GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF SURGERY (UROLOGY)

A STUDY OF PROSTATE CANCER DETECTION RATES IN MEN UNDERGOING TRANS-RECTAL ULTRASOUND-GUIDED PROSTATE BIOPSY AT KATH, KUMASI

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SEPTEMBER, 2024

Ghana College of Physicians and Surgeons

Faculty of Surgery (Urology)

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Submitted to the Faculty of Surgery, in partial fulfillment of the requirements for the conferment of a Fellow of the Ghana College of Surgeons (FGCS)

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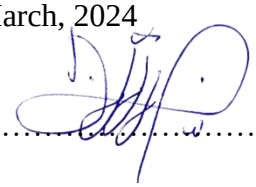
DECLARATION BY CANDIDATE

I, Dr. Dominic Annor Mintah, declare that this work submitted is the result of my compilation, apart from those from other individuals, which have been duly acknowledged and referenced. I certify that this work has not been submitted, either in part or as a whole, to another institution for degrees or diploma in the past. I am solely in charge of the content of this dissertation.

Date: 28th March, 2024

Signature……  ……

ATTESTATION BY SUPERVISORS

We confirm that we have supervised the research work titled:

"A Study of Prostate Cancer Detection Rates in Men Undergoing Trans-rectal Ultrasound-Guided Prostate Biopsy at Kath, Kumasi", undertaken by Dr. Dominic Annor Mintah in partial fulfilment of the requirements for the Ghana College of Surgeons fellowship.

SUPERVISOR: **DR. KWAKU ADDAI APPIAH ARHIN**

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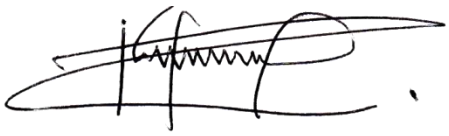
SIGNATURE: 

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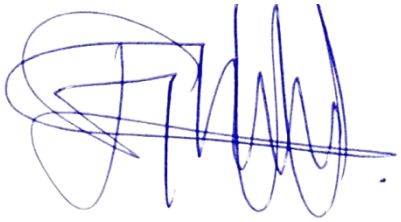
SIGNATURE: 

ATTESTATION BY FACULTY HEAD OF DIRECTORATE

I hereby attest that Dr. Dominic Annor Mintah is a senior resident currently pursuing his fellowship (senior residency) training in the Directorate of Surgery of the Komfo Anokye Teaching Hospital. His project is titled: “A Study of Prostate Cancer Detection Rates in Men Undergoing Trans-rectal Ultrasound-Guided Prostate Biopsy at Kath, Kumasi". This work is being submitted in compliance with the requirements of the fellowship training at the Ghana College of Physicians and Surgeons.

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ABSTRACT

Introduction: Prostate cancer is the second most common cancer among men worldwide. The risk of developing prostate cancer increases with advancing age, elevated serum PSA level, a family history of prostate cancer, and being black or of African ancestry. The diagnosis of prostate cancer is made by histopathological evaluation of the prostate gland. TRUS-guided biopsy of the prostate gland is the gold standard technique for obtaining prostate gland specimen for histopathological evaluation of the prostate gland and for the diagnosis of prostate cancer. This study sought to evaluate the prostate cancer detection rate of TRUS-guided prostate biopsy and analyze its characteristics among the men undergoing prostate biopsy at Komfo Anokye Teaching Hospital, Kumasi.

Method: A total of 218 men were referred on various indications for TRUS-guided prostate biopsies at the Urology Unit of the Directorate of Surgery of the Komfo Anokye Teaching Hospital from September 2022 to October 2023 participated in this study. The study participants were prospectively evaluated, and the data analyzed to determine the prostate cancer detection rate and its characteristics.

Results: The mean age of the study participants was 69.84 $\pm$ 8.10 years with a range of 45 - 89 years. Of the 218 men who underwent-guided prostate biopsy, 121 (55.5%) were detected to have adenocarcinoma of the prostate whilst 97 (44.5%) had no cancer. The indications for prostate biopsy from this study were elevated serum PSA level (61.5%), suspicious DRE findings (32.1%) and a combination of both (6.4%). The cancer detection rates for men who underwent biopsy with indications of suspicious DRE findings alone, abnormal serum PSA levels alone, and a combination of both were 14.3, 50.4 and 67.9%. The cancer detection rate was found in the study to increase with increasing serum PSA level and advancing age, and decreases with increasing volume of the prostate gland in the study population.

Conclusion: TRUS-guided biopsy of the prostate gland detects more prostate cancer cases than non-cancer cases. The indication with the highest positive predictive value for prostate cancer was the presence of both elevated serum PSA level and suspicious DRE findings. The risk of diagnosis increases with increasing levels of serum PSA and advancing age in the study population. Whilst the risk of being diagnosed with prostate cancer decreases with increasing prostate volume (size).

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ASIR	Age-Standardized Incidence Rate
ASMR	Age-Standardized Mortality Rate
CaP	Prostate Cancer (Cancer of the Prostate)
CDR	Cancer Detection Rate
CHRPE	Committee on Human Research, Publications, and Ethics
CI	Confidence Interval
DRE	Digital Rectal Examination
KATH	Komfo Anokye Teaching Hospital
KNUST	Kwame Nkrumah University of Science and Technology
mp-MRI	Multi-Parametric Magnetic Resonance Imaging
GWAS	Genome-Wide Association Studies
NGS	Next Generation Sequencing
PNB	Periprostatic neurovascular bundle block
PCa	Prostate Cancer
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PT-INR	Prothrombin Time – International Normalized Ratio
TRUS	Trans Rectal Ultrasound
VPIS	Verbal Pain Intensity Scale

CHAPTER ONE

Introduction

1.0 Background of the Study

Prostate cancer (PCa) is the most common cancer, beside lung cancer, affecting men around the world, with an estimated 1.4 million new cases and 375,000 deaths worldwide in 2020, representing a significant global health concern. [1] It is essentially a disease of the elderly, with over 33% of men over 60 years having a latent form of the disease; therefore, the disease is likely to be more prevalent than what is currently documented. [2,3] Prostate cancer presents more aggressively among black men and people of African ancestry, with patients presenting with advanced disease and with poor clinical outcomes; several reasons have been offered as the underlying explanations for this observation. [2–8] The same trend has been observed in men of African descent both in and outside continental Africa. [4,7,8] The high prostate cancer burden and poor outcomes among African men and men of African descent have been attributed to molecular factors, genetics, poor prostate cancer awareness, a low level to near absence of prostate cancer screening programmes across continental Africa, late presentation, and delayed diagnosis and treatment of the disease. [2–4,7,8] Each of these aforementioned factors appears to impact various stages of the prostate cancer continuum, from screening, incidence, diagnosis, staging, treatment, and overall outcomes, irrespective of treatment modality. [4]

The incidence and mortality rates of prostate cancer are not the same worldwide. It varies from one population to another and from one geographical region to another. Continental Africa and the Caribbean, with their large populations of people of African ancestry, are believed to have a very high burden of prostate cancer, but the exact magnitude is difficult to calculate accurately due to the absence of adequately resourced cancer registration systems.

People widely regard prostate-specific antigen (PSA) as an important basic screening marker for early detection of prostate cancer. PSA is used to check for prostate cancer so that it can be found early, when it can be treated successfully, and there is a lower risk of death from both the disease and other causes. [15,16] Catalona et al. (1991) showed that PSA could be used as a first-line screening test for prostate cancer in men with no evidence of the disease on physical examination, including digital rectal examination. Before Catalona et al. confirmed a cut-off point of 4.0 ng/mL as a requirement for a prostate biopsy, this test was used to decide if a biopsy was needed, to track how well treatment was working for prostate

cancer, to see if the disease came back after radical treatment for prostate cancer, and to stage and predict the outcome of the disease. [17] Subsequently, serum PSA has become widely adopted as a screening marker for prostate cancer, but not without controversy. Recent analysis has shown that it is prone to over-diagnosis and its associated overtreatment. The unmasking of clinically undetectable and mostly indolent diseases, most of which would not adversely affect individuals if not detected, has led to an increase in the incidence rate of prostate cancer globally. [18] Currently, serum PSA, digital rectal examination (DRE), and trans-rectal ultrasonography are the common methods used for prostate cancer screening. However, there is ongoing debate about the benefits and risks of routine prostate cancer screening. [19,20]

One of the most controversial topics in clinical practice and public health is the use of serum PSA as a screening tool for prostate cancer. Using serum PSA for prostate cancer screening leads to a lot of unnecessary prostate biopsies, the detection of a large number of clinically insignificant low-risk prostate cancers that require no treatment, over-diagnosis, and consequent overtreatment, as well as under-diagnosis and missed diagnosis with the attendant inappropriate treatment. [21,22] Furthermore, there are a number of unintended consequences linked to the PCa screening procedure. These deficiencies of PSA-based screening have called into question its utility as an efficient screening tool, leading to a search for an alternative that remedies the over-detection of clinically insignificant disease and safeguards patients from the potential harmful side-effects resulting from unnecessary prostate biopsies and treatment on account of elevated PSA. [22-24] While this search for a better means for screening for prostate cancer will detect only important cancers whose treatment would be of benefit to the patient, serum PSA remains the most common tool for screening in our environment. It is of enormous benefit if judiciously used with other investigative modalities to increase its sensitivity and specificity.

Researchers have identified multi-parametric magnetic resonance imaging (mp-MRI) of the prostate as an investigative tool that could mitigate these diagnostic deficiencies of serum PSA. [21-24] It is used in the screening, diagnosis, localization, staging, and risk stratification of clinically significant prostate cancer, as well as for treatment planning. Mp-MRI is also used to identify, and risk stratify men with prostate cancer who are candidates for active surveillance. [24-31] It is also used for the detection of local recurrence in men diagnosed with prostate cancer after treatment with either radical prostatectomy or external beam radiotherapy. [24,32] Despite all these numerous advantages of mp-MRI, it is not widely used in Ghana since it is expensive and unavailable in almost all the major referral centres. This is set to change in the near future as technology becomes cheaper with time and as more local centres are able to acquire setup and offer the service at an affordable rate across the country and Africa as a whole. The incidence of prostate

cancer differs significantly among different populations around the world, with some populations having rates several times higher than others.

The incidence also varies from one race to the next and from one geographical region to the next. Among the different races, African men and men of African ancestry have the highest incidence rate of prostate cancer in the world and are diagnosed at an earlier age with prostate cancer compared to the other races. Even in the same country, the detection rate of prostate cancer is variable in different areas with different environmental conditions. [1,4,7,8,14]

A TRUS-guided prostate biopsy has been generally acknowledged as the gold standard procedure for the definite diagnosis of prostate cancer in clinical practice, especially in our environment where trans-perineal prostate biopsy is not routinely available. [33] It has been the preferred means of obtaining prostatic tissue for the histological diagnosis of prostate cancer for well over the past 30 years. [34] The techniques involved in TRUS-guided prostate biopsy have been refined over this period to improve the cancer detection rate, improve tumour burden estimation, and provide more detail for better definite treatment planning. Trans-perineal prostate biopsy is slowly challenging the leading role of TRUS-prostate biopsy in other jurisdictions due to concerns over safety and diagnostic yield rate; however, it is not the default method in our settings due to its limited availability. TRUS-guided prostate biopsy is what is routinely done in the Urology Unit of the Directorate of Surgery, KATH. It offers a reliable, quick, easily accessible, and convenient tool for performing biopsy of the prostate gland for the definitive histological diagnosis of prostate cancer in our setting.

As far as we know, there aren't many studies that look at how often prostate cancer is found with a TRUS-guided biopsy of the prostate gland in Ghana. There is also not a lot of information about the clinical and pathological features of prostate cancers found in Kumasi and the surrounding areas. The study seeks to evaluate the detection rates of prostate cancer of TRUS-biopsy among men in Kumasi according to age, serum PSA level, and DRE findings.

1.1 Research Problem

There is a paucity of studies on TRUS-guided biopsies in Ghana, despite it being the main diagnostic tool that is routinely used to obtain a prostatic sample for the histological diagnosis of prostate cancer. This study will determine the prostate cancer detection rate in men undergoing TRUS-guided prostate biopsy at KATH, then evaluate the rates according to age, serum PSA level, and DRE findings.

1.2 Justification for the Study

Prostate cancer has become a disease of great public health concern due to increasing public awareness, increasing incidence, and increasing life expectancy. TRUS-guided prostate biopsy is the routine means of obtaining a prostate specimen for histological diagnosis. But few published studies are looking at TRUS-guided prostate biopsy in our environment. This study will determine the prostate cancer detection rates and then evaluate them according to age, serum PSA level, and DRE findings in men undergoing TRUS-guided biopsy at the Urology Unit of the Directorate of Surgery at KATH, Kumasi.

1.3 Relevance to Urology

The findings from this study will provide data derived from our environment that will inform our management of prostate cancer through screening, investigations, including TRUS-guided prostate biopsy, and deciding on the various treatment options. This will help increase the utility of this diagnostic procedure in a low-resource environment such as ours. The data generated will also influence the practice of urology in our environment.

1.4 Study Objectives

1.4.1 Main Objective

The study aims to evaluate the detection rates of prostate cancer using TRUS-guided prostate biopsy and analyse its characteristics among the men undergoing prostate biopsy at KATH, Kumasi.

1.4.2 Specific Objectives:

1 To evaluate the indications for TRUS-guided prostate biopsy in patients undergoing the procedure at the Urology Unit of KATH.
2 To evaluate the age, serum PSA level, DRE findings, and prostate volume of patients undergoing TRUS-guided prostate biopsy.
3 To determine the prostate cancer detection rates among the study population.
4 To evaluate the prostate cancer detection rates of TRUS-guided prostate biopsy according to age, serum PSA level, DRE findings, and prostate volume.

1.5 Study Hypotheses

1.5.1 Null Hypothesis

There are no differences in prostate cancer detection rates based on age, serum PSA level, DRE findings, and prostate volume among men who undergo TRUS-guided prostate biopsy at KATH, Kumasi.

1.5.2 Alternate Hypothesis

There are differences in prostate cancer detection rates based on age, serum PSA level, DRE findings, and prostate volume among men who undergo TRUS-guided prostate biopsy at KATH, Kumasi.

CHAPTER TWO

Literature Review

2.0 Introduction

The prostate gland is a very important part of the accessory glands of the reproductive system of a man. It is located immediately below the base of the bladder and surrounds the prostatic urethra. Benign prostate hyperplasia (BPH), prostate cancer (PCa), and prostatitis are three types of clinically relevant pathologies that have an impact on it. PCa is the most common malignant condition affecting men aged 65 years and older. [1,35-37]

It already represents a significant challenge for healthcare systems in most parts of the world, especially here in sub-Saharan Africa. Epidemiologically, the incidence of prostate cancer has risen across the world over the past decade. [1,38] Factors predisposing to the development of prostate cancer include hormonal imbalance, environmental pollutants, oxidative stress, inflammation, hereditary factors, ageing, and, more particularly, stromal-epithelial cell crosstalk. [36,42-44] However, the exact cellular and molecular mechanisms underlying the pathogenesis and development of prostate cancer are still not well understood.

