward E., Ferlay J., Brawley O. and Bray F. (2012) International variation in prostate cancer incidence and mortality rates. *European urology* 61(6), 1079-1092.

Chicharro-Molero J., Burgos-Rodriguez R., Sanchez-Cruz J., del Rosal-Samaniego J., Rodero-Carcia P. and Rodriguez-Vallejo J. (1998) Prevalence of benign prostatic

hyperplasia in Spanish men 40 years old or older. *The Journal of urology* 159(3), 878-882.

Chokkalingam A., Yeboah E., Demarzo A., Netto G., Yu K., Biritwum R., Tettey Y., Adjei A., Jadallah S. and Li Y. (2012) Prevalence of BPH and lower urinary tract symptoms in West Africans. *Prostate cancer and prostatic diseases* 15(2), 170-176.

Chu L.W., Ritchey J., Devesa S.S., Quraishi S.M., Zhang H. and Hsing A.W. (2011) Prostate cancer incidence rates in Africa. *Prostate Cancer* 2011.

Chua M.E., Tanseco P.P., Mendoza J.S., Castillo J.C., Morales M.L. and Luna S.L. (2015) Configuration and validation of a novel prostate disease nomogram predicting prostate biopsy outcome: A prospective study correlating clinical indicators among Filipino adult males with elevated PSA level. *Asian Journal of Urology*.

Chun F.K.H., Karakiewicz P.I., Briganti A., Walz J., Kattan M.W., Huland H. and Graefen M. (2007) A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. *BJU international* 99(4), 794-800.

Clegg L.X., Li F.P., Hankey B.F., Chu K. and Edwards B.K. (2002) Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology, and End Results) Program population-based study. *Archives of Internal Medicine* 162(17), 1985-1993.

Coffey D. and Isaacs J. (1981) Control of prostate growth. *Urology* 17(Suppl 3), 17-24.

Cohen R.J., Shannon B.A., Phillips M., Moorin R.E., Wheeler T.M. and Garrett K.L. (2008) Central zone carcinoma of the prostate gland: a distinct tumor type with poor prognostic features. *The Journal of urology* 179(5), 1762-1767.

Collins M.M., STAFFORD R.S., O'LEARY M.P. and BARRY M.J. (1998) How common is prostatitis? A national survey of physician visits. *The Journal of urology* 159(4), 1224-1228.

Committee A.P.G. (2003) AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *The Journal of urology* 170(2), 530-547.

Cook L.S., GOLDOFT M., Schwartz S.M. and Weiss N.S. (1999) Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. *The Journal of urology* 161(1), 152-155.

Corner J. and Bailey C. (2001) *Cancer nursing : care in context*. Oxford: Blackwell Science;.

Cotran R.S., Kumar V., Collins T. and Robbins S.L. (1999) Robbins pathologic basis of disease.

Cruz F. and Desgrandchamps F. (2010) New concepts and pathophysiology of lower urinary tract symptoms in men. *European Urology Supplements* 9(4), 472-476.

Dahle S.E., Chokkalingam A.P., Gao Y.-T., Deng J., Stanczyk F.Z. and Hsing A.W. (2002) Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. *The Journal of urology* 168(2), 599-604.

Deliveliotis C., Louras G., Kyriazis P., Gyftopoulos A., Louka L. and Alargof E. (1998) The value of prostatic specific antigen density in the early diagnosis of prostate cancer. *International urology and nephrology* 30(3), 305-310.

Di Silverio F., Gentile V., De Matteis A., Mariotti G., Giuseppe V., Luigi P.A. and Sciarra A. (2003) Distribution of inflammation, pre-malignant lesions, incidental

carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *European urology* 43(2), 164-175.

Difuccia B., Keith I., Teunissen B. and Moon T. (2005) Diagnosis of prostatic inflammation: efficacy of needle biopsies versus tissue blocks. *Urology* 65(3), 445448.

Dixon S.C., Kruger E.A., Bauer K.S. and Figg W.D. (1999) Thalidomide up-regulates prostate-specific antigen secretion from LNCaP cells. *Cancer chemotherapy and pharmacology* 43(1), S78-S84.

Djavan B., Nickel J., De La Rosette J. and Abrams P. (2002a) The urologist view of BPH progression: results of an international survey. *European urology* 41(5), 490-496.

Djavan B., Remzi M., Zlotta A., Seitz C., Snow P. and Marberger M. (2002b) Novel artificial neural network for early detection of prostate cancer. *Journal of Clinical Oncology* 20(4), 921-929.

Doble A. (2000) An evidence-based approach to the treatment of prostatitis: is it possible? *Current urology reports* 1(2), 142-147.

Donovan J., Hamdy F., Neal D., Peters T., Oliver S., Brindle L., Jewell D., Powell P., Gillatt D. and Dedman D. (2003) *Prostate testing for cancer and treatment (ProtecT) feasibility study*: Core Research on belhalf of the NCCHTA.

Efron B. (2003) Second thoughts on the bootstrap. *Statistical Science* 18(2), 135-140.

Efron B. and Tibshirani R.J. (1994) *An introduction to the bootstrap*: CRC press.

Engström G., Walker-Engström M.-L., Lööf L. and Leppert J. (2003) Prevalence of three lower urinary tract symptoms in men—a population-based study. *Family practice* 20(1), 7-10.

Epstein J.I. and Herawi M. (2006) Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *The Journal of urology* 175(3), 820-834.

Ezeanyika L.U., Ejike C.E., Obidoa O. and Elom S.O. (2006) Prostate disorders in an apparently normal Nigerian population 1: Prevalence. *Biokemistri* 18(2).

Fair W. and Cordonnier J. (1978) The pH of prostatic fluid: a reappraisal and therapeutic implications. *The Journal of urology* 120(6), 695-698.