2.0.1 Gross Anatomy and Function of the Prostate Gland

The prostate gland is the largest of the accessory glands of the male reproductive system. The rest of the glands in the male accessory reproductive system are the ampullae of the vas deferens, bulbourethral glands of Cowper, urethral glands of Littre, and preputial glands. The prostate consists of approximately 70% glandular tissue and 30% fibromuscular stroma. [44-46] These accessory reproductive organs, including the prostate gland, produce various secretions that collectively perform important functions in reproduction. The secretions of these glands nourish and activate the spermatozoa, facilitate the transit of spermatozoa through the female reproductive tract, clear the urethral tract before ejaculation, and block the female tract after insemination to aid in fertilisation and prevent polyspermy. [1,35-37]

Specifically, the prostate gland performs an important function in the male reproductive system by secreting an alkaline solution, which is a constituent of the ejaculate or semen released after ejaculation. The prostatic secretion is secreted on the luminal aspect of the secretory epithelial cells lining the ducts and acini of the glands of the prostate glands. The prostatic secretions contain zinc, calcium, citric acid,

phosphates, and other enzymes, including prostate-specific antigen (PSA), essential for the health and motility of the sperm. The prostatic secretion, being alkaline, is protective for sperm in the acidic environment of the vagina. [47] The secretions exit the prostate gland via ducts that open into the prostatic urethra through 10–12 openings at the side of the seminal colliculus (verumontanum). [46,48] The fluid neutralises the vaginal acidity, increasing the overall lifespan of the sperm and allowing the maximum length of time for successful fertilisation of the egg. [46,48] The fluid also contains enzymes, supportive proteins, and other substances that provide sustenance to the sperm. The volume of the prostatic secretion which adds up to the seminal fluid and sperm allows for easier mechanical expulsion out of the urethra. [46,48] The prostatic secretion is rich in the enzyme prostate-specific antigen (PSA), which, as part of the ejaculate, liquefies semen in the seminal coagulum and allows the sperm to be freely mobile. [49,50] It also dissolves the cervical mucus, therefore allowing the sperm to enter the endometrial cavity. [51]

The normal prostate gland is about 20 g in volume with a length of 3 cm, a width of 4 cm, and a depth of 2 cm. The prostate gland's size changes in men as they age due to benign prostatic hyperplasia. The prostate gland is located just below he urinary bladder, behind the pubic bone, and anterior to the rectum. It sits on top of the perineal membrane with the prostatic urethra running through it in an essentially craniocaudal direction. The gland is enclosed in a capsule made primarily of elastin, collagen, and smooth muscle. Three different layers of fascia cover the anterior, lateral, and posterior surfaces of the prostate. [1,35-37]

Multiple layers of fascia have been described in studies, which may allow layers carrying nerve fibres to be separated without cutting into prostate tissues. Along with the anterior and anterolateral fascia that cover the gland, the true capsule of the prostate is made up of the deep dorsal vein of the penis and its branches. The fascia merges laterally with the levator fascia. It is possible for the fibromuscular tissue of the capsule to blend and fuse with the outer longitudinal fibres of the detrusor muscle in the bladder. The rectovesical (Denonvilliers) fascia covers the posterior aspects of the prostate and separates it from the rectal wall. [1,35-37]

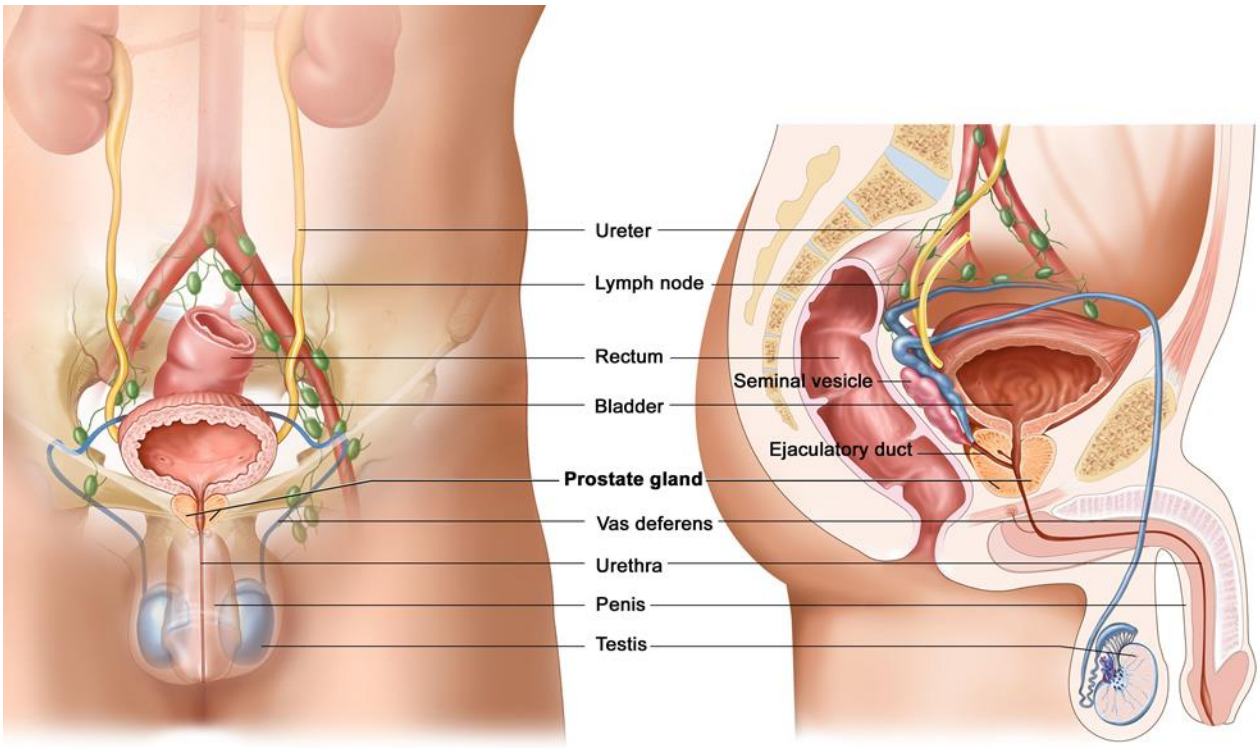

Figure 1: The Prostate Gland and its Relationships Source: Winslow, T. (2008). Genitourinary System, Male, Testicular, Anatomy [Photograph]. National Cancer Institute. https://visualsonline.cancer.gov/details.cfm?imageid [96]

The prostate gland is shaped like an inverted pyramid and surrounds the prostatic urethra, which traverses the prostate close to its anterior surface at the superior aspect and becomes more central at the inferior aspect. It has a base that is oriented superiorly and lies just below the base of the urinary bladder, while its apex, oriented inferiorly, is in contact with the superior surface of the pelvic diaphragm. [45, 47, 52, 53]

It has anterior, posterior, and inferolateral surfaces. The anterior surface of the prostate lies behind the pubic symphysis, forming the posterior limit of the retropubic space of Retzius, while its triangular flat posterior surface with a vertical groove, palpable during digital rectal examination (DRE), is anterior to the rectum and separated from it by the rectovesical fascia (Denonvilliers' fascia). The puboprostatic ligaments connect the prostate gland to the pubic bone, with the inferolateral surfaces resting on the levator ani fascia. [45-47]

Anatomists divide the prostate gland into five lobes: the anterior, posterior, median, and a pair of lateral lobes. [46] This description is what is seen in most anatomy textbooks, while in routine clinical discussion by the physician at the clinics, it is described as having three lobes: two lateral (right and left) lobes and a

single median lobe. However, the variation in the number of lobes is not uncommon, with some individuals having as few as one lobe and others having up to five lobes. [46]

2.0.2 Histology of the Prostate Gland

The prostate consists of three distinct zones with their distinct embryologic origins. These are: peripheral zone, central zone, and transition zone. The largest of the zones is the peripheral zone (PZ), which is cup-shaped, encompasses the central and transition zones, and accounts for approximately 70% of the total prostate volume in a young adult. [45–48, 52-54]

The peripheral zone extends from the posterolateral aspects of the base of the prostate gland to its apex and surrounds the distal prostatic urethra. On the anterior aspects of the gland, where it is lacking, the anterior fibromuscular stroma (AFMS) replaces the PZ. Most prostate cancers occur in the PZ. [45-46]

The central zone (CZ) is small and wedge-shaped, constituting up to about 25% of the prostate volume and containing the ejaculatory ducts. It is posterior to the prostatic urethra and forms the base of the prostate. [45–48, 52-54]

The transition zone (TZ) is the smallest of the zones and makes up the remaining 5% of the prostatic volume. It is predominantly anterolateral to the prostatic urethra. [45–48, 52-54] The transition zone is the site for the development of benign prostatic hypertrophy. [53,54]

Three different cell types—luminal, basal, and neuroendocrine cells line the acini and ducts of the prostate gland. [53,54] Luminal cells are specialised to secrete a variety of products into the lumen, which contribute to the formation of the seminal fluid. [53,54] PSA immunohistochemistry shows that luminal cells are strongly positive. This is because PSA is part of the products that luminal cells release. [53,54] The basal cells are adjacent to the basement membrane and have inconspicuous cytoplasm and ovoid nuclei. The number of basal cells can be variable between glands in an individual prostate. [53,54] Neuroendocrine cells cannot be reliably identified on hematoxylin and eosin (H&E) sections but can be highlighted by immunohistochemistry for neuroendocrine markers such as chromogranin and synaptophysin. [5,54]

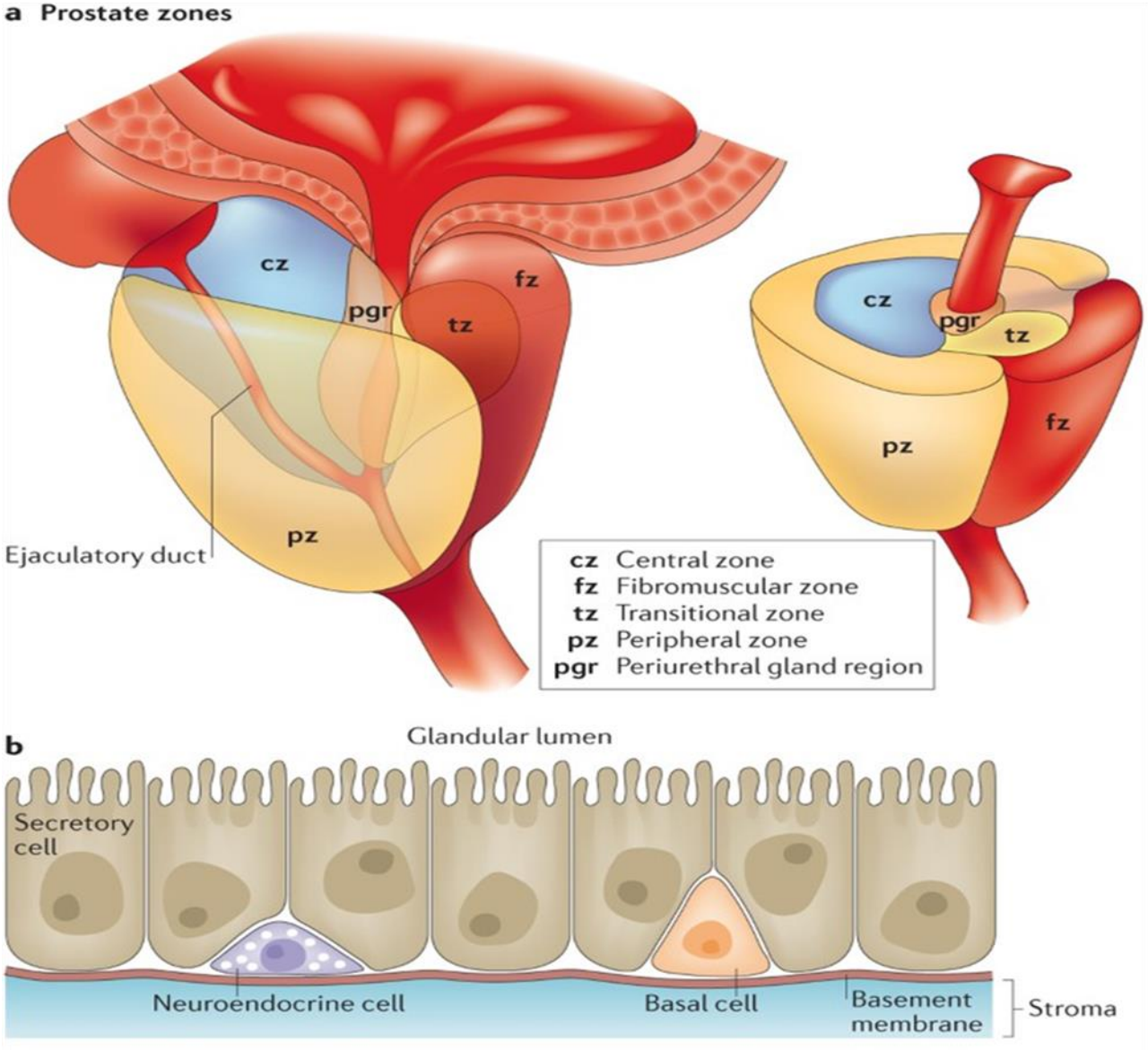

Figure 2: a. The zones of the prostate gland; b. The cells lining its lumen. Source: Verze, P., Cai, T., and Lorenzetti, S. The role of the prostate in male fertility, health, and disease. Nat Rev Urol 13, 379–386 (2016). https://doi.org/10.1038/nrurol.2016.89 [97]

The prostatic stroma is fibromuscular, with a large proportion of smooth muscle cells with fibroblasts, nerves, and blood vessels interspersed in it. There is no adipose in the prostate gland. Skeletal muscle fibres are essentially outside the prostate but may extend into the outer portion of the prostate as well. The presence of skeletal muscle fibres in the outer portion of the prostate is important for maintaining structural support and aiding in ejaculation. [53,54]

The prostate gland in humans often shows a wide variety of changes in the epithelium and stroma. Changes such as atrophy of the glandular epithelium are extremely common, as is basal cell hyperplasia. Chronic inflammation is also very common, and variable degrees of acute inflammation, from focal to extensive with abscess formation, can be seen. The presence of reactive atypia and occasional squamous metaplasia may also be observed. [53,54]

2.0.3 Vascular Supply of the Prostate Gland

The main artery supplying the prostate, the prostatic artery, comes from the inferior vesical artery, which is one of the anterior branches of the internal iliac artery. [45,46] The middle rectal and internal pudendal arteries each send some small branches to supply the inferior part of the gland. The inferior vesical artery gives off branches supplying the distal ureter, the base of the bladder, and the seminal vesicle, and then terminates as small branches supplying the prostate gland. [45,46,54,55] These terminal arteries, the prostatic arteries, subdivide into two groups of arteries: the urethral branches, which supply primarily the deep part of the gland, and the urethra, while the capsular group supplies the capsule and peripheral parts of the gland. [45,46,54,55]

Between the true and false capsules of the prostate, the prostatic venous plexus drains the prostate gland. This plexus drains into the dorsal venous plexus of the penis, which in turn drains into the internal iliac vein. A network of veins, including the Batson venous plexus, also connects the prostatic venous plexus posteriorly to the internal vertebral venous plexus. The Batson venous plexus allows for potential metastasis of prostate cancer to the vertebral column. [45,46,54,55]

2.0.4 Lymphatic Drainage of the Prostate Gland

The lymphatic drainage of the prostate is primarily into the obturator and the internal iliac lymph nodes. There are also lymphatic channels providing connections in between the external iliac, pre-sacral, and para-aortic lymph nodes. Additionally, lymphatic vessels from the prostate can also drain into the inguinal lymph nodes. [45,46,54,55]

2.0.5 Innervations of the Prostate Gland

The prostate receives autonomic innervation from the pelvic plexuses formed by the parasympathetic fibres that arise from the sacral levels (S2-S4) and the sympathetic fibres from the thoracolumbar levels (L1-L2). The prostate gland also receives sensory innervation from branches of the pudendal nerve. [47,48,56,57] The sympathetic and parasympathetic fibres that come from the pelvic plexuses travel to the prostate through the cavernous nerves, which run on the posterolateral aspects of the prostate in the lateral prostatic fascia. [46,47,55,56] Two-thirds of the nerve fibres run along the traditional posterolateral aspect of the prostate; however, it has been demonstrated through surgical anatomy studies of the prostate that the remaining third of the nerve fibres are more anterior and lie in the anterior lateral aspect of the prostate. [47,48,56-58] The parasympathetic nerves end at the acini and lead to prostatic secretion. The sympathetic nerves lead to the contraction of the smooth muscle of the capsule and the stroma. [47,48,56-58]

2.0.6 Embryology of the Prostate Gland

The prostate gland grows from epithelial invaginations in the urogenital sinus wall into the mesenchyme below. During the third month of pregnancy, epithelial buds start to form. These epithelial buds branch into numerous solid cords, which are canalised into the acini and ducts. [13,22,23] The hormone dihydrotestosterone (DHT) is needed for the prostate gland to develop normally. [23,24,25] DHT is synthesised from foetal testosterone produced by the leydic cells of the testis by the action of the enzyme 5α-reductase localised in the urogenital sinus and the external genitalia. [13,23,24,25] Deficiency of 5α-reductase may case agenesis of the prostate gland. In addition to this, there may be several abnormalities of the external genitalia in the presence of normally developed epididymis, vas differentia, and seminal vesicles. [13,23,24,25] The constitution of the human prostate remains relatively identical during the pre-pubertal ages. It then undergoes morphological changes shaping it into the adult phenotype with progress of puberty. The gland ultimately enlarges to reach the average adult weight of about 20 g by 25–30 years of age. [12,23,24,25]

2.1 Serum PSA

Prostate-specific antigen (PSA) is a serine protease enzyme produce primarily, but not exclusively, by the secretory epithelial cells lining the acini and ducts of the glands in the prostate. It is a type of the tissue kallikreins and is excreted abundantly as one of the constituents of the prostatic secretions from the

prostate gland. [59,60] It has a chymotrypsin-like activity and plays a role in the dissolution of the seminal coagulum formed after ejaculation, therefore playing an important role in fertilization. Initially, researchers believed the prostate gland produced it exclusively, and they used it as a biomarker for prostate cancer. Recent studies have confirmed its widespread distribution in several normal body tissues, tumour cells, and biological fluids. [59,60,61] It is essentially in the seminal secretion, where it has the highest concentration, but can also be found in the serum as some escape into the blood. Two teams of scientists from Japan and the USA independently discovered PSA after their respective governments requested their research to identify semen in rape victims. The protein has been found in other parts of the body and also in women, thereby making the name prostate-specific antigen a misnomer. [59,60,61]

2.1.1 Biology of Serum PSA

Prostate-specific antigen is a member of the tissue kallikrein family, with the gene for its production located on the long arm of chromosome 19 (19q13.4). Kallikreins were initially defined as serine proteases that degraded some high-molecular-weight molecules, specifically proteins, releasing bioactive peptides called kinins as a product. [50] The posttranslational processing of polypeptides to their bioactive or inactive forms is primarily performed by the kallikreins through their enzymatic activity. Upon further studies, the kallikreins have been classified into two groups: tissue and plasma kallikreins. The liver is the sole source of human plasma kallikreins, with the gene encoding its production located on chromosome 4. [50,51,59] It cleaves bradykinine from high-molecular-weight kininogen.

Until recently, only three tissue kallikreins had been discovered and were thought of as the only ones they were. [50,51,59] These are human kallikrein 1 (hK1; pancreatic-renal kallikrein), hK2 (glandular kallikrein), and hK3 (PSA). Several more have been recently discovered, and recent studies have uncovered 15 kallikrein tissue genes located on chromosome 19q13.3–q13.4. These genes are encoded by five exons of similar size and have 40–80% sequence homology. [50,51,59] Multiple tissues express the kallikrein genes, which are regulated by steroid hormones. Three tissue kallikreins, PSA, hk2, and hK4, are androgen-regulated and principally expressed in the prostate gland. [50,51,59] There is a close linkage in the genes responsible for the production of PSA, hK2, and hK4. The close linkage of these three genes with their principal expression in the prostate gland indicates that a common prostate-specific regulatory element may be controlling their expression. PSA and possibly hK4, though expressed in much lower quantities, may be used as biomarkers for prostate cancer. [59,60]

2.1.2 PSA Biosynthesis:

The prostate-specific antigen, also known as kallikrein-3 (KLK3), is a glycoprotein enzyme encoded by the KLK3 gene in humans. PSA is one of the kallikrein-related peptidase family enzymes that is secreted by the epithelial cells lining the ducts and acini of the prostate gland in men and the paraurethral glands in women. [59] PSA is initially synthesised as a larger inactive molecule, pre-proPSA, which undergoes cleavage, initially producing an inactive 244-amino acid precursor protein, proPSA. The active enzyme, PSA, is then subsequently generated from the proPSA through the cleavage of its seven N-terminal amino acids. The final active PSA molecule is a 33-kD, 237 amino acid-residue single-chain glycoprotein with four carbohydrate side chains and multiple disulfide bonds. [59-61]

2.1.3 Protein binding and pharmacokinetics

PSA, a serine protease, exists mostly in the bound form; only a small percentage exists in the unbound free PSA (fPSA). The bound or complexed PSA (cPSA) is bound to either alpha1-antichymotrypsin (ACT) or alpha2-macroglobulin (AMG). They are the two major inhibitors of proteases in the blood. [59, 60] PSA is in very high concentration in the semen in the free or unbound form, with a concentration of around 1 million ng/mL. [59-61] The half-life of PSA was found by Stamey et al. to be 2.2 $\pm$ 0.8 days, while Oesterling et al. reported it to be 3.2 $\pm$ 0.1 days. Therefore, a minimum of 2–3-week period is required after radical prostatectomy for the serum PSA to reach an undetectable level. [62,63]

2.1.4 Mechanism of Action of PSA

The physiological function of PSA (KLK3) is to, by its proteolytic action, dissolve the seminal coagulum that forms after ejaculation, trapping the sperm and preventing their movement. The seminal coagulum, the sperm-entrapping gel, is composed of fibronectins and semenogelins. Its activation is highly well-regulated. [49]

It exists as a pro-enzyme in the form of pro-PSA, which is converted to its active form by the action of the enzyme KLK2, another member of the kallikrein family of peptidases. The prostate gland has the

highest concentration of zinc ions in the body. It has about 10 times the concentration of zinc ions as it does in other parts of the body. This is another layer of control over the activity of PSA as an enzyme. The activity of PSA (KLK3) and its pro-form activator, KLK2, is strongly inhibited by zinc ions. [50] Another layer of regulation of the enzymatic action of PSA is through pH variations. The activity of PSA increases with rising pH, which is negated by the inhibitory effect of zinc ions, which also increases with increasing pH. [50,51] The semen has a slightly alkaline pH and a very high concentration of zinc. Under normal physiological conditions, semen is exposed to the low pH of the lactic acid-rich environment of the vagina after ejaculation. In healthy couples, the pH of the vaginal fluid at the end of sex is around 6-7. This is a pH range where zinc has much less of an effect on sperm production than PSA, which is found in large amounts in the ejaculate. This allows the slow dissolution and liquefaction of the seminal coagulum and the release of the sperm in a well-regulated manner. [50,51]

2.1.5 Factors influencing serum PSA levels

1. ***The presence of malignant prostate tissue:***

Prostate-specific antigen (PSA), for clinical purposes, is considered prostate gland-specific but not prostate cancer-specific. There is a large overlap between serum PSA values for benign conditions of the prostate, like BPH and prostatitis, and those of prostate cancer. This is a major limitation in the diagnostic utility of serum PSA in diagnosing prostate cancer. PSA is produced by all the epithelial cells lining the glands and ducts of the prostate be they normal, hyperplastic, and malignant. Some anaplastic epithelial cells may lose the ability to produce and secrete PSA. The malignant epithelial cells generally produce about ten times the amount of PSA produced per a gram of tissue by the normal or hyperplastic cells. [50,51]

2. ***Hyperplastic tissue and epithelial-stromal ratio:***

The transitional zone of the prostate gland produces the most PSA. The peripheral zone, the seat of about 70–80% of prostate cancer, produces relatively little PSA. A large amount of PSA tends to be produced by cancers that develop in the transitional zone, which is relatively uncommon. Very aggressive and high-grade prostate cancers tend to be anaplastic, with a loss of the ability to produce PSA. Therefore, patients with such cancer tend to have a low PSA. [49-51]

3. Pharmacologic factors:

Various medications may influence the level of serum PSA in the body. Typical examples of such medications are 5-alpha reductase inhibitors used in treating BPH, and luteinizing hormone-releasing hormone agonists or antagonists used for androgen suppression in treating prostate cancer. The 5-alpha reductase inhibitor finasteride causes a variable effect on the serum PSA level, typically causing a 50% reduction within six months of the start of the medication. The extent of the effect on the serum PSA level fluctuates widely, ranging from an 80% decrease to a 20% increase. This therefore necessitates a recheck of the serum PSA level 3–4 months after the initiation of therapy to establish the new baseline PSA level. [50,51]

Agents that affect the serum testosterone level may profoundly affect the serum PSA level as well. Using a luteinizing hormone-releasing hormone agonist or antagonist to suppress testicular testosterone production in androgen deprivation therapy in prostate cancer patients has a profound effect on the serum PSA level. This may decrease serum PSA to an undetectable level. This is caused by atrophy of the PSA-secreting epithelial cells present in the acini and ducts of the prostate gland. There is some recovery of PSA production when the serum testosterone levels rise again after withdrawal of the therapy. [50,51]

Other medications, despite their effect on the prostate gland, may have little or no effect on the serum PSA levels. Medications such as alpha1-andrenergic antagonists like tamsulosin and phyto-therapeutic agents like saw palmetto, which are widely used to treat BPH, do not affect the PSA level.

4. Benign prostatic conditions and urologic manipulations:

Benign prostatic diseases and urologic procedures may also cause a rise in serum PSA levels. Conditions such as acute and chronic prostatitis, BPH, and acute and chronic urinary retentions are examples of such benign urologic conditions.

A procedure such as a digital rectal examination, if gently done, does not cause a rise in the serum PSA levels. But a vigorous massage of the prostate gland may cause a two-fold increase in the baseline serum PSA level. There is a median rise of 7.9 ng/mL in the baseline serum PSA level within minutes of a needle biopsy of the prostate gland. It may take between 2 and 4 weeks for the serum PSA level to return to pre-biopsy levels. This proceeds to fall over several days. [62,63] The serum PSA level may continue to surge instead of falling if there is an infection of the gland after the procedure.

Urinary retention causes a rise in serum PSA levels. This falls rapidly after relief of the retention, with about a 50% decrease in the level of serum PSA within 24-48 hours of relief of the retention. Acute prostatitis may cause a huge surge in the baseline serum PSA level, which returns to normal over about 6–8 weeks with the resolution of the infection. [62,63]

5. ***Race and age:***

Black men have a higher incidence of prostate cancer than men of other races. It has been reported by several studies that black men tend to have high serum PSA levels, even when age, Gleason grade, and clinical stage have been controlled. PSA levels tend to increase with age because of increasing prostate volume. The transition zone of the prostate gland is the seat for the production of most PSA. This zone increases in volume from BPH with age, hence increasing PSA production and serum PSA levels. [11,36,50]

2.2 Prostate Cancer

Prostate cancer is the most common cancer, after lung cancer, in men around the world, with an estimated 1.4 million new cases and 375,000 deaths worldwide in 2019. 1 Prostate cancer is a disease of the elderly, with over 33% of men over 60 years old having a latent form of the disease. [2,37,38]

2.2.1 Incidence

Globally for 2020, the crude incidence rate of prostate cancer was 36.0, while the age-standardised incidence rate (ASIR) was 30.7 per 100,000 males.[1,9] The data analysis by continents reveals that the crude incidence rates for prostate cancer were 131.2 per 100,000 males in North America, 130.9 in Europe, 105.0 in Oceania, 66.7 in Latin America and the Caribbean, 13.9 in Africa, and 15.6 in Asia.[1,9] While the ASIRs were 73.0 in North America, 70.3 in Oceania, 63.4 in Europe, 59.2 in Latin America and the Caribbean, 29.7 in Africa, and 13.6 in Asia, all per 100,000 males. [1,9] Oceania came in second with 20.4 per 100,000 males, and Europe had the highest crude mortality rate at 29.9. The distribution of the age-standardised mortality rates (ASMRs) was 16.3, 14.2, 11.1, 11.0, 8.3, and 4.1 per 10,000 males in Africa, Latin America, and the Caribbean, in Europe, Oceania, North America, and Asia, respectively. [1,9]

2.2.2 Etiology of Prostate Cancer

Unlike other cancers, the aetiology of prostate cancer is not fully understood and is the focus of numerous studies. [39] The established risk factors for PCa are advanced age, ethnicity or race, genetic factors, and family history. [54-57] Other factors that are positively associated with prostate cancer include diet, physical

inactivity, obesity, inflammation, diabetes mellitus, infections, and environmental exposure to chemicals or ionising radiation. These factors, when present, can increase the risk of developing prostate cancer. [54–57]

2.2.3 The Risk Factors of Prostate Cancer

In general, all men with prostate glands are at risk of developing prostate cancer. However, some specific factors increase one's risk of developing prostate cancer. These risk factors are:

1. ***Advanced age:***

PCa is a disease of elderly men, most diagnosed at or above the age of 65. [58,59] It is very uncommon below the age of 50, with a rate of 1 in 451 men, after which it steadily increases: 1 in 55 for men in the age bracket of 50–59, 1 in 20 for ages 60–69, and then 1 in 12 for men 70 years of age or older. 58–60: About 60% of PCa is diagnosed in men aged over 65 years. [58-60]

Dysplastic lesions frequently precede prostate cancer for years, sometimes even decades, and it frequently develops slowly. Extrapolations from studies conducted post-mortem indicate that most men who live to be more than 100 years old will have prostate cancer. [58-60] Small, localised prostate cancers can go unrecognised for many years before progressing into a clinically significant disease. At the age of 50, the average person has a 42% risk of developing prostate cancer and a 3% risk of dying from prostate cancer. [58-60]

2. ***Race (Ethnicity):***

Prostate cancer incidence rates vary across populations. [40] A sizable heritable component of this disease helps to explain some of these variations. [40] It has been established that men with African ancestry are predisposed to PCa and can have an earlier onset and a more aggressive course, thereby leading to poorer outcomes. [62-64] This is demonstrated in the United States of America, where the PCa incidence is lowest in Native Americans (46.9) and Asian/Pacific Islanders (52.4), followed by white men (93.9), while African American men have the highest rate (157.6) and twice the mortality rate as white men. [62-64]

3. ***Family history and genetic factors:***

It is estimated that about 20% of PCa patients have a family history of the disease, and this may be due to shared genes, exposure bias, and common lifestyle habits. [39,65] Several studies have reported that an inherited genetic background is associated with an increased risk for PCa and contributes to about 5% of

disease risks. [39,65,66] A first-degree relative with PCa increases the risk of developing prostate cancer by about 2 to 2.5 times among black, white, and Asian men. [7,68-70] This risk increases by more than 4 times among whites and Asian men and by as much as 10 times among black men, when two or more first-degree relatives have prostate cancer. [65]

Studies on the human genome have revealed a significant association between prostate cancer and several genes and chromosomal regions. Various linkage studies, genome-wide association studies (GWAS), case-control studies, admixture mapping studies, and next-generation sequencing (NGS) have confirmed this association. [71-73,78,79] Deleterious mutations in genes such as BRCA1, BRCA2, HOXB13, and mismatch repair genes confer a moderate lifetime risk of developing prostate cancer but do not fully account for the genetic risk of prostate cancer. [71]

4. Diet

Dietary factors may play a role in the development of PCa, with significant credence lent to this suspicion by multiple studies on immigrants who migrate from developing countries, which are low-risk areas, to industrialised countries, areas of higher risk. These studies have shown that a change to a "westernised" lifestyle leads to an increased risk of developing PCa. [39]

Two classic studies illustrate this observation: a study by Chu et al. reported a 40-fold increase in the prostate cancer incidence rate among Africans living in the United States compared to those in Africa, while Hsing et al. showed the prostate cancer incidence rate was 16 times higher for Chinese who have migrated to the United States compared to those in China. They concluded that environmental factors play an important role in prostate cancer development. [74-76] There is evidence that certain foods increase the risk of prostate cancer, while others are protective.