Ferlay J., Shin H.R., Bray F., Forman D., Mathers C. and Parkin D.M. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer* 127(12), 2893-2917.

Gabriel J. (2007) *The biology of cancer.*, 2nd ed. ed. ed. Chichester

Hoboken, N.J.: Wiley ;.

Gacci M., Corona G., Salvi M., Vignozzi L., McVary K.T., Kaplan S.A., Roehrborn C.G., Serni S., Mirone V. and Carini M. (2012) A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with $\alpha$blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *European urology* 61(5), 994-1003.

Gann P.H., Hennekens C.H., Grodstein F., Stampfer M.J., Longcope C. and VerhoekOftedahl W. (1995) A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. *The prostate* 26(1), 4049.

Gann P.H., Hennekens C.H., Ma J., Longcope C. and Stampfer M.J. (1996) Prospective study of sex hormone levels and risk of prostate cancer. *Journal of the National Cancer Institute* 88(16), 1118-1126.

Garzotto M., Hudson R.G., Peters L., Hsieh Y.C., Barrera E., Mori M., Beer T.M. and Klein T. (2003) Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels≤ 10 ng/mL. *Cancer* 98(7), 1417-1422.

Gerstenbluth R.E., D S.A., Nehemia H., G O.M. and I R.M. (2002) The accuracy of the increased prostate specific antigen level (greater than or equal to 20 ng./ml.) in predicting prostate cancer: is biopsy always required? *The Journal of urology* 168(5), 1990-1993.

Ghafoori M., Peyman V., Jalil H.S., Mojgan A. and Madjid S. (2009) Value of prostatespecific antigen and prostate-specific antigen density in detection of prostate cancer in an Iranian population of men. *Urology journal* 6(3), 182-188.

Giovannucci E., Rimm E.B., Liu Y., Stampfer M.J. and Willett W.C. (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. *Journal of the National Cancer Institute* 94(5), 391-398.

Girman C. (1998) Population-based studies of the epidemiology of benign prostatic hyperplasia. *British journal of urology. Supplement* 82(1), 34-43.

Glover F.E., Coffey D.S., Douglas L.L., Cadogan M., Russell H., Tulloch T., Baker T.D., Wan R.L. and Walsh P.C. (1998) The epidemiology of prostate cancer in Jamaica. *The Journal of urology* 159(6), 1984-1987.

Glynn R.J., CAMPION E.W., BOUCHARD G.R. and SILBERT J.E. (1985) The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. *American journal of epidemiology* 121(1), 78-90.

Gong Z., Neuhouser M.L., Goodman P.J., Albanes D., Chi C., Hsing A.W., Lippman S.M., Platz E.A., Pollak M.N. and Thompson I.M. (2006) Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiology Biomarkers & Prevention* 15(10), 1977-1983.

Graefen M., Karakiewicz P.I., Cagiannos I., Hammerer P.G., Haese A., Palisaar J., Fernandez S., Noldus J., Erbersdobler A. and Huland H. (2002) A validation of two preoperative nomograms predicting recurrence following radical prostatectomy in a cohort of European men. *Urologic Oncology: Seminars and Original Investigations* **7**, 141-146.

Grover P.L. and Martin F.L. (2002) The initiation of breast and prostate cancer. *Carcinogenesis* 23(7), 1095-1102.

Haas G.P. and Sakr W.A. (1997) Epidemiology of prostate cancer. *CA: Cancer Journal for Clinicians* 47(5), 273-287.

Habermacher G.M., Chason J.T. and Schaeffer A.J. (2006) Prostatitis/chronic pelvic pain syndrome. *Annu. Rev. Med.* 57195-206.

Haidinger G., Temml C., Schatzl G., Brössner C., Roehlich M., Schmidbauer C.P. and Madersbacher S. (2000) Risk factors for lower urinary tract symptoms in elderly men. *European Journal of Urology* 37(4), 413-420.

Hammarsten J. and Högstedt B. (2001) Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. *European urology* 39(2), 151-158.

Hammarsten J. and Högstedt B. (2004) Clinical, haemodynamic, anthropometric, metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. *Blood Pressure* 13(1), 47-55.

Hara R., Jo Y., Fujii T., Kondo N., Yokoyoma T., Miyaji Y. and Nagai A. (2008) Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology* 71(2), 191-195.

Hernandez D.J., Han M., Humphreys E.B., Mangold L.A., Taneja S.S., Childs S.J., Bartsch G. and Partin A.W. (2009) Predicting the outcome of prostate biopsy: comparison of a novel logistic regression-based model, the prostate cancer risk calculator, and prostate-specific antigen level alone. *BJU international* 103(5), 609614.

Heyns C., Mathee S., Isaacs A., Kharwa A., De Beer P. and Pretorius M. (2003) Problems with prostate specific antigen screening for prostate cancer in the primary healthcare setting in South Africa. *BJU international* 91(9), 785-788.

Honda G., Bernstein L., Ross R., Greenland S., Gerkins V. and Henderson B. (1988) Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *British journal of cancer* 57(3), 326.

Hosmer Jr D.W. and Lemeshow S. (2004) *Applied logistic regression*: John Wiley & Sons.

Howlader N., Noone A., Krapcho M., Neyman N., Aminou R., Waldron W., Altekruse S., Kosary C., Ruhl J. and Tatalovich Z. (2011) SEER cancer statistics review, 1975–2008. *Bethesda, MD: National Cancer Institute* 19.

Hsing A.W. and Devesa S.S. (2001) Trends and patterns of prostate cancer: what do they suggest? *Epidemiologic Reviews* 23(1), 3-13.

Hsing A.W., Gao Y.-T., Chua S., Deng J. and Stanczyk F.Z. (2003) Insulin resistance and prostate cancer risk. *Journal of the National Cancer Institute* 95(1), 67-71.

Hsing A.W., Yeboah E., Biritwum R., Tettey Y., De Marzo A.M., Adjei A., Netto G.J., Yu K., Li Y. and Chokkalingam A.P. (2014) High prevalence of screen detected prostate cancer in West Africans: implications for racial disparity of prostate cancer. *The Journal of urology* 192(3), 730-736.

Hudson M., Catalona W., Scardino P., Richie J., Ahmann F., Flanigan R., Dekernion J., Ratliff T., Kavoussi L. and Dalkin B. (1994) Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves. *The Journal of urology* 152(6 Pt 1), 2037-2042.

Iasonos A., Schrag D., Raj G.V. and Panageas K.S. (2008) How to build and interpret a nomogram for cancer prognosis. *Journal of Clinical Oncology* 26(8), 1364-1370.

Irani J., Brown C., Van der Meulen J. and Emberton M. (2003) A review of guidelines on benign prostatic hyperplasia and lower urinary tract symptoms: are all guidelines the same? *BJU international* 92(9), 937-942.

Jacobsen S.J., Girman C.J. and Lieber M.M. (2001) Natural history of benign prostatic hyperplasia. *Urology* 58(6), 5-16.

Jedy-Agba E.E., Curado M.-P., Oga E., Samaila M.O., Ezeome E.R., Obiorah C., Erinomo O.O., Ima-obong A.E., Uka C. and Mayun A. (2012) The role of hospital-based

cancer registries in low and middle income countries—The Nigerian Case Study. *Cancer epidemiology* 36(5), 430-435.

Jemal A., Bray F., Forman D., O'Brien M., Ferlay J., Center M. and Parkin D.M. (2012) Cancer burden in Africa and opportunities for prevention. *Cancer* 118(18), 43724384.

Kamoi K. and Babaian R.J. (1999) Advances in the application of prostate-specific antigen in the detection of early-stage prostate cancer. *Seminars in oncology* **26**, 140-149.

Kandouci A.B. (2014) Utility of Combination of Diagnostic Tests in Early Detection of Prostate Tumors in West Algerian Hospital. *European Journal of Medicine* 5(3).

Kang D., Andriole G., Van De Vooren R., Crawford D., Chia D., Urban D., Reding D., Huang W.Y. and Hayes R. (2004) Risk behaviours and benign prostatic hyperplasia. *BJU international* 93(9), 1241-1245.

Karakiewicz P.I., Benayoun S., Kattan M.W., Perrotte P., Valiquette L., Scardino P.T., Cagiannos I., Heinzer H., Tanguay S. and Aprikian A.G. (2005) Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. *The Journal of urology* 173(6), 1930-1934.

Kefi A., Irer B., Ozdemir I., Tuna B., Goktay Y., Yorukoğlu K. and Esen A. (2005) Predictive value of the international prostate symptom score for positive prostate needle biopsy in the low-intermediate prostate-specific antigen range. *Urologia internationalis* 75(3), 222-226.

Key T. (1994) Risk factors for prostate cancer. *Cancer surveys* 2363-77.

Kimura T. (2012) East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians. *Chinese journal of cancer* 31(9), 421.

Klufio G. (2004) A review of genitourinary cancers at the Korle-Bu teaching hospital Accra, Ghana. *West African journal of medicine* 23(2), 131-134.

Kramer G., Mitteregger D. and Marberger M. (2007) Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? *European urology* 51(5), 1202-1216.

Krieger J.N., JACOBS R.R. and ROSS S.O. (2000) Does the chronic prostatitis/pelvic pain syndrome differ from nonbacterial prostatitis and prostatodynia? *The Journal of urology* 164(5), 1554-1558.

Krumholtz J.S., Carvalhal G.F., Ramos C.G., Smith D.S., Thorson P., Yan Y., Humphrey P.A., Roehl K.A. and Catalona W.J. (2002) Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. *Urology* 60(3), 469-473.

Kuo H.-C. (2007) Differential diagnosis of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and non-benign prostatic hyperplasia. *Incont Pelvic Floor Dysfunct* 1(Suppl 1), 3-6.

Kuo S.-C., Hung S.-H., Wang H.-Y., Chien C.-C., Lu C.-L., Lin H.-J., Guo H.-R., Zou J.-F., Lin C.-S. and Huang C.-C. (2013) Chinese nomogram to predict probability of positive initial prostate biopsy: a study in Taiwan region. *Asian journal of andrology* 15(6), 780.

Kupelian V., Wei J.T., O'Leary M.P., Kusek J.W., Litman H.J., Link C.L. and McKinlay J.B. (2006) Prevalence of lower urinary tract symptoms and effect on quality of life in

a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. *Archives of Internal Medicine* 166(21), 23812387.

Kuritzky L. (2004) Role of primary care clinicians in the diagnosis and treatment of LUTS and BPH. *Reviews in urology* 6(Suppl 9), S53.

Lachat C., Otchere S., Roberfroid D., Abdulai A., Seret F.M.A., Milesevic J., Xuereb G., Candeias V. and Kolsteren P. (2013) Diet and physical activity for the prevention of noncommunicable diseases in low-and middle-income countries: a systematic policy review. *PLoS Med* 10(6), e1001465.

Laryea D.O., Awuah B., Amoako Y.A., Osei-Bonsu E., Dogbe J., Larsen-Reindorf R., Ansong D., Yeboah-Awudzi K., Oppong J.K. and Konney T.O. (2014) Cancer incidence in Ghana, 2012: evidence from a population-based cancer registry. *BMC cancer* 14(1), 1.

Lee S.C., Cheol L.S. and Jae K.W. (2004) Value of PSA density, PSA velocity and percent free PSA for detection of prostate cancer in patients with serum PSA 4-10ng/ml patients. *Korean Journal of Urology* 45(8), 747-752.