2.2.4 Prostate Volume and Prostate Cancer

Uzzo et al prospectively evaluated 1021 men who underwent TRUS-guided sextant core biopsy of the prostate to determine the influence of prostate size on prostate cancer detection rate. [146] They reported statistically significant difference in the cancer detection rates between small and large prostates. The cancer detection rate was higher in small prostates (38%) than large prostate (23%). [146] The mean prostate volume for patients with prostate cancer was smaller (40 $\pm$ 26 mL) than that of those without prostate cancer (51 mL $\pm$ 33) ($P < 0.01$). Only 14% (8 of 58) of patients with prostate volume of > 100.0 mL were detected to have prostate cancer compared to 49% (118 of 239) of those with prostate volume of $\leq$ 25.0

mL. [146] In 2021, Yamashiro et al. published their findings from a meta-analysis of various studies performed which evaluated the relationship between prostate volume and prostate cancer detection rate over the previous 3 decades prior to their systemic review. [147] This included 41 single institutional and multi-institutional studies with sample sizes ranging from 114 to 6692 patients. [147] They reported an inverse relationship between incidence of prostate cancer and prostate volume. [147] They found 95% (39 out of 41) of the studies showed statistically significant negative relation. [147] They therefore concluded from their findings from the systemic review that a larger prostate may be protective of prostate cancer compared to smaller prostates. [147]

2.2.5 DRE and Prostate Cancer

Digital rectal examination is a means for examining the posterior aspect of the prostate with a gloved index finger through the anterior rectal wall. Though, this may provide useful but information about the prostate gland, it is most often of limited depth and accuracy. [148] It is therefore, a poor tool for evaluating the prostate gland for the presence of prostate cancer. In 2023, Krilaviciute et al. reported their findings from a multicenter, population-based, randomized, screening trial, which enrolled more than 46000 men aged 45 years to test risk-adapted PSA screening for prostate cancer. [148] The study aimed to determine the diagnostic performance of DRE in a screening trial. [148] The study participants were randomized to either screening at the age of 45 years on recruitment (immediate screening arm) or at 50 years (deferred screening arm). [148] This study evaluated DRE as a one-time, stand-alone screening offer at the age of 45 years in 6,537 men in one arm of the trial DRE prostate cancer was evaluated at the time of a prostate biopsy. [148] Of the 6,537 men randomized to the immediate-screening arm at the age of 45 years, 57 of were found to have suspicious DRE findings. [148] When prospectively followed up, 3 of the 57 men were diagnosed with prostate cancer, giving a DRE PCa detection rate of 0.05% (3 out of 6537) whilst the PCa detection rate of PSA was 0.21% with 48 of 23,301 of PSA screened patients with abnormal PSA levels were diagnosed with PCa after prospective follow up. [148] This shows a four-fold higher cancer detection rate for PSA screening relative to DRE screening. [148] They reported a true-positive PCa detection rate by DRE relative to PSA-screening of 0.22 (95% confidence interval [CI] = [0.07-0.72]) and a false-negative PCa detection rate by DRE of 2.2 (95% CI = [1.50-3.17]). [148] Eighty-six percent (86%) of the PSA-screen detected PCa cases had unsuspicious DRE findings with sensitivity of 14% relative to PSA. [148] The study concluded that the DRE is a poor tool for screening for PCa and it does not improve the detection of PSA-screen detected PCa. [148]

Matsukawa et al., in August 2023, undertook meta-analysis of studies which simultaneously investigated the diagnostic performance of DRE and PSA screening in the PubMed, Scopus, and Web of Science databases. They identified eight studies with a total of 85,798 participants, of which three were prospective diagnostic studies and three were random controlled trials. [149] Thy reported a pooled positive predictive value (PPV) of 0.21 (95% confidence interval [CI] 0.13–0.33) for DRE, which was similar to the PPV of 0.22 for PSA (95% CI 0.15–0.30; p = 0.9). [149] They found no benefit combining DRE and PSA (PPV 0.19, 95% CI 0.13–0.26; p = 0.5). [149] The cancer detection rate (CDR) of DRE (0.01, 95% CI: 0.01–0.02), was however significantly lower than that of PSA (0.03, 95% CI 0.02–0.03; $p < 0.05$) and PSA and DRE combined (0.03, 95% CI 0.02–0.04; $p < 0.05$). the CDR (p=0.5) and PPV (p=0.5) for screening strategy utilizing PSA alone were not different from that of strategy which combine DRE and PSA. [149] They concluded from their comprehensive review and meta-analysis, that DRE shows a notable low diagnostic value both as an independent test and as a supplementary measure to PSA for prostate cancer detection. Based on these findings from their review, they therefore recommended against the use of DRE for prostate cancer screening and early cancer detection. [149]

2.2.6 Demography and Prostate Cancer

The literature about prostate cancer incidence, stage at diagnosis, and survival has examined several social, economic, and geographic determinants of health. These determinants include education and income level (socioeconomic status), neighbourhood disadvantage, immigration status, social support, social network, access to health services, and insurance coverage. [76-81]

Socioeconomic factors such as lack of education, immigration status, poverty, income inequality, lack of social support, and social isolation are important for the prostate cancer stage at diagnosis and survival. [76] People with low incomes are at increased risk of several different adverse health outcomes and are more likely to die prematurely. The impact of socioeconomic factors on health outcomes should be considered in both clinical practice and public health interventions. [76]

2.3 Prostate Cancer Screening

There are a lot of uncertainties as to whether the benefits of prostate cancer screening, using serum PSA testing, is worth the risks of over diagnosis and over treatment. This has led to different professional bodies giving different recommendations for prostate cancer screening. [51]

PSA has been approved for prostate cancer screening by the Food and Drug Administration (FDA) of the United States for men who are 50 years of age and older. It requires the patient to be counselled on the risk and benefit of PSA testing before the test is undertaken. The National Health Service (NHS) of the United Kingdom does not mandate or advise prostate cancer screening using PSA. [52] It rather encourages patients to decide based on the advice of their doctors. Based on similar reasons, the NHS does not offer general PSA screening. [18, 53]

Serum PSA levels of 4.0–10.0 ng/mL are considered suspicious, and this may warrant further evaluation and a prostate biopsy after confirming the PSA level with a repeat test. A prostate biopsy is done, if indicated, to obtain a prostatic tissue sample for histopathological investigations. About 1 in 1000 men may avoid death with the help of PSA testing, but 4 to 5 in 1,000 men would still die from prostate cancer over 20 years even with prostate cancer. This shows PSA screening may reduce prostate cancer mortality by about 20–25%. Screening for prostate cancer through PSA testing caused harm in the form of anxiety suffered by those with false-positive results, biopsy pain, infections, bleeding, and other complications from the biopsy for a false-positive PSA test. [37-39]

PSA tests have a questionable level of accuracy. It has a high false-positive and high false-negative rate. False-positive results cause undue anxiety and confusion and lead to unnecessary prostate biopsies, with their associated complications and resource utilization. False-negative results may lead to a delayed or missed prostate cancer diagnosis and its associated sequelae. Of the men diagnosed with prostate cancer, there is a high level of overtreatment due to the fact that a large percentage of prostate cancers are slow-growing and may not cause any adverse effects if not detected.

Therefore, many men treated for prostate cancer would experience the side effects of a treatment that they would have done well without. Some of the side-effects of prostate cancer treatments suffered by those who undergo treatment are erectile dysfunction (occurring in 29 out of every 1000 men screened), urinary incontinence (occurring in 18 out of every 1000 men screened), serious cardiovascular events (occurring in 2 out of every 1000 men screened), pulmonary embolism (occurring in 1 out of every 1000 men screened), and perioperative deaths (occurring in 1 out of every 1000 men screened). [37-39]

2.4 Indications for Prostate Biopsy

The gold-standard diagnostic technique for diagnosing prostate cancer is the prostate biopsy, and it has traditionally been done based on the following: The decision to perform a prostate biopsy is complex,

evolving, and should be individualised. A biopsy of the prostate gland is traditionally performed for three general indications: an abnormal digital rectal exam (DRE) finding, increased serum prostate-specific antigen (PSA), and clinical suspicion of prostate cancer. [57-63]

Before PSA was discovered and used for screening, a prostate biopsy was only done when there were signs of something being wrong with the DRE, like unevenness, nodules, or generalised firmness. Digital rectal examination has a poor positive predictive value for prostate cancer of about 5–30% and is therefore not recommended for use as a sole prostate cancer screening tool. [57–63]

2.5 Patient Preparations for TRUS-Guided Prostate Biopsy

TRUS-guided prostate biopsy is usually performed on outpatient basis under local anesthesia. It may occasionally be done under general or spinal anesthesia in the theatre.

2.5.1 Reducing the risk of bleeding

Anticoagulants (e.g. heparin, warfarin, etc.) and antiplatelet (e.g. aspirin, clopidogrel, etc.) should be generally discontinued at least 5 days prior to the procedure to reduce the risk of bleeding.[100] The risk of bleeding may be assessed, when necessary, by measuring platelet counts and PT-INR levels. This may be adjusted to the appropriate levels for the procedure (PT-INR < 1.5; platelet count > 50000/μL). this minimizes the risk of significant bleeding during and after the procedure.[100]

2.5.2 Cleansing Enema

There is no strong evidence to recommend bowel preparation or otherwise before TRUS-guided biopsy. The rectum should preferably be emptied before the procedure.[100] This may be achieved with rectal cleansing enema using agents such a glycerin. Pre-biopsy enema essentially empties the rectum of stools and improves the sonic window and removes confounding shadowing. [100,101] There is controversy over the efficacy of enema in the prevention of post-biopsy infection. The incidence of bacteremia after TRUS-guided biopsy is higher in patients who received no enema than in those who were given enema. This observation was independent of antibiotic use. [102] A study by Carey and Korman reported no significant benefit in giving patients pre-biopsy enema despite increase in cost and patients' inconvenience. [103] To the contrary, however, several published studies have subsequently reported reduction in infectious m in reducing post-biopsy infectious side effects after pre-biopsy enema. [104-106] Mechanical bowel preparation with ingestion of polyethylene glycol (PEG) solution achieves effect similar to effect achieved with glycerin enema with in reducing post biopsy infectious complications, despite being reported by patients

to be less comfortable.[107] Rectal enema suffices for bowel preparation for TRUS-guided prostate biopsy. [100-107]

2.5.3 Dietary restriction

TRUS-Guided biopsy is routinely done under local anesthesia and therefore does not routinely require dietary restriction prior to the procedure. The patient may be fasted overnight if the procedure is done under general or spinal anesthesia. [100-107]

2.5.4 Intravenous antibiotics

The practice of antibiotic prophylaxis reduces the risk of post-biopsy infectious complication. [100,108,109] Prophylactic antibiotic therapy reduces the risk of post biopsy complications to 1% or less. [100-111] The recommended antibiotics for antimicrobial prophylaxis for TRUS-guided biopsy are fluoroquinolone and first-, second-, and third-generation cephalosporin. This should be given 1–2 hours before the procedure. [108,109,112] The route of administration has been found not to influence the efficacy of the antibiotic prophylaxis. There is controversy over the duration of antibiotic administration after the biopsy. [101] A retrospective multicenter study Nash et al. in 1996 reported post-biopsy infectious complication rate reduction of 90% with the use of a single-dose gentamicin intramuscular before biopsy followed with a three-day levofloxacin oral administration after biopsy, compared to the administration of post-biopsy antibiotics only. [113]

The most frequent practice in antibiotics use in TRUS-guided biopsy are third-generation cephalosporin, followed by quinolones and second-generation cephalosporin. [100] Post-biopsy antibiotics are usually administered for one week. [100,107]

2.5.5 Biopsy-Related Pain Management

The pain experienced by a patient undergoing TRUS-guided prostate biopsy is caused by the insertion of the ultrasound probe into the rectum and the driving of the biopsy needed through the rectal wall into the prostate gland to sample the gland. The intensity of pain is influenced by the size of the ultrasound probe used and the number of biopsies taken. [100]

The pain experienced on insertion of the ultrasound probe is as a result of forceful expansion of the anal canal below the dentate line as the probe enters the canal. This part of the anal canal is supplied by somatic nerves and has a high concentration of sensory nerve distribution. The rectal mucosa lacks pain receptors and therefore insensitive to pain. The prostate capsule and prostate parenchyma are richly innervated with

nociceptors and are therefore very sensitive to pain. This spreads through the periprostatic neurovascular bundle. [100-102]

Periprostatic neurovascular bundle block (PNB) is performed using either a Chiba needle or a long spinal needle (7-inch, 22-gauge). About 5 mL of 1–2% lidocaine is injected in the region of the vascular pedicle supplying the prostate gland which is located at the base of the prostate immediately lateral to the junction between the prostate and seminal vesicle. [100,113] PNB is the best proven method for providing analgesia in TRUS-guided biopsy.[100] In a series of meta-analysis by Tiong et al. and Hergan et al., periprostatic local analgesia was found to significantly reduce pain in TRUS-guided biopsy compared to placebo. [114,115]