Leissner K.-H. and Tisell L.-E. (1979) The weight of the human prostate. *Scandinavian journal of urology and nephrology* 13(2), 137-142.

Lepor H., Williford W.O., Barry M.J., Brawer M.K., Dixon C.M., Gormley G., Haakenson C., Machi M., Narayan P. and Padley R.J. (1996) The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *New England Journal of Medicine* 335(8), 533-540.

Linzer D.G., Stock R.G., Stone N.N., Ratnow R., Ianuzzi C. and Unger P. (1996) Seminal vesicle biopsy: accuracy and implications for staging of prostate cancer. *Urology* 48(5), 757-761.

Loeb S., Carter H.B., Berndt S.I., Ricker W. and Schaeffer E.M. (2011) Complications after prostate biopsy: data from SEER-Medicare. *The Journal of urology* 186(5), 1830-1834.

Loeb S., van den Heuvel S., Zhu X., Bangma C.H., Schröder F.H. and Roobol M.J. (2012) Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. *European urology* 61(6), 1110-1114.

Lopez-Corona E., Ohori M., Scardino P.T., Reuter V.E., Gonen M. and Kattan M.W. (2003) A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session. *The Journal of urology* 170(4), 1184-1188.

Lozano R., Naghavi M., Foreman K., Lim S., Shibuya K., Aboyans V., Abraham J., Adair T., Aggarwal R. and Ahn S.Y. (2013) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 380(9859), 2095-2128.

Lughezzani G., Lazzeri M., Larcher A., Lista G., Scattoni V., Cestari A., Buffi N.M., Bini V. and Guazzoni G. (2012) Development and internal validation of a Prostate Health Index based nomogram for predicting prostate cancer at extended biopsy. *The Journal of urology* 188(4), 1144-1150.

Madersbacher S., Alivizatos G., Nordling J., Sanz C.R., Emberton M. and de la Rosette J.J. (2004) EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *European urology* 46(5), 547-554.

Madersbacher S., Haidinger G., Temml C. and Schmidbauer C.P. (1998) Prevalence of lower urinary tract symptoms in Austria as assessed by an open survey of 2,096 men. *European urology* 34(2), 136-141.

Mammen E. (1993) Bootstrap and wild bootstrap for high dimensional linear models. *The Annals of Statistics*255-285.

Markland A.D., Thompson I.M., Ankerst D.P., Higgins B. and Kraus S.R. (2007) Lack of disparity in lower urinary tract symptom severity between community-dwelling non-Hispanic white, Mexican-American, and African-American men. *Urology* 69(4), 697-702.

McConnell J.D. (1994) *Benign prostatic hyperplasia: diagnosis and treatment*: US Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.

McNeal J. (1972) The prostate and prostatic urethra: a morphologic synthesis. *The Journal of urology* 107(6), 1008-1016.

McNeal J.E. (1981) The zonal anatomy of the prostate. *The Prostate* 2(1), 35-49.

McNeal J.E. (1988) Normal histology of the prostate. *The American journal of surgical pathology* 12(8), 619-633.

Meigs J.B., Mohr B., Barry M.J., Collins M.M. and McKinlay J.B. (2001) Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *Journal of clinical epidemiology* 54(9), 935-944.

Merrimen J.L., Jones G., Walker D., Leung C.S., Kapusta L.R. and Srigley J.R. (2009) Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic adenocarcinoma. *The Journal of urology* 182(2), 485-490.

Meyer H. and Bootz F. (2003) TNM-Classification of malignant tumors. UICC International Union Against Cancer: Springer, Berlin Heidelberg New York.

Miller E.C., Giovannucci E., Erdman J.W., Bahnson R., Schwartz S.J. and Clinton S.K. (2002) Tomato products, lycopene, and prostate cancer risk. *Urologic Clinics of North America* 29(1), 83-93.

Milord R.A., Kahane H. and Epstein J.I. (2000) Infarct of the prostate gland: experience on needle biopsy specimens. *The American journal of surgical pathology* 24(10), 1378-1384.

Moore C.K., Karikehalli S., Nazeer T., Fisher H.A., Kaufman R.P. and Mian B.M. (2005) Prognostic significance of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the contemporary era. *The Journal of urology* 173(1), 70-72.

Moran B.J., Braccioforte M.H. and Conterato D.J. (2006) Re-biopsy of the prostate using a stereotactic transperineal technique. *The Journal of urology* 176(4), 1376-1381.

Morgan T.O., Jacobsen S.J., McCarthy W.F., Jacobson D.J., McLeod D.G. and Moul J.W. (1996) Age-specific reference ranges for serum prostate-specific antigen in black men. *New England Journal of Medicine* 335(5), 304-310.

Moul J.W., Sesterhenn I.A., Connelly R.R., Douglas T., Srivastava S., Mostofi F.K. and McLeod D.G. (1995) Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. *Jama* 274(16), 1277-1281.

Murray N.P., Reyes E., Orellana N., Fuentealba C. and Dueñas R. (2014) A comparative performance analysis of total PSA, percentage free PSA, PSA velocity, and PSA

density versus the detection of primary circulating prostate cells in predicting initial prostate biopsy findings in Chilean men. *BioMed research international* 2014.

Naing L., Winn T. and Rusli B. (2006) Practical issues in calculating the sample size for prevalence studies. *Archives of orofacial Sciences* 1(1), 9-14.

Nam R.K., Saskin R., Lee Y., Liu Y., Law C., Klotz L.H., Loblaw D.A., Trachtenberg J., Stanimirovic A. and Simor A.E. (2010) Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *The Journal of urology* 183(3), 963-969.

Naslund M., Gilsenan A., Midkiff K., Bown A., Wolford E. and Wang J. (2007) Prevalence of lower urinary tract symptoms and prostate enlargement in the primary care setting. *International journal of clinical practice* 61(9), 1437-1445.

Neal D.E., Moon T.D., Clejan S. and Sarma D. (1992) Prostate specific antigen and prostatitis I. Effect of prostatitis on serum PSA in the human and nonhuman primate. *The Prostate* 20(2), 105-111.

Nickel J.C., Downey J., Hunter D. and Clark J. (2001) Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. *The Journal of urology* 165(3), 842-845.

Norman R., Nickel J., Fish D. and Pickett S. (1994) 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. *British journal of urology* 74(5), 542-550.

Nukui M. (1997) [Epidemiological study on diet, smoking and alcohol drinking in the relationship to prostatic weight]. *Nihon Hinyokika Gakkai zasshi. The japanese journal of urology* 88(11), 950-956.

Obu R. (2014) Study of prevalence and sonographic diagnosis of benign prostate hypertrophy and malignant tumours among Ghanaian men. Global Research Journal of Public Health and Epidemiology(2360-7920 2(4)), pp 443-455.

Oelke M., Bachmann A., Descazeaud A., Emberton M., Gravas S., Michel M.C., N'Dow J., Nordling J. and Jean J. (2013) EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European urology* 64(1), 118-140.

Ohori M. and Swindle P. (2002) Nomograms and instruments for the initial prostate evaluation: the ability to estimate the likelihood of identifying prostate cancer. *Seminars in urologic oncology* **20**, 116-122.

Optenberg S.A., Clark J.Y., Brawer M.K., Thompson I.M., Stein C.R. and Friedrichs P. (1997) Development of a decision-making tool to predict risk of prostate cancer: the Cancer of the Prostate Risk Index (CAPRI) test. *Urology* 50(5), 665-672.

Orsini N., RashidKhani B., Andersson S.-O., Karlberg L., Johansson J.-E. and Wolk A. (2006) Long-term physical activity and lower urinary tract symptoms in men. *The Journal of urology* 176(6), 2546-2550.

Park J.Y., Yoon S., Park M.S., Cho D.-Y., Park H.-S., Moon D.G. and Yoon D.K. (2011) Initial biopsy outcome prediction in Korean patients-comparison of a noble webbased Korean prostate cancer risk calculator versus prostate-specific antigen testing. *Journal of Korean medical science* 26(1), 85-91.

Parkin D.M. (2006) The evolution of the population-based cancer registry. *Nature Reviews Cancer* 6(8), 603-612.

Parsons J.K. (2010) Benign prostatic hyperplasia and male lower urinary tract symptoms: epidemiology and risk factors. *Current bladder dysfunction reports* 5(4), 212-218.

Partin A.W. and Oesterling J. (1994) The clinical usefulness of prostate specific antigen: update 1994. *The Journal of urology* 152(5 Pt 1), 1358-1368.

Patel A.R. and Klein E.A. (2009) Risk factors for prostate cancer. *Nature Clinical Practice Urology* 6(2), 87-95.

Pelzer A.E., Bektic J., Berger A.P., Halpern E.J., Koppelstätter F., Klauser A., Rehder P., Horninger W., Bartsch G. and Frauscher F. (2005) Are transition zone biopsies still necessary to improve prostate cancer detection?: Results from the Tyrol screening project. *European urology* 48(6), 916-921.

Persson B.-E. and Ronquist G. (1996) Evidence for a mechanistic association between nonbacterial prostatitis and levels of urate and creatinine in expressed prostatic secretion. *The Journal of urology* 155(3), 958-960.

Peters T., Donovan J., Kay H., Abrams P., De La Rosette J., Porru D. and Thuroff J. (1997) The International Continence Society "benign prostatic hyperplasia" study: the bothersomeness of urinary symptoms. *The Journal of urology* 157(3), 885-889.

Platz E.A., Kawachio I., Rimm E.B., Willet W.C. and Gcciiovannu E. (2000) Race, ethnicity and benign prostatic hyperplasia in the health professionals follow-up study. *The Journal of urology* 163(2), 490-495.

Platz E.A., Rimm E.B., Kawachi I., Colditz G.A., Stampfer M.J., Willett W.C. and Giovannucci E. (1999) Alcohol consumption, cigarette smoking, and risk of benign prostatic hyperplasia. *American journal of epidemiology* 149(2), 106-115.

Polascik T.J., E O.J. and W P.A. (1999) Prostate specific antigen: a decade of discoverywhat we have learned and where we are going. *The Journal of urology* 162(2), 293306.

Potter S.R., Horniger W., Tinzl M., Bartsch G. and Partin A.W. (2001) Age, prostatespecific antigen, and digital rectal examination as determinants of the probability of having prostate cancer. *Urology* 57(6), 1100-1104.

Pu Y., Chiang H., Lin C., Huang C., Huang K. and Chen J. (2004) Changing trends of prostate cancer in Asia. *The Aging Male* 7(2), 120-132.

Punglia R.S., D'Amico A.V., Catalona W.J., Roehl K.A. and Kuntz K.M. (2006) Impact of age, benign prostatic hyperplasia, and cancer on prostate-specific antigen level. *Cancer* 106(7), 1507-1513.

Rao C.N., Singh M.K., Shekhar T., Venugopal K., Prasad M.R., Saleem K.L. and Satyanarayana U. (2004) Causes of lower urinary tract symptoms (LUTS) in adult Indian males. *Indian Journal of Urology* 20(2), 95.

Rebbeck T.R., Devesa S.S., Chang B.-L., Bunker C.H., Cheng I., Cooney K., Eeles R., Fernandez P., Giri V.N. and Gueye S.M. (2013) Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. *Prostate cancer* 2013.

Reiter R. and De Kernion J. (2002) Epidemiology, etiology, and prevention of prostate cancer. *Campbell's urology* 42489-2495.