2.6 Complications of TRUS-Guided Prostate Biopsy

Trans-rectal ultrasound guided needle biopsy of the prostate is the procedure of choice for diagnosing prostate cancer and it is routinely performed to obtain prostatic sample for histopathological studies on the prostate gland. [116] It is generally considered safe and is usually performed on ambulatory basis. Although TRUS-guided biopsy is considered very safe, because of its invasive nature and its rectal approach, it can result in several possible complications. [116] Indeed, the first published studies evaluating the outcomes of prostate biopsies, reported very high rates serious of complications such as post-biopsy infections and mortalities. [116] The rates of serious post-biopsy complications fell significantly over the subsequent years as results of adoption of these improved methods and technologies such as biopsy technique, use of automatic biopsy gun, antibiotic prophylaxis, and appropriate patient preparation before the biopsy procedure. Despite the significant reduction in the rates of serious post-biopsy complications witnessed with these advancements, minor complications still remain considerable. [116,117] Djavan et al. reported a minor and serious complication rate of 69.7 and 0.01% from a multicenter European Prostate Cancer Screening Study which performed 98-coreTRUS-guidedbopsy of the prostate on 1051 men. [117] Efesoy et al. reported minor and serious post-biopsy complications rate of 79.2 and 1.3% from their study involving 2049 men who underwent TRUS-guided 12-core prostate biopsy. [116]

Bleeding episodes are the leading complication after TRUS-guided prostate biopsy. Bleeding complications may present as hematuria, hematospermia or hematochezia. This may present with varying severity ranging from minor bleeding to life-threatening disseminated intravascular coagulopathy. [116,117]

Hematuria is the most common complication patients experience after TRUS-guided prostate biopsy. Hematuria following TRUS-guided prostate biopsy has an incidence rate of 14.4 - 84%, lasting averagely 2.7 to 5.1 days and may persist for up to about 3week. [116-123] hematuria encountered after TRUS-guided

biopsy is most of time self-limiting, requiring no intervention to be instituted for resolution. However, in about 0.25–0.7% of the cases, it may be complicated by clot retention, or excessive bleeding requiring hemotransfusion. [116,123] Hematospermia has been reported as complication in about 5.7 - 89% of TRUS-guided prostate biopsy. [116,118-123] Hematospermia, though generally self-limiting and does not generally require treatment, may lead to serious concerns in patients who had not been previously counselled about the possibility of it occurring as a complication after the procedure. Hematospermia after TRUS-guided biopsy generally lasts an average of 10.9 days, but may occasionally persist beyond this duration. [116,127] Hematochezia occurs in about 1.3 - 39.6% of the cases and generally lasts for 1-5 days, mostly resolving spontaneously. [116,118-130] Occasionally, the bleeding may persist for up to 15 days and in about 0.01 – 2.1% of the cases it may be severe or prolonged enough to require hemotransfusion. [116] Hemostasis is often achieved by application of intra-rectal pressure at the bleeding point using a finger, the ultrasound probe, an anoscope, or by packing the rectum with an intra-rectal tampon. Failure of these methods may require colonoscopy with endoscopic sclerotherapy. In a serious by Djavan et al. which involved 2049 men who underwent 12-core TRUS-guided, hematuria, hematospermia, and rectal bleeding seen as minor complications were detected in 66.3, 38.8, and 28.4%, of the study participant, respectively. Severe bleeding as hematuria or rectal bleeding requiring transfusion occurred in 0.05, and 0.3% of the cases, respectively. [116,117]

Post-biopsy infectious complications that occur may ranges from asymptomatic bacteriuria to septic shock. Septic shock most likely develops from manipulation of infected prostatic tissue during the biopsy procedure, seeding the blood, urine, and prostate tissue with rectal flora with the aid of the biopsy needle. Most serious complications that are developed after TRUS-guided prostate biopsy are infection related. [116] The infectious complications that develop after TRUS-guided biopsy are often caused by Escherichia coli, Enterobacter and Enterococcus spp. [112] An area of controversy regarding post-biopsy infectious complications is the role of pre-biopsy rectal cleansing, most often using enema. Several contrary findings have been reported by various authors on the effect of pre-biopsy rectal cleansing on post-biopsy infectious complications ranging from decreased rates, no change in rates to increased rates. [132] The role of prophylactic antibiotics in the control of post-biopsy infectious complications have been evaluated through multiple prospective, randomized controlled studies. [119,120] In a study by Puig et al. of 1018 patients undergoing TRUS-guided biopsy, 614 patients were given prophylactic antibiotics whilst 404 had no prophylactic antibiotics after the biopsy. [133] The post-biopsy infectious complication rates were 3.7 vs. 10.3% among those who had antibiotics prophylaxis and those who had no antibiotic prophylaxis respectively ($p = 0.0001$). [133] They also reported serious post-biopsy infectious complication rate lower in

the antibiotic prophylactic group (24%) compared to the group with no antibiotic prophylaxis (75.6%) (p=0.0140). [133] Currently there is consensus on the requirement for antibiotic prophylaxis for TRUS-guided prostate biopsy, there is still controversy over the choice of appropriate antibiotics and the duration of antibiotic prophylaxis. [116,118-133]

2.7 Cancer Detection Rates by TRUS-Guided Prostate Biopsy

Jia et al. reported an overall cancer detection rate of 42.8% in a study among the Han Chinese population undergoing TRUS-guided prostate biopsy in Northern China. [33] The prostate cancer detection rates in the age brackets of < 50, 51–60, 61–70, 71–80, and > 80 years were 7.1, 28.1, 33.3, 48.7, and 62.2%, respectively. [33] The prostate cancer detection rates for PSA ranges of < 4.0, 4.1–10.0, 10.1–20, 20.1–100.0, and > 100.1 ng/ml, irrespective of the DRE findings, were 0.0, 23.3, 54.3, 85.2, and 100.0, respectively. [33] With normal DRE findings, the chances of finding cancer were 0.0% for PSA levels below 4.0, 28.3% for levels between 4.0 and 10.0, 80.0% for levels between 20.0 and 100.0, and 100% for levels over 100.0. 33 For patients with suspicious DRE findings, the cancer detection rates for the serum PSA ranges of < 4.0, 4.0–10.0, 10.0–20.0, 20.0–100.0, and ≥ 100.0 ng/ml were 33.3, 58.2, 59.6, 62.8, and 96.7%, respectively. [33] For patients with normal prostatic imaging findings with serum PSA levels of < 4.0, 4.0–10.0, 10.0–20.0, 20.0–100.0, and ≥ 100.0 ng/ml were 27.5, 11.2, 25.7, 54.4, and 0%, respectively. [33]

In a study by Ng et al. in Australia, out of 2194 patients who underwent TRUS-guided prostate biopsy for the first time, 1129 were found to have prostate cancer, giving an overall prostate cancer detection rate of 52%. [90] The cancer detection rate without considering the DRE findings at serum PSA levels of < 4.0, 4.0–10.0, and > 10.0 ng/ml were 25.0, 41.0, and 68.0%, respectively. [90] When the PSA levels and the DRE findings were considered together, the cancer detection rates for PSA levels of <4.0, 4.0–10.0, and >10.0 ng/ml were 9.0, 31.0, and 48.0%, respectively, for patients with normal DRE findings. [90] For patients with suspicious DRE findings, the cancer detection rate for serum PSA levels <4.0, 4.0–10.0, and >10.0 were 27.0%, 67.0%, and 85.0%, respectively. [90]

Laddha et al. analysed data from 853 men who underwent a TRUS-guided prostate biopsy for elevated serum PSA levels and/or suspicious DRE findings at a single institution in India. [91] The study population had a mean age of 69.5 ± 8.2 years, a median prostate volume of 39 g, and a median serum PSA level of 14 ng/ml. [91] Three hundred and eighty-two patients out of the study population of 853 were detected to have prostate cancer, giving an overall prostate cancer detection rate of 44.8%. [91] The mean age of patients

with prostate cancer was 71 ± 8.5 years, while that of those with a negative biopsy was 68.3 ± 7.7 years. [83] The cancer detection rates for the serum PSA ranges of <4.0, 4.1–10.0, 10.1-20.0, 21.0–40.0, and >40.0 ng/ml were 13.0, 21.9, 38.1, 52.3, and 84.1%, respectively. [91] The median serum PSA level was higher in patients with prostate cancer, 29.74 ng/mL, versus 9.77 ng/mL in those without prostate cancer. [91] The cancer detection rate is 39% for patients with normal DRE findings and 80.06% for those with suspicious DRE findings. When the serum PSA and the DRE findings were considered together, the cancer detection rates for the PSA ranges of < 4.0, 4.1-10.0, 10.1-20.0, 20.1-40.0, and >40.0 were 0, 16.25, 27.65%, 31.08, and 22.22% for patients with normal DRE findings, versus 13.04%, 54.76%, 69.64%, 82.69%, and 98.13% in the group with suspicious DRE findings. [91] There was an insignificant difference in the size of the prostate in either group in the study: a mean prostate size of 38.9 g for the group of patients with prostate cancer and 40.6 g in those without prostate cancer. Patients with prostate cancer were more likely to have suspicious DRE findings as compared to those without (69.4% vs. 14.0%). [91]

Narayanaswamy et al. studied the records of 153 patients with a mean age group of 65 years who underwent TRUS-guided biopsy of the prostate in Kuwait. [92] The overall prostate cancer detection rate was 27.4%. [92] When the ages of the participants were stratified, the detection rates for the age groups of <55, 56-65, 66-75, and >76 years were 16.7, 17.6, 33.3, and 40.7%, respectively. [92] The cancer detection rates for the prostate glands of sizes <30g, 31-50g, 51-70g, and > 70g were 42.9, 30.8, 223.8, and 18.2%, respectively. [92] On stratification, the cancer detection rates for the serum PSA ranges of 4–10, 10–20, 20–100, and >100 ng/ml were 11.8, 20.5, 47.1, and 883.3%, respectively. [92] The mean PSA level was 153.2 $\pm$ 278.2 ng/ml in participants with prostate cancer and 13.17 $\pm$ 21 ng/ml for those without prostate cancer. [92]

Ogbetere et al., in a study in Nigeria involving 120 men who had a TRUS-guided prostate biopsy, reported an overall prostate cancer detection rate of 65%. [93] When the ages of the participants were considered, the prostate cancer detection rates in age brackets of 50–59, 60–69, 70–79, 80–89, and 90–100 years were 75%, 46.7%, 72.3%, 85.7%, and 100%, respectively. 85 The cancer detection rates at PSA levels of 44.0–10.0, 110.1–20.0, 20.1–50.0, 50.1–100.0, and >100.0 ng/ml were 25%, 54.7%, 67.4%, 100%, and 100%, respectively, when DRE findings are not considered. [93] For patients with normal DRE, the cancer detection rates for PSA levels 4.0–10.0, 10.1–20.0, 50.1–100.0, and > 100.0 ng/ml were 0.0%, 34.6%, 0.0%, 100.0%, and 100%. [93] The cancer detection rate for people with an abnormal DRE was 33.3% for PSA levels between 4.0 and 10.0, 10.1 and 20.0, 20.1 and 50.0, 50.1 and 100.0, and > 100.0 ng/ml. The rates

were 74.1%, 88.6%, 100%, and 100%. [93] The prostate cancer detection rate was significantly higher in men with suspicious DRE and suspicious prostate ultrasound findings. [93]

In a study by Hsing et al. in Ghana to estimate prostate cancer burden via population-based screening, 1,037 men were recruited with an age range of 50–74 years. [94] It reported an overall cancer detection rate of 42.8%. [94] Three hundred and fifty-two men (33.9%) had a positive screen result with serum PSA > 2.5 ng/ml or suspicious DRE findings and were therefore recommended to undergo prostate biopsy. [94] Only 307 (87%) underwent the procedure, of which 73 were diagnosed with prostate cancer, yielding an overall cancer detection rate of 7.0%. [94] The proportion of the participants with suspicious DRE findings rates for serum PSA ranges of > 2.5, 2.5–3.9, 4.0–9.9, and >10.0 ng/ml were 7.7%, 4.6%, 36.9%, and 50.8%. [94] The mean prostate volume for participants with prostate cancer in the serum PSA ranges of <4.0, 44.0–10.0, and >10.0 were 29.7 $\pm$ 12.9, 35.3 + 17.3, and 50.3 $\pm$ 27.1 ml, respectively. [94] For those without prostate cancer, the mean prostate volumes in the PSA ranges of <4.0, 4.0–10.0, and >10.0 were 26.5 $\pm$ 16.9, 44.6 $\pm$ 22.9, and 59.3 $\pm$ 35.0 ml, respectively. [94] The study confirmed that the prevalence of elevated serum PSA levels, abnormal DRE findings, and prostate cancer increases with advancing age. [94]

CHAPTER THREE

Research Methodology

3.0 Introduction

The research methodology of a study refers to the systematic methods and principles employed in the study. This chapter lays out and describes the various scientific approaches employed in this study. It has been subdivided for better appreciation under these headings: study site, research design, target population, data collection, and data analysis. In addition, ethical considerations are also discussed.

3.1 Study Design

This is a cross-sectional, prospective comparative study involving 218 participants. The study participants were patients who underwent TRUS-guided prostate biopsy at the Urology Unit of the Directorate of Surgery of the Komfo Anokye Teaching Hospital during the study period. Only patients who met the inclusion criteria, had none of the exclusion criteria, and had been referred for TRUS-guided prostate biopsy during the study period were recruited into the study.