Richie J.P., Catalona W.J., Ahmann F.R., M'Liss A.H., Scardino P.T., Flanigan R.C., Dekernion J.B., Ratliff T.L., Kavoussi L.R. and Dalkin B.L. (1993) Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology* 42(4), 365-374.

Rodriguez L.V. and Terriz M.K. (1998) Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. *The Journal of urology* 160(6), 2115-2120.

Roehrborn C.G., Boyle P., Gould A.L. and Waldstreicher J. (1999) Serum prostatespecific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 53(3), 581-589.

Roehrborn C.G., Girman C.J., Rhodes T., Hanson K.A., Collins G.N., Sech S.M., Jacobsen S.J., Garraway W.M. and Lieber M.M. (1997) Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. *Urology* 49(4), 548-557.

Roehrborn C.G., Lukkarinen O., Mark S., Siami P., Ramsdell J. and Zinner N. (2005) Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5$\alpha$-reductase inhibitor dutasteride: results of 4-year studies. *BJU international* 96(4), 572-577.

Rogers K. (2010) *The Reproductive System*, First Edition ed: Britannica Educational Publishing New York, NY, 10010.

Rosen R., Altwein J., Boyle P., Kirby R.S., Lukacs B., Meuleman E., O'Leary M.P., Puppo P., Robertson C. and Giuliano F. (2003) Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *European urology* 44(6), 637-649.

Safarinejad M.R. (2008) Prevalence of benign prostatic hyperplasia in a populationbased study in Iranian men 40 years old or older. *International urology and nephrology* 40(4), 921-931.

Sagnier P., MacFarlane G., Richard F., Botto H., Teillac P. and Boyle P. (1994) Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. *The Journal of urology* 151(5), 1266-1270.

Samowitz W.S., Curtin K., Ma K.-N., Schaffer D., Coleman L.W., Leppert M. and Slattery M.L. (2001) Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiology Biomarkers & Prevention* 10(9), 917-923.

Sarma A.V., Wei J.T., Jacobson D.J., Dunn R.L., Roberts R.O., Girman C.J., Lieber M.M., Cooney K.A., Schottenfeld D. and Montie J.E. (2003) Comparison of lower urinary tract symptom severity and associated bother between communitydwelling black and white men: the Olmsted County Study of Urinary Symptoms and Health Status and the Flint Men's Health Study. *Urology* 61(6), 1086-1091.

Sasaki R., Habuchi T., Sato K., Akao T., Kakinuma H., Li-Qing Z., Lizhong W., Matsuo S., Sasaki S. and Ogawa O. (2000) The clinical utility of measuring total PSA, PSA density, $\gamma$-seminoprotein and $\gamma$-seminoprotein/total PSA in prostate cancer prediction. *Japanese journal of clinical oncology* 30(8), 337-342.

Scattoni V., Raber M., Montorsi F., Da Pozzo L., Brausi M., Calori G., Freschi M. and Rigatti P. (1999) Percent of free serum prostate-specific antigen and histological findings in patients undergoing open prostatectomy for benign prostatic hyperplasia. *European urology* 36(6), 621-630.

Schröder F. and Kattan M.W. (2008) The comparability of models for predicting the risk of a positive prostate biopsy with prostate-specific antigen alone: a systematic review. *European urology* 54(2), 274-290.

Schultheiss D., Machtens S. and Jonas U. (2004) Review article Testosterone therapy in the ageing male: what about the prostate? *Andrologia* 36(6), 355-365.

Shariat S.F., Karakiewicz P.I., Suardi N. and Kattan M.W. (2008) Comparison of nomograms with other methods for predicting outcomes in prostate cancer: a critical analysis of the literature. *Clinical cancer research* 14(14), 4400-4407.

Sheikh M., Al-Saeed O., Kehinde E., Sinan T., Anim J. and Ali Y. (2005) Utility of volume adjusted prostate specific antigen density in the diagnosis of prostate cancer in Arab men. *International urology and nephrology* 37(4), 721-726.

Sherwood E., Berg L., Mitchell N., McNeal J., Kozlowski J. and Lee C. (1990) Differential cytokeratin expression in normal, hyperplastic and malignant epithelial cells from human prostate. *The Journal of urology* 143(1), 167-171.

Shimizu H., Ross R., Bernstein L., Yatani R., Henderson B. and Mack T. (1991) Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *British journal of cancer* 63(6), 963.

Shimizu T.S., Uchida T., Satoh J., Imai K. and Yamanaka H. (1995) PROSTATESPECIFIC ANTIGEN IN MASS SCREENING FOR CARCINOMA OF THE PROSTATE. *International Journal of Urology* 2(4), 257-260.

Shirai T., Asamoto M., Takahashi S. and Imaida K. (2002) Diet and prostate cancer. *Toxicology* 18189-94.

Sidney S., Quesenberry C., Sadler M.C., Lydick E.G., Guess H.A. and Cattolica E.V. (1991) Risk factors for surgically treatedbenign prostatic hyperplasia in a prepaid health care plan. *Urology* 38(1), 13-19.

Signorello L., Tzonou A., Lagiou P., Samoli E., Zavitsanos X. and Trichopoulos D. (1999) The epidemiology of benign prostatic hyperplasia: a study in Greece. *BJU international* 84286-291.

Simard J., Dumont M., Soucy P. and Labrie F. (2002) Perspective: prostate cancer susceptibility genes. *Endocrinology* 143(6), 2029-2040.

Skolarikos A., Thorpe A. and Neal D. (2004) Lower urinary tract symptoms and benign prostatic hyperplasia. *Minerva urologica e nefrologica= The Italian journal of urology and nephrology* 56(2), 109-122.