3.2 Study Site

The study was conducted at the Urology Unit of the Directorate of Surgery of the Komfo Anokye Teaching Hospital (KATH). The hospital is located in Kumasi, the regional capital of the Ashanti Region of Ghana, West Africa. The Ashanti Region is one of the 16 administrative regions of Ghana. Ghana has Ivory Coast, Burkina Faso, and Togo as its most immediate western, northern, and eastern West African neighbouring states, and the Gulf of Guinea in the south. It has a population of 30.8 million people, with 15.2 million males (49.3%) and 15.6 million females (50.7%). Ashanti Region is the second most populous region with a population of 5.4 million people (17.6% of the country's population) and the third largest region by land mass, occupying 24,389 km^2 (10.2% of the total land area of the country). [134-142]

The regional capital of the Ashanti Region, Kumasi, is also the second largest and second most populous city in Ghana; the largest and most populous city is Accra, the national capital. Kumasi is located at the centre of the region and stretches between the latitudes 6.35º N and 6.40º N and the longitudes 1.30º W and 1.35º W. It covers 254.3 square kilometres, which represents about 1.0% of the total land area of the region. [140-142] Located 46.3km southeastwardly from the city is a 10.5-square-kilometre natural lake and a popular tourist attraction: Lake Bosomtwe. [140-142] It was formed from the impact crater of an asteroid that hit the Earth 1.07 million years ago. Kumasi is also the political capital of the Asante kingdom, hence the site for the Royal Court and the official residence of the King of the Ashanti Kingdom, the Asantehene. [139-142] Traditionally, Kumasi is one of the 33 traditional areas of the Ashante Kingdom, headed by Paramount Chiefs, who together constitute the Asanteman Council. The 16th King of the Asante Kingdom, Otumfuo Osei Tutu Ababio II, serves as the council's leader. The predominant economic activities of the people of Kumasi are finance and commerce, poultry, arts and crafts, clothing and textiles, and trading. Traders come from all across the country and West Africa to ply their trade. [134-142]

There are several notable educational institutions dotted all across the city, from the basic level of education through the secondary to the tertiary level. These include 7 universities, 3 teacher colleges of education, 5 nursing training colleges, and more than 25 high schools. Komfo Anokye Teaching Hospital is the largest hospital in Kumasi and the second-largest hospital in the country. [140-145] It is a 1200-bed tertiary health facility and serves as the main referral facility for the middle and northern belts of the country. [143-145]

Because of its status and location, it receives referrals from 13 out of the 16 other regions of the country, namely: Ahafo, Bono East, Bono, Central, Eastern, North East, Upper East, Upper West, Northern, Western North, Western, and Savannah Regions, besides the Ashanti Region. It also serves clients from

neighbouring countries such as Burkina Faso, Togo, and Cote d'Ivoire. The hospital is a major centre for the training of medical doctors, postgraduate medical and dental practitioners, and all categories of nurses. [142-145]

The hospital has 13 clinical and 2 non-clinical directorates, as well as other support units. The 13 clinical directorates are: trauma and orthopaedics, surgery, emergency medicine, medicine, obstetrics and gynaecology, family medicine, and child health. The rest are the Directorates of Oncology, Eye, Ear, Nose, and Throat (EENT), Laboratory Services, Radiology, Oral Health and Anaesthesia, and Intensive Care. The non-clinical directorates are Domestic Services and Technical Services. The support units are biostatistics, chaplaincy, finance, general administration, human resource management, internal audit, information and communication technology (ICT), and pharmacy. The rest are public health, policy, planning, monitoring and evaluation, public relations, quality assurance, research and development, security, social welfare, supply chain management, and transfusion medicine. The directorate of surgery consists of the following units: general surgery, neurosurgery, plastic and reconstructive surgery, genito-urinary surgery, cardiothoracic and vascular surgery, and paediatric surgery. The remaining units are the Breast Care Centre, Endoscopy and Ultrasound, Administration/Accounts, BICU (Burns Intensive Care Unit), Main Theatre, and Pharmacy Units. [142-145]

The various units of the directorate provide inpatient, outpatient, and emergency care services through the various diagnostic suites, clinics, and operating rooms. The various clinical teams of the directorate run their main OPD clinics at Consulting Room 9, which consists of 5 consulting rooms, by taking turns with a mixture of morning and afternoon clinics. The Directorate has 2 adult male wards, 2 adult female wards, and a paediatric ward. The wards are B1 and B2 adult male wards with 33 beds each, C3 and C4 adult female wards with 15 beds each, and B3 paediatric ward with 40 beds. The Directorate admits patients to the various wards from the Accident and Emergency Unit (A&E Unit), the Paediatric Emergency Unit (PEU), the OPD clinics, and the theatres. It also receives transferred patients from the hospital's other directorate and also by direct admission onto the wards. Patients with medical conditions requiring emergency care are first routed through either the A&E or the PEU for resuscitation and then later transferred to either the theatre or the wards, or discharged when appropriate. [142-145]

The Urology Unit has three clinical teams: Teams A, B, and C, who run OPD clinics three times a week in Consulting Room 9 and take turns running a week-long emergency duty. Each of the three teams runs a week-long emergency call, managing all urological emergencies in the hospital for that week. Each year has a day at the main theatre every week for elective surgeries but has around-the-clock access to the

theatre for emergency surgeries. The unit has a procedure suite equipped with a Sonoscape A6 12-inch screen and an ultrasound machine dedicated to performing TRUS-guided prostate biopsies and minor procedures.

The TRUS-guided prostate biopsies were performed using a Sonoscape A6 12-inch screen ultrasound machine with a 9.0-4.0 MHz endoluminal probe manufactured by Sonoscape Medical Corp., China, and a 25-mm-long, 18-gauge disposable automatic core biopsy gun (Curaway Automatic Core Biopsy Instrument) manufactured by Zhejiang Curaway Medical Technology Co. Ltd., China. All the TRUS-guided prostate biopsies were performed in this suite. The study participants were all patients referred by their attending physicians to the urology procedure room for a prostate biopsy. The majority were referred from the several internal clinics of the hospital, including the Specialist Urology Clinic, which is held in 'Consulting Room 9'. A few were referred from outside the teaching hospital by other physicians, often urologists, working with other health facilities.

3.3 Sample Size Determination

The sample was determined using the formula for estimating a single population proportion. Epidemiological studies have shown the prevalence of prostate cancer in Ghana to be >200 per 100,000 populations, compared to lower rates of 127 and 130 per 100,000 populations in Nigeria and Cameroun, respectively. [87] This equates to a prostate cancer prevalence rate of 0.2% in Ghana.

To calculate the sample size for a study that seeks to determine the cancer detection rate of a TRUS-guided biopsy of the prostate gland, the Cochran formula as stated below is used:

$$\boldsymbol{n = \frac{Z^2.pq}{d^2}}$$

The following terms in the formula are defined below:

n = sample size;

p = the prevalence rate of prostate cancer in Ghana;

q = p - 1.

Z = the critical value of the desired confidence interval;

d = the margin of error, set at 5% (0.05).

The values of each term in the formula are given below:

p = 0.20

q = 0.80

Z = 1.96

d = 0.05

Substituting the values of the variables into the formula gives the value of n, the calculated sample size:

n = 1.962 x 0.2 x 0.8 0.052

n = 245.86

The study assumes a non-response rate of 10% (245.86 x 0.1 = 24.49). Therefore, the total study sample size is 245.86 + 24.59 = 270.45. Rounding it off to the nearest unit, the total study sample size is 271.

The study required a total of 246 participants who met all inclusion criteria and none of the exclusion criteria to be fully powered. Only 218 study participants were successfully recruited and followed through to the end, with their data used for the final analysis. Since the required number of study participants could not be recruited, it was therefore underpowered.

3.4 Inclusion Criteria

Men 45 years of age or older were referred for TRUS-guided prostate biopsy for the first time at the Urology Unit of KATH during the study period.

3.5 Exclusion Criteria:

Men with any of the under-listed points below were excluded from the study:

1. Prior prostate biopsy.
2. Patient with a prior history of prostate cancer diagnosis or treatment.
3. Failure to secure consent for the biopsy procedure or inclusion in the study.
4. The presence of any condition that is a contraindication for prostate biopsy, such as:
    a. presence of acute prostatitis
    b. significant immunosuppression
    c. coagulopathy
    d. bleeding disorders or a tendency to bleed
    e. painful anorectal conditions
    f. absence of rectum

3.6 Study Flow

Ethical approval from the Research and Development Unit (Institutional Review Board) of KATH, was acquired before the commencement of the study. All patients who underwent a TRUS-guided prostate biopsy at the Urology Unit of the Directorate of Surgery at KATH were eligible for recruitment into the study.

Recruitment was essentially done at the urology procedure suite, where the study participants had been referred by their attending physicians for prostate biopsies. Patients who met the inclusion criteria with none of the exclusion criteria were adequately counselled. The associated risk of participating in the study and the risk inherent in the biopsy procedure (rectal bleeding, hematuria, acute urine retention, and infection) were explained to the patients, informed consent was obtained, and then recruitment into the study was done. The patients were then scheduled for the procedure. At the time of the biopsy, the recruited study participants were interviewed individually, and the data collection instruments were filled.

The following steps were followed for each patient undergoing a TRUS-guided prostate biopsy:

a. The appropriate instrumentation and equipment setup were done.
b. The patient would be assisted in undressing and dressing appropriately.
c. An intravenous (IV) line would be secured, IV antibiotics would be constituted and administered, and the patient would be positioned supine on the examination bed.
d. Local analgesia would then be administered into the prostate gland under ultrasound guidance for the procedure using about 10 ml of 2% xylocaine with adrenaline.
e. The patient would then be positioned in the left lateral decubitus position with the hip and knee joints flexed at 900.
f. A DRE would be performed with a lubricated, doubly gloved index finger and findings documented.
g. About 10–15 ml of xylocaine gel would be administered rectally to lubricate the rectum, anaesthetize the rectal mucosa, and ensure good coupling between the ultrasound probe and the rectal wall.
h. The patient would then be reassured, the endoluminal ultrasound probe placed into the rectum, a scout scan done, and findings noted.
i. A standard 12-core needle biopsy would then be performed, and the collected specimen would be placed in a labelled leak-proof specimen container with a 10% buffered formalin solution for preservation.

j. The patient would then be sanitised and assisted in dressing up. The patient's data collection tool would then be completed with the necessary information obtained from the procedure and a histopathology request form filled out for the specimen.

The patient would then be detained for 2 hours for stability of vital signs and signs of bleeding or any other complications looked out for. The patient would then be discharged when there was a satisfactory monitoring outcome, on oral antibiotics and analgesics to cover the subsequent 7–10 days after the procedure, and then scheduled for a follow-up review in a week.

The biopsy specimen is then dispatched to the pathology unit for histopathological studies and a report. A meeting would then be held with the patient at a scheduled date for the collection of the histopathology report, the completion of the data collection instrument, and counselling. The patient would then be assisted in scheduling an appointment with his attending physician for a follow-up review for further management.

3.7 Data collection

The data obtained from the study population was recorded on case forms (Appendix 1). Upon completion of the forms, they were doubly entered into a predesigned e-database using MS Access and Epidata 3.1 software.

The database was evaluated every month for integrity and consistency and then cleaned of errors.

3.8 Data analysis

The statistical analysis was done using Epidata 3.1 software.

3.9 Ethical considerations

Ethical approval was sought and obtained from the Komfo Anokye Teaching Hospitals' Institutional Ethical Review Board (KATH IRB/AP/160/23). Informed consents were obtained from every study participant before recruitment into the study and before every procedure involving the study participant. Confidentiality and anonymity were assured all the respondents and ensured throughout the study. Only the researcher and supervisors had access to the raw data.

3.10 Dissemination of Results

The final report of this study will be made available to the Directorate of Surgery of the Komfo Anokye Teaching Hospital and the Faculty of Surgery of the Ghana College of Physicians and Surgeons. It would also be presented at the clinical meeting of the Urology Unit of the Directorate of Surgery of the Komfo Anokye Teaching Hospital, Kumasi.

CHAPTER FOUR

Results of Study

4.0 Introduction

Two hundred and twenty-five (225) men were successfully recruited into the study over the study period when they reported to the Urology Procedure Room for a prostate biopsy. Out of this number, seven failed to show up for the subsequent follow-up reviews, for which the data on them was incomplete. Data analysis was therefore done only on the 218 participants for whom there was complete data.

4.1 Participant Demographics

The demographic details of the study participants that were captured in the study were age, ethnicity, residence, and level of education. The rest were occupation, marital status, number of children, and health insurance coverage. The details of these characteristics of the study participants as captured are provided below with the aid of various data visualisation tools.

4.1.1 The Age Characteristics of the Study Participants

The age of the 218 study participants ranged from 45 to 89 years, with a mean of 69.84 + 8.10 years. The majority of the participants (80.7%) were in the age brackets of 60–69 (39.9%) and 70–79 (40.8%) years.

Only one person was younger than 50 years; of the remaining 20, 87, 89, and 21 participants were in the age groups of 50–59, 60–69, 70–79, and > 80 years, respectively. Further evaluation of the study results showed that the mean age of the study participants diagnosed with PCa was higher than that of those without cancer (72.35 ± 8.02 vs. 66.72 ± 7.07 years, P < 0.001).

Table 4.1 Age Distribution of Study Participants

Variable	Frequency (N=218)	Percentage
Age group	**69.8 ± 8.1**	
< 50	1	0.5
50-59	20	9.2
60-69	87	39.9
70-79	89	40.8
>80	21	9.6

Source: Field Data, 2023.

4.1.2 Ethnicity of the Study Participants

The majority of the study participants (130, 60.0%) were Akan, while the remaining 88 (40.0%) were from several other diverse ethnic backgrounds.

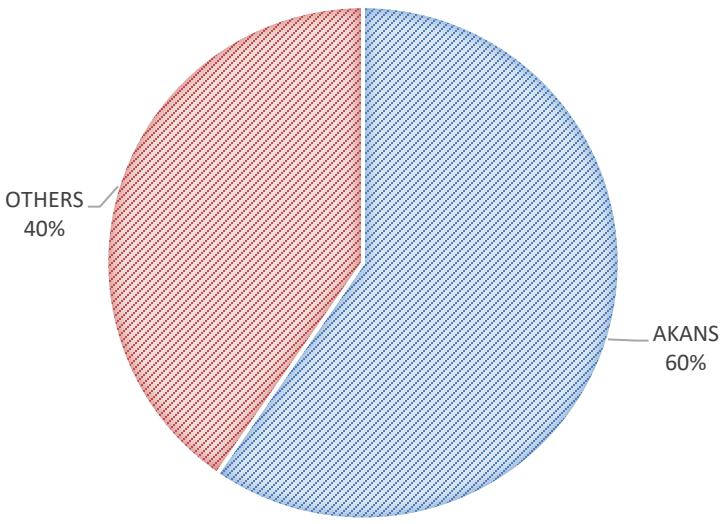

Figure 3: Ethnicity of Study Participants.

Source: Field Data, 2023.

4.1.3 Residence of the Study Participants

One hundred and thirty-seven study participants (62.8%) resided in urban areas; forty-one (18.8%) resided in rural areas; and the remaining forty study participants (18.3%) lived in peri-urban areas.

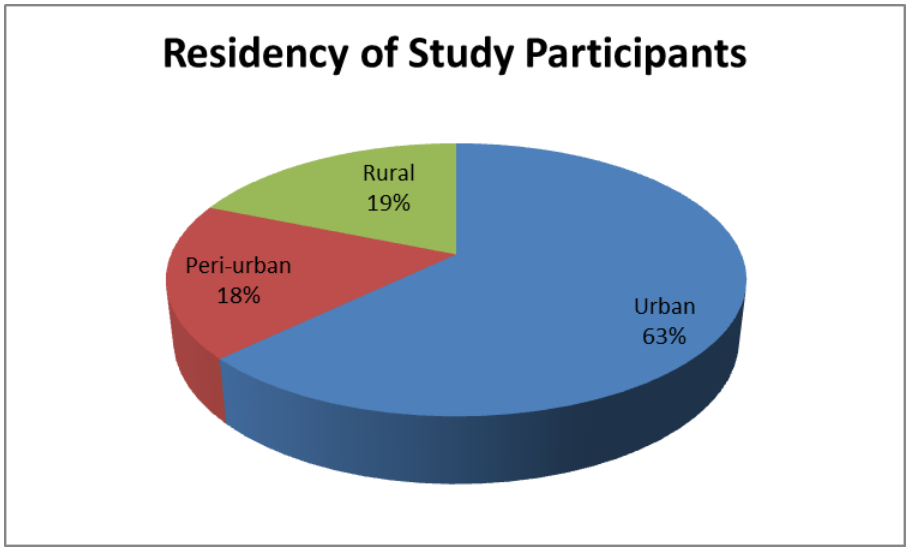

Figure 4: Residence of Study Participants.

Source: Field Data, 2023.

4.4 Educational Background of Study Participants

The study participants had varied educational backgrounds: one hundred and thirty-one (60.1%) had basic education, forty-one (18.8%) had graduated from secondary school, thirty-nine (17.9%) had been educated up to the tertiary level, and seven (3.2%) had had no formal education.