Smith S.C., Clark L.T., Cooper R.S., Daniels S.R., Kumanyika S.K., Ofili E., Quinones M.A., Sanchez E.J., Saunders E. and Tiukinhoy S.D. (2005) Discovering the Full Spectrum of Cardiovascular Disease Minority Health Summit 2003: Report of the Obesity, Metabolic Syndrome, and Hypertension Writing Group. *Circulation* 111(10), e134-e139.

Sözen S., Eskicorapci S., Küpeli B., İrkilata L., Altinel M., Özer G., Uygur C., Alkibay T. and Özen H. (2005) Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20ng/ml: results of a prospective multicenter study. *European urology* 47(3), 302-307.

Stamey T.A., Freiha F., McNeal J., Redwine E., Whittemore A. and Schmid H. (1993) Localized prostate cancer. *Cancer* 71(S3), 933-938.

Steinberg G.D., Carter B.S., Beaty T.H., Childs B. and Walsh P.C. (1990) Family history and the risk of prostate cancer. *The prostate* 17(4), 337-347.

Stephan C., Klaas M., Müller C., Schnorr D., Loening S.A. and Jung K. (2006) Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. *Clinical chemistry* 52(1), 59-64.

Stephan C., Stroebel G., Heinau M., Lenz A., Roemer A., Lein M., Schnorr D., Loening S.A. and Jung K. (2005) The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of< 4 ng/mL. *Cancer* 104(5), 993-1003.

Steuber T., Graefen M., Haese A., Erbersdobler A., Chun F.K.-H., Schlom T., Perrotte P., Huland H. and Karakiewicz P.I. (2006) Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. *The Journal of urology* 175(3), 939-944.

Su L., Guess H.A., Girman C.J., Jacobsen S.J., Oesterling J.E., Panser L.A. and Lieber M.M. (1996) Adverse effects of medications on urinary symptoms and flow rate: a community-based study. *Journal of clinical epidemiology* 49(4), 483-487.

Suzuki H., Komiya A., Kamiya N., Imamoto T., Kawamura K., Miura J., Suzuki N., Nakatsu H., Hata A. and Ichikawa T. (2006) Development of a nomogram to predict probability of positive initial prostate biopsy among Japanese patients. *Urology* 67(1), 131-136.

Takenaka A., Hara R., Ishimura T., Fujii T., Jo Y., Nagai A. and Fujisawa M. (2008) A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate cancer and prostatic diseases* 11(2), 134-138.

Tang P., Chen H., Uhlman M., Lin Y.-R., Deng X.-R., Wang B., Yang W.-J. and Xie K.-J. (2013) A nomogram based on age, prostate-specific antigen level, prostate volume and digital rectal examination for predicting risk of prostate cancer. *Asian J Androl* 15(1), 129-133.

Tang P., Du W., Xie K., Fu J., Chen H., Yang W. and Moul J.W. (2012) Characteristics of baseline PSA and PSA velocity in young men without prostate cancer: racial differences. *The Prostate* 72(2), 173-180.

Teoh J.Y., Yuen S., Tsu J., Wong C.K., Ho B.S., Ng A.T., Ma W.-K., Ho K.-L. and Yiu M.K. (2015) Prostate cancer detection upon transrectal ultrasound-guided biopsy in relation to digital rectal examination and prostate-specific antigen level: what to expect in the Chinese population? *Asian journal of andrology* 17(5)( 821).

Thompson I.M., Ankerst D.P., Chi C., Goodman P.J., Tangen C.M., Lucia M.S., Feng Z., Parnes H.L. and Coltman C.A. (2006) Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of the National Cancer Institute* 98(8), 529-534.

Thompson I.M., Pauler D.K., Goodman P.J., Tangen C.M., Lucia M.S., Parnes H.L., Minasian L.M., Ford L.G., Lippman S.M. and Crawford E.D. (2004) Prevalence of prostate cancer among men with a prostate-specific antigen level≤ 4.0 ng per milliliter. *New England Journal of Medicine* 350(22), 2239-2246.

Tsukamoto T., Masumori N., Rahman M. and Crane M.M. (2007) Change in International Prostate Symptom Score, prostrate-specific antigen and prostate volume in patients with benign prostatic hyperplasia followed longitudinally. *International journal of urology* 14(4), 321-324.

Untergasser G., Gander R., Lilg C., Lepperdinger G., Plas E. and Berger P. (2005) Profiling molecular targets of TGF-β1 in prostate fibroblast-to-myofibroblast transdifferentiation. *Mechanisms of ageing and development* 126(1), 59-69.

Varian H. (2005) Bootstrap tutorial. *Mathematica Journal* 9(4), 768-775.

Verhagen A.P., Aalders T.W., Ramaekers F., Debruyne F.M. and Schalken J.A. (1988) Differential expression of keratins in the basal and luminal compartments of rat prostatic epithelium during degeneration and regeneration. *The Prostate* 13(1), 25-38.

Verhamme K., Dieleman J., Bleumink G., Van der Lei J., Sturkenboom M. and Panel T.P.E.E. (2002) Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care—the Triumph project. *European urology* 42(4), 323-328.

Vogt T.M., Ziegler R.G., Graubard B.I., Swanson C.A., Greenberg R.S., Schoenberg J.B., Swanson G.M., Hayes R.B. and Mayne S.T. (2003) Serum selenium and risk of prostate cancer in US blacks and whites. *International journal of cancer* 103(5), 664670.

Wabinga H. (2003) Cancer registry development in Africa. *Proceedings of the 4th International Conference on Cancer in Africa. Accra, October*, 6-10.

Ward E., Jemal A., Cokkinides V., Singh G.K., Cardinez C., Ghafoor A. and Thun M. (2004) Cancer disparities by race/ethnicity and socioeconomic status. *CA: a cancer journal for clinicians* 54(2), 78-93.

Whittemore A.S., Kolonel L.N., Wu A.H., John E.M., Gallagher R.P., Howe G.R., Burch J.D., Hankin J., Dreon D.M. and West D.W. (1995) Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. *Journal of the National Cancer Institute* 87(9), 652-661.

Wintherington R., JANOSKO J.H.E., BOROSSO D.C.C., FALK10 S. and ROUNDER J. (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *British journal of urology* 81730734.

Wiredu E.K. and Armah H.B. (2006) Cancer mortality patterns in Ghana: a 10-year review of autopsies and hospital mortality. *BMC public health* 6(1), 1.

Yoon D.K., Park J.Y., Yoon S., Park M.S., Moon D.G., Lee J.G. and Schröder F.H. (2012) Can the prostate risk calculator based on Western population be applied to Asian population? *The Prostate* 72(7), 721-729.

Zaichick V.Y., Sviridova T. and Zaichick S. (1996) Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma and cancer. *International urology and nephrology* 28(5), 687-694.

Zhu Y., Wang J.-Y., Shen Y.-J., Dai B., Ma C.-G., Xiao W.-J., Lin G.-W., Yao X.-D., Zhang S.-L. and Ye D.-W. (2012) External validation of the Prostate Cancer Prevention Trial and the European Randomized Study of Screening for Prostate Cancer risk calculators in a Chinese cohort. *Asian journal of andrology* 14(5), 738-744.

Zigeuner R., Schips L., Lipsky K., Auprich M., Salfellner M., Rehak P., Pummer K. and Hubmer G. (2003) Detection of prostate cancer by TURP or open surgery in patients with previously negative transrectal prostate biopsies. *Urology* 62(5), 883-887.

http://www.vantasimplant.com/the-prostate-gland/ 13th juyl 2016, 13.00pm

http://www.gov.cancer.com, 26th June, 2016, 15:00pm



## APPENDIX

**KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY**
**COLLEGE OF HEALTH SCIENCE**
**SCHOOL OF MEDICAL SCIENCES**
**DEPARTMENT OF MOLECULAR MEDICINE**

**PROSTATE CANCER NEW PATIENT QUESTIONNAIRE**

**Dear Respondent**,
You are being asked to take a survey on prostate cancer. Because your answers are confidential and shall be used for academic purposes, I ask you to respond honestly as you can.

**ParticipantAddress**……
……

**Mobile Number**…….

**Study ID:** _____**Today's date**: _____

**Age** _____

**Family History of Cancer**

**Type/location of cancer Age at diagnosis**

Brother/sister_____

Father_____ _____

Mother_____

Current occupation _____ # years_____

Previous occupation _____ # years _____

**Social History**

Do you drink alcohol **Y/N** If yes average number of drinks per day_____?

How long have you been married? _____

How many sexual partners have you had? _____

At what age did you start sexual activities? _____

**Diagnosis**

First Diagnosed_____ Date_____
Previous PSA test **Y/N**; If yes, what was the report_____
Previous DRE test **Y/N**; if yes what was the report_____
Previous Biopsy test **Y/N**; if yes what was the report _____

Previous radiation therapy **Y /N**; If yes, to what part of the body? _____

Facility name _____ Dates: _____

Previous or current chemotherapy **Y / N** If yes, facility name_____

Date: _____

**Any Surgery**

| Type of Operation | Approximate Date | Type of Operation | Approximate Date |
|---|---|---|---|
| _____ | _____ | _____ | _____ |
| _____ | | _____ | |
| _____ | | _____ | |

Other illnesses/hospitalizations_____

**Medical History**

| | | | |
|---|---|---|---|
| Previous Cancer | **Y/N** | Stroke | **Y/N** |
| High Blood Pressure | **Y/N** | Diabetes | **Y/N** |
| Heart Attack | **Y/N** | Hypertension | **Y/N** |

Kidney Loss, dysfunction or abnormality **Y/N**

Rheumatoid Arthritis **Y/N**

Prostate Surgery 1. (Transurethral resection of prostate "TURP") **Y/N** If yes when_____

Open Prostatectomy A. Freyer B Millin

**Review of systems Have you developed any of these symptoms in the past years?**

| | | | |
|---|---|---|---|
| Incontinence | **Y/N** | chest pain | **Y/N** |
| Blood in urine | **Y/N** | Bone pain | **Y/N** |
| Waist pain | **Y/N** | Swollen gland | **Y/N** |
| Pain upon Urinating | **Y/N** | Bleeding problems | **Y/N** |
| Straining | **Y/N** | Dribbling | **Y/N** |
| Change in urination | **Y/N** | Weakness | **Y/N** |
| Weight Loss | **Y/N** | | |

**UROFLOWMETER FINDINGS**

Measured Parameters

**$T_{100}$** ……..

**TQmax** ……

**Qmax** ……

**Qave** ……

**Vcomp** ……

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HELATH SCIENCE
SCHOOL OF MEDICAL SCINECES
DEPARTMENT OF MOLECULAR MEDICINE

PROSTATE CANER RESEARCH

DIGITAL RECTAL EXAMINATION (DRE) FINDINGS

1 SHAPE: …….

2. SIZE (cm) (A.cm X B. cm): ……cm X…….cm

3. SULCUS: □ Palpable □ Non-Palpable □ Indeterminate

4. SYMMETRY □ Symmetric □ Asymmetric □ Indeterminate

5. SURFACE □ Smooth □ Nodular □ Nodule

6. CONSISTENCY □ Firm □ Hard □ Soft

7. MOBLITY OF RECTAL MUCOSA □ Mobile □ Not Mobile

8. EDGE □ Well Defined □ Ill Defined □ Indeterminate

9. TENDERNESS □ Tender □ Non-Tender

CLINICAL DIAGNOSIS:

- Normal Prostate
- BPH
- Prostate Cancer
- Prostatitis