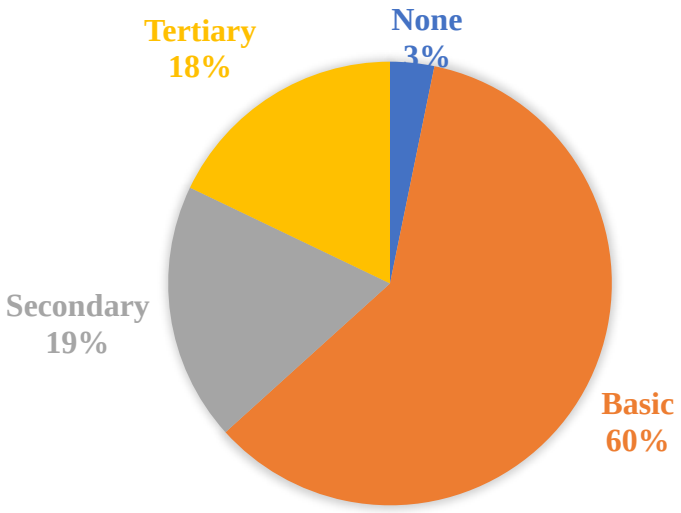

Figure 5: Educational Level of Study Participants.

Source: Field Data, 2023.

4.1.5 Occupation of the Study Participants

Ninety-one participants (41.7%) were manual workers, sixty-two (28.4%) were technical workers, thirty-nine (17.9%) were professionals, fifteen (6.9%) were managers, and eleven (5.0%) were clerical workers.

Table 4.2 Occupation of the Study Participants

Variable	Frequency (N=218)	Percentage
Occupation		
Manuel laborer	91	41.7
Technical workers	62	28.4
Professionals	39	17.9
Managers	15	6.9
Clerical worker	11	5.0

Source: Field Data, 2023.

4.1.6 Marital Status of the Study Participants

One hundred and sixty-four study participants (75.2%) were married, 35 (16.1%) were widowed, 12 (5.5%) were divorced, and 7 (3.2%) were single.

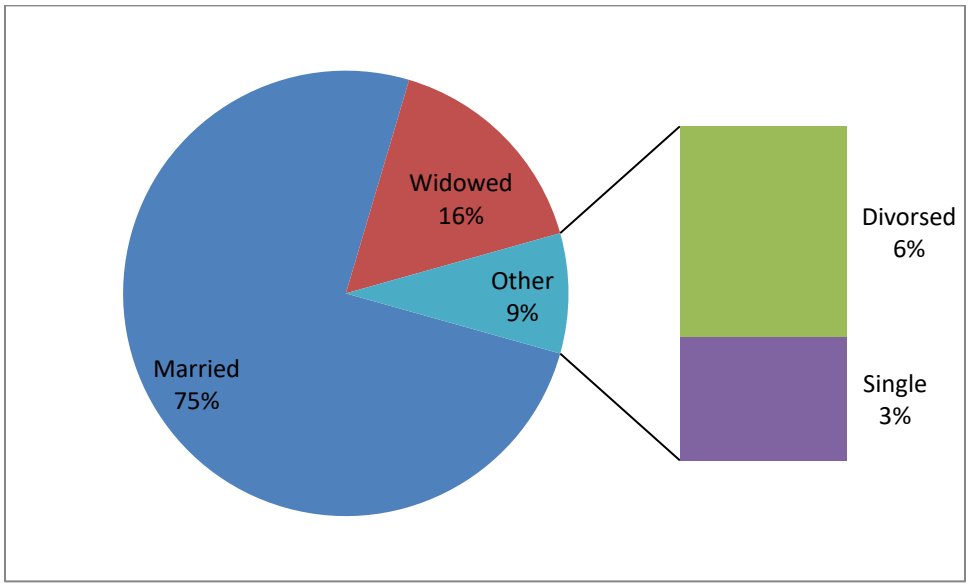

Figure 6: Marital Status of Study Participants.

Source: Field Data, 2023.

4.1.7 Number of Children of the Study Participants

One hundred and nine; about half of the participants (49.5%) had 4-6 children; 73 (33.5%) had more than 6 children; and 36 (16.5%) had 0–3 children.

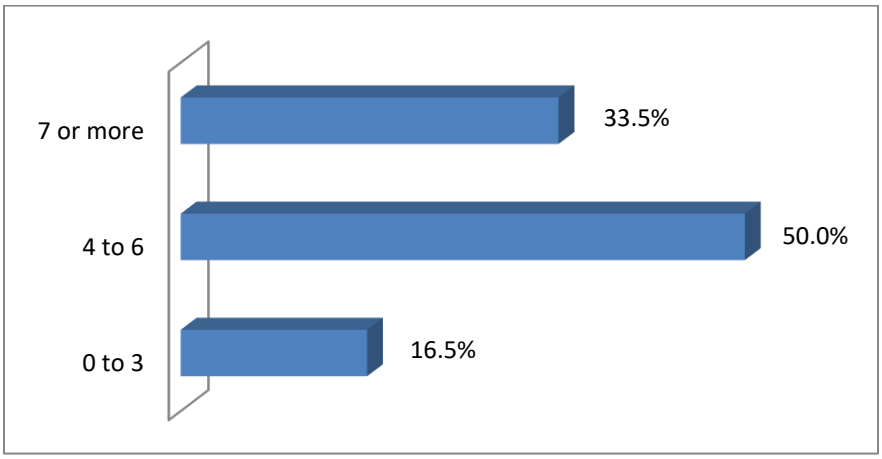

Figure 7: Number of Children of Study Participants.

Source: Field Data, 2023.

4.1.8 Health Insurance Coverage of the Study Participants

One hundred and ninety study participants (87.2%) had health insurance coverage. All the one hundred and ninety study participants with health insurance coverage were registered members of the National Health Insurance Scheme (NHIS). The remaining 28 study participants had no insurance coverage. None of the study participants had any private insurance coverage.

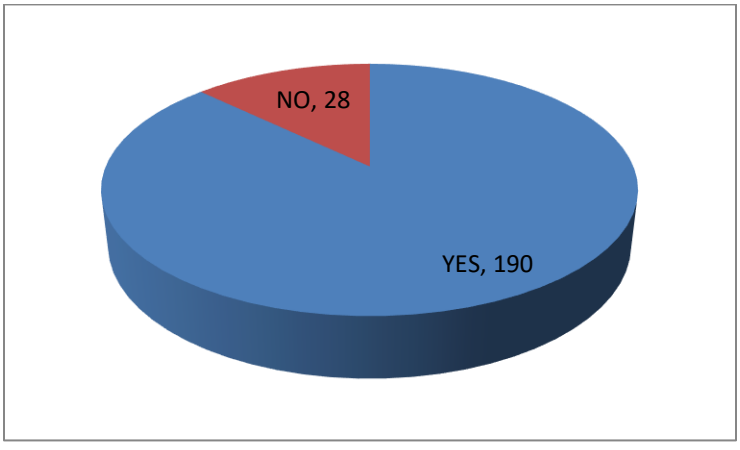

Figure 8: Health Insurance Coverage.

Source: Field Data, 2023.

4.2 Indications for Prostate Biopsy

The indications for a TRUS-guided prostate biopsy were elevated or abnormal serum PSA levels, suspicious DRE findings, and the presence of both abnormal serum PSA and suspicious DRE findings. One hundred and thirty-four (61.5%) of the study participants were referred for the prostate biopsy on account of abnormal or elevated serum PSA levels; seventy study participants (32.1%) were referred on account of suspicious DRE findings; and fourteen (6.5%) were referred on account of the presence of both abnormal serum PSA and suspicious DRE findings.

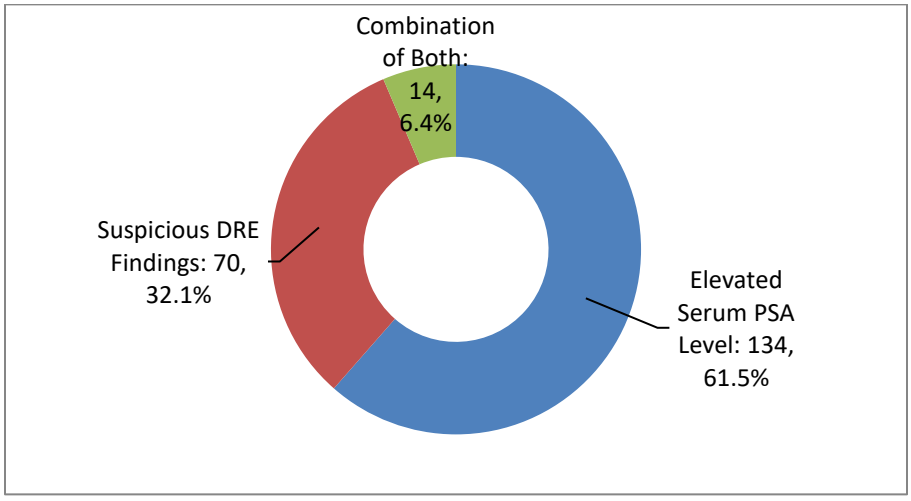

Figure 9: Indications for Prostate Biopsy.

Source: Field Data, 2023.

4.3 Clinicopathologic Presentation of the Study Participants

All the study participants had at least one genitourinary or neuromuscular symptom; 89.4% (195) had urinary frequency and had noticed they were voiding too many times in a day compared to several months prior. One hundred and eighty-five study participants (84.9%) had urgency with recent onset (within the past three months). One hundred and eighty-six (85.3%) had nocturia, voiding more than two times in the night. One hundred and seventy-five study participants (80.3%) had noticed weakness in their urine flow when micturiting. One hundred and fifty-nine (72.9%) had urinary intermittency with onset over the past three months. One hundred and twenty study participants (55.0%) had straining on micturition with onset within the past three months. Eighty-nine study participants (40.8%) had experienced dysuria within the past three months. Eighty-one study participants (37.2%) had the sensation of not being able to empty the bladder completely on micturition. Forty-nine participants (22.5%) had a history of acute urine retention within the immediate past three months. Sixty-seven participants (30.7%) admitted to erectile dysfunction,

while 64 participants (29.4%) had waist, lower back, or pelvic pains. Forty-eight participants (22.0%) had a history of weakness in the lower limb with onset within the past three months.

Table 4.3 Symptomatology of the Study Participants

Symptoms	Status		Percentage with Symptoms (%)
	Positive	Negative	
Frequency	195	23	89.4
Urgency	185	33	84.9
Nocturia	186	32	85.3
Weak Flow	175	43	80.3
Intermittency	159	59	72.9
Straining	120	98	55.0
Incomplete Emptying	81	137	31.2
Acute Urine Retention	49	169	22.5
Erectile Dysfunction	67	151	30.7
Lower Limb Weakness	48	170	22.0

Source: Field Data, 2023.

4.3.1 Post-void Residual Urine Volume

Of the 218 study participants, 55 (25.2%) had either urethral (35, 16.1%) or suprapubic catheters (20, 9.2%). The remaining 163 study participants had no form of urinary diversion and were voiding without a catheter. These study participants had their residual urine volume measured on ultrasound. Of the 163 participants who were voiding per urethra, 27 could empty their bladder fully and had no postvoid residual urine volume. Fifty-seven (57) had a residual urine volume of 50 ml or less after voiding; 41 had 51–100

ml, 15 had 101–200 ml, 8 had 20–1300 ml, and 10 had 301–400 ml, while the remaining 5 had more than 400 ml of residual urine volume.

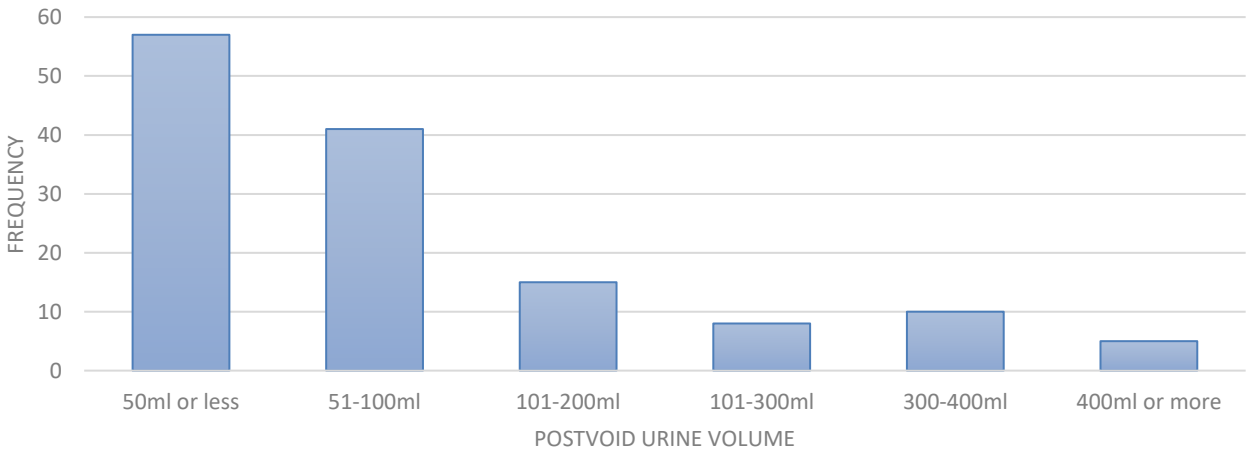

Figure 10: Post-void Residual Urine Volume of Study Participants without Catheter

Source: Field Data, 2023.

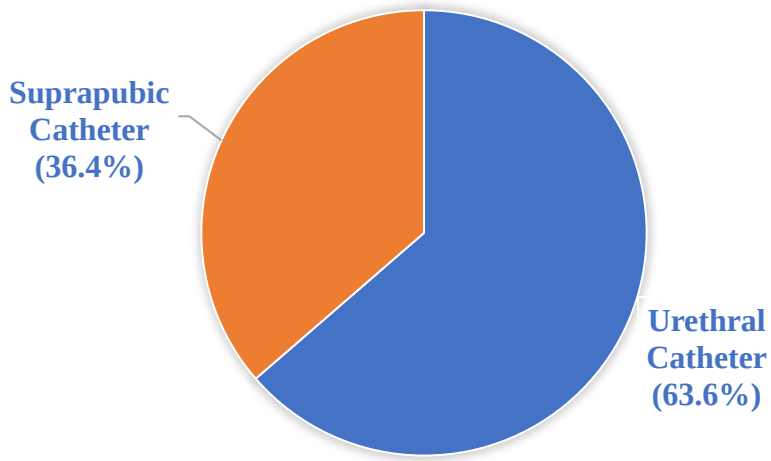

Figure 11: Presence of Lower Urinary Tract Diversion

Source: Field Data, 2023.

4.3.2 Family History of Prostate and Breast Cancer, and Smoking History

Forty-four participants (20.2%) had a family history of prostate cancer. Out of these thirty-two (72.7%) fathers with a history of prostate cancer, nine (20.5%) had maternal uncles who had a history of prostate cancer, while three had brothers with a history of prostate cancer. Thirty-four patients (15.6%) had a family history of breast cancer, out of which 18 (52.9%), 10 (29.4%), and 6 (17.6%) study participants had mothers, maternal aunties, and paternal aunties diagnosed with breast cancer, respectively. None of the study participants had a sister with a history of breast cancer. Twenty-five study participants (11.5%) admitted to a history of smoking cigarettes, while 40 participants (18.3%) had a history of regular alcohol consumption.

4.4 Prostate Cancer Detection Rates

4.4.1 Overall Prostate Cancer Detection Rate

Of the 218 study participants analysed, 121 were histologically diagnosed with adenocarcinoma of the prostate after the TRUS-guided prostate biopsy in the study, giving an overall prostate cancer detection rate of 55.5%. The remaining 97 study participants were diagnosed with benign prostatic hyperplasia (BPH), resulting in a non-cancer detection rate of 44.5%.

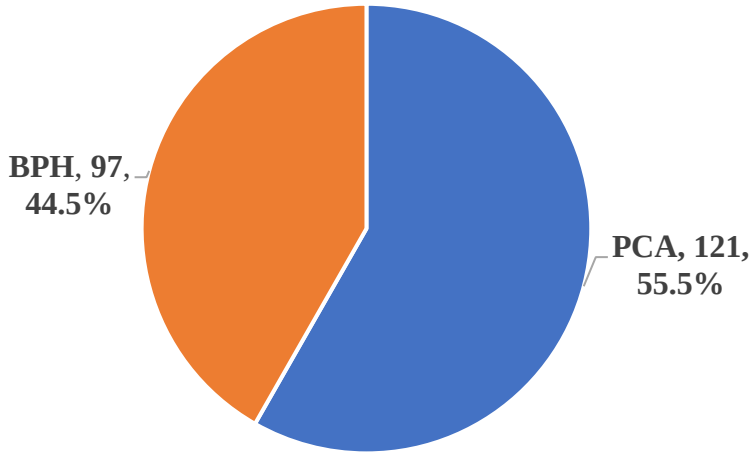

Figure 12: Overall Prostate Cancer Detection Rate

Source: Field Data, 2023.

4.4.2 Serum PSA Levels and Prostate Cancer Detection Rates

The serum PSA of the study participants ranged from 2.0 to 150.0 mg/mL, with a mean of 49.226 ± 43.18 ng/ml. On stratifying the serum PSA levels into subgroups of < 4.0, 4.1-10.0, 10.1-20.0, 20.1-100.0, and >100.0 ng/ml, the number of study participants in these serum PSA ranges was 4 (1.8%), 60 (27.5%), 83 (38.1%), 61 (28.0%), and 10 (4.6%), respectively. The cancer detection rates, considering only the serum PSA levels for the PSA ranges of < 4.0, 4.1-10.0, 10.1-20.0, 20.1-100.0, and >100.1 ng/ml, were 0, 23.3, 54.2, 85.2, and 100.0%, respectively.

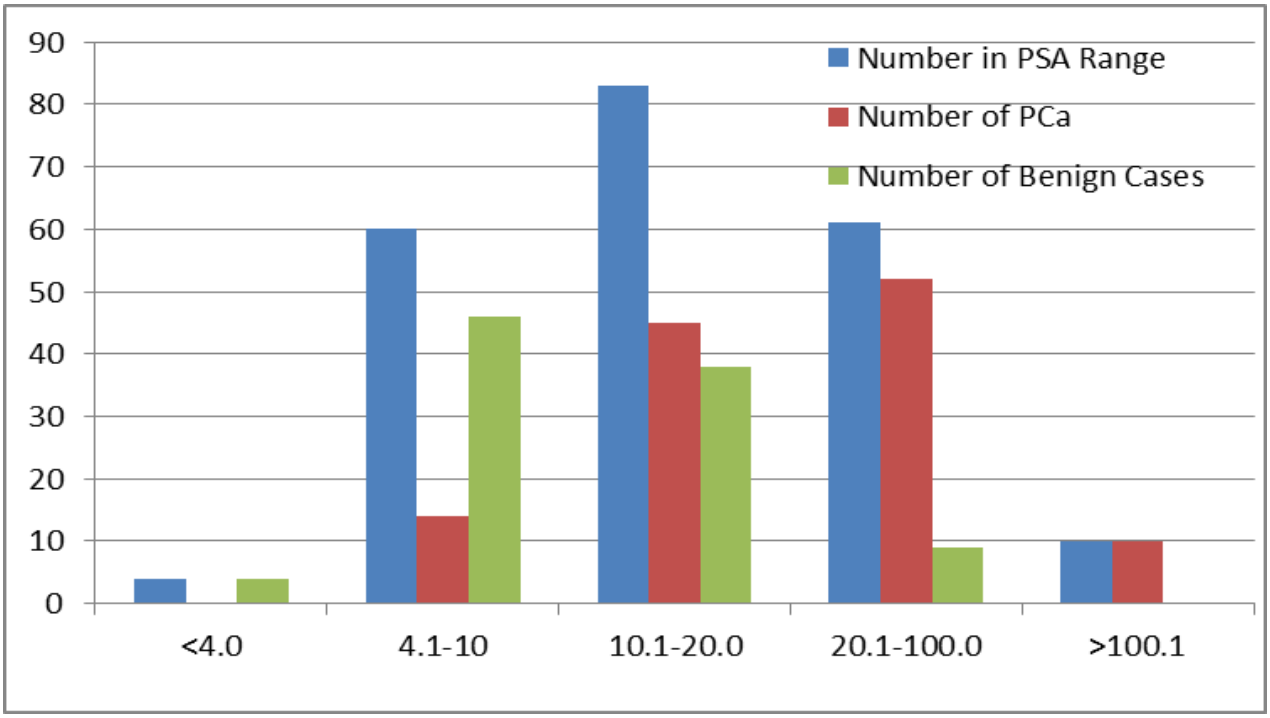

Figure 13: Distribution of PCa and Benign Cases in Each PSA Range.

Source: Field Data, 2023.

4.4.3 Age and Prostate Cancer Detection Rates

On stratifying the study participants into 5 subgroups based on their age, there were 1, 20, 87, 89 and 21 participants in the subgroups of <50, 50-59, 60-69, 70-79, and 80 years or more. There was only one study participant in the age group of <50 years with a serum PSA of 100.00 ng/mL. While the mean serum PSA of the study participants in the age groups of 50–59, 60–69, 70–79, and >80 years were 59.19 ± 46.87, 36.25 ± 34.58, 48.93 ± 45.45, and 96.65 ± 25.80 ng/ml, respectively. The cancer detection rates with the age subgroups of <50, 50-59, 60-69, 70-79, and 80 years or more were found to be 0.0, 55.0, 47.1, 61.8, and 66.7%, respectively. The mean age of the study participants diagnosed with prostate cancer was 72.35 ± 8.02 years, whilst the mean age of those without prostate cancer was 66.72 ± 7.07 years ($p < 0.001$).

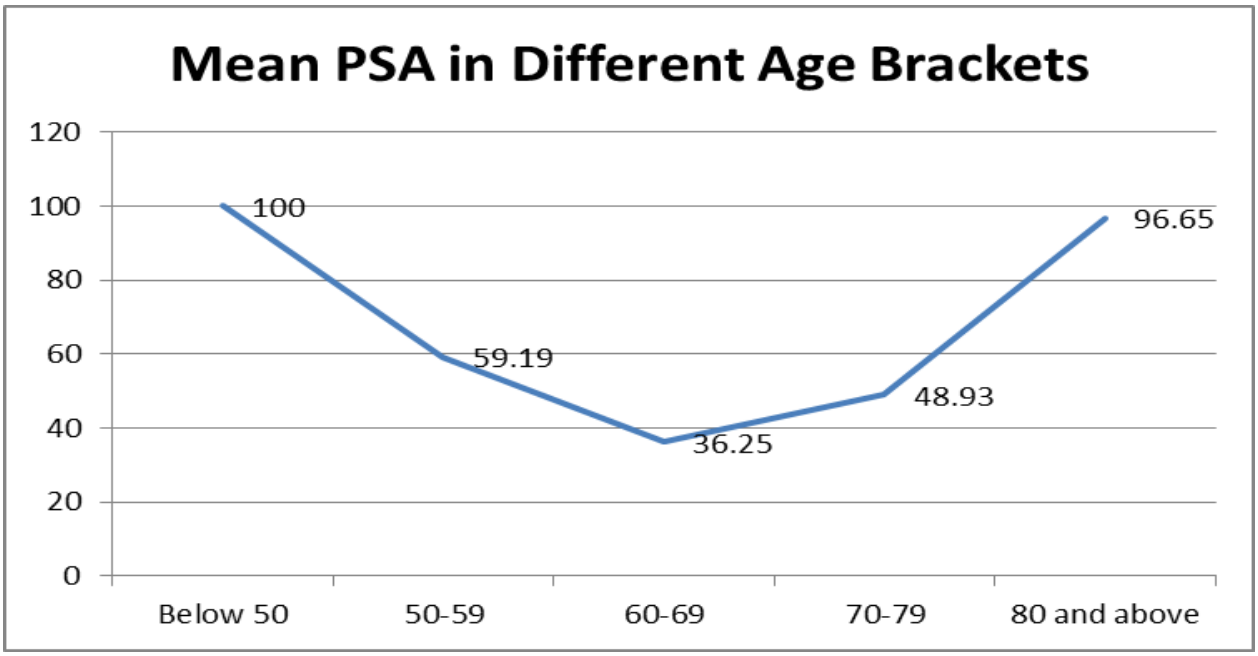

Figure 14: Mean PSA Levels in Age Brackets.

Source: Field Data, 2023.

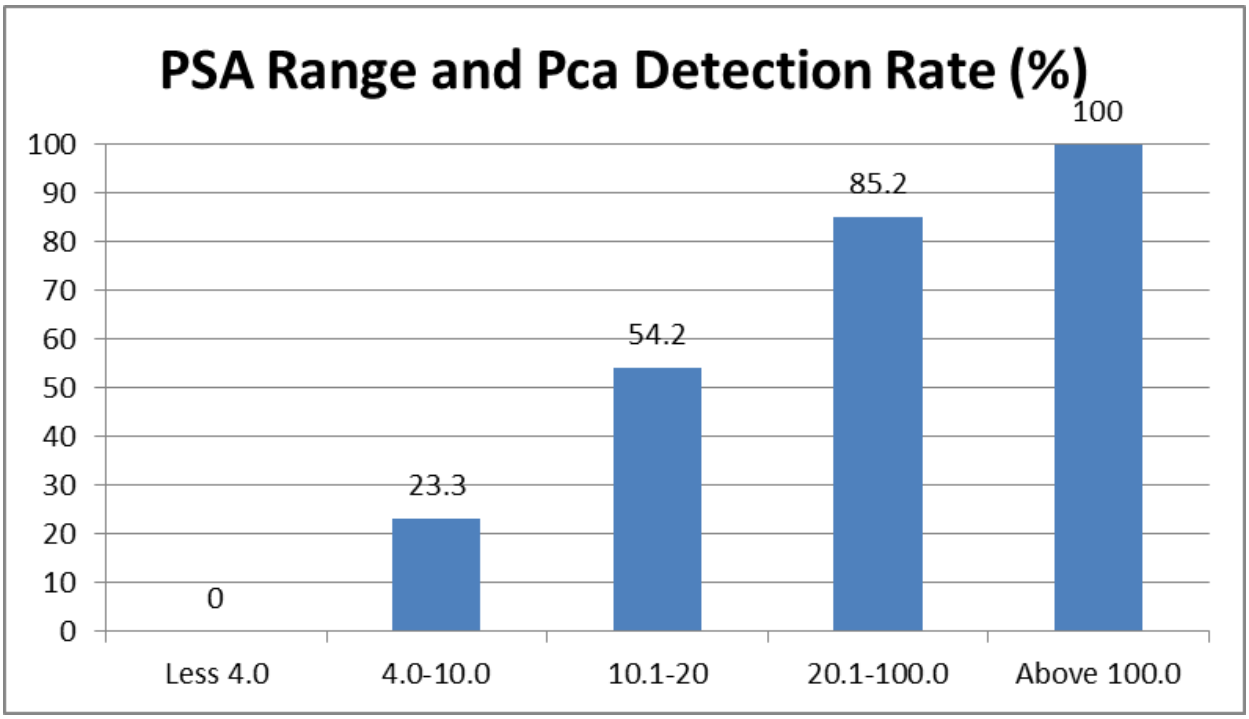

Figure 15: Cancer Detection Rates with Increasing PSA Levels

Source: Field Data, 2023.

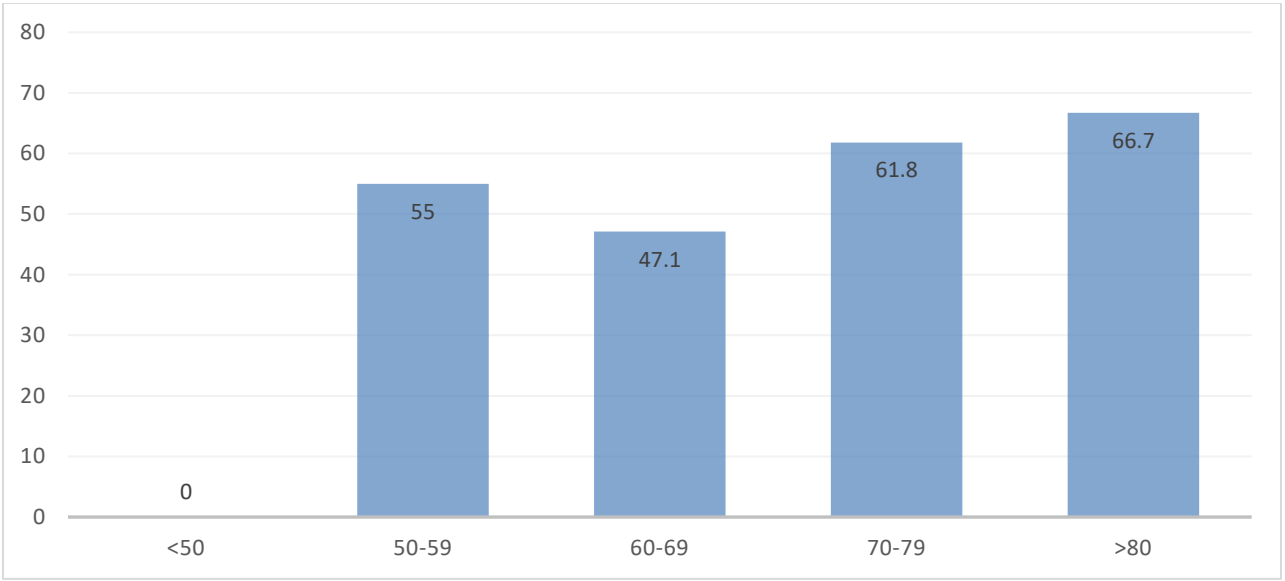

Figure 16: Prostate Cancer Detection Rate with Increasing Age.

Source: Field Data, 2023.

4.4.4 DRE Findings and Cancer Detection Rates

One hundred and thirty-three (61.0%) of the study participants had normal digital rectal examination (negative DRE) findings, while the remaining 85 had suspicious (positive) DRE findings. Fifty-four out of the 133 study participants with negative DRE findings had were diagnosed with prostate cancer, giving a cancer detection rate of 50.4% in group.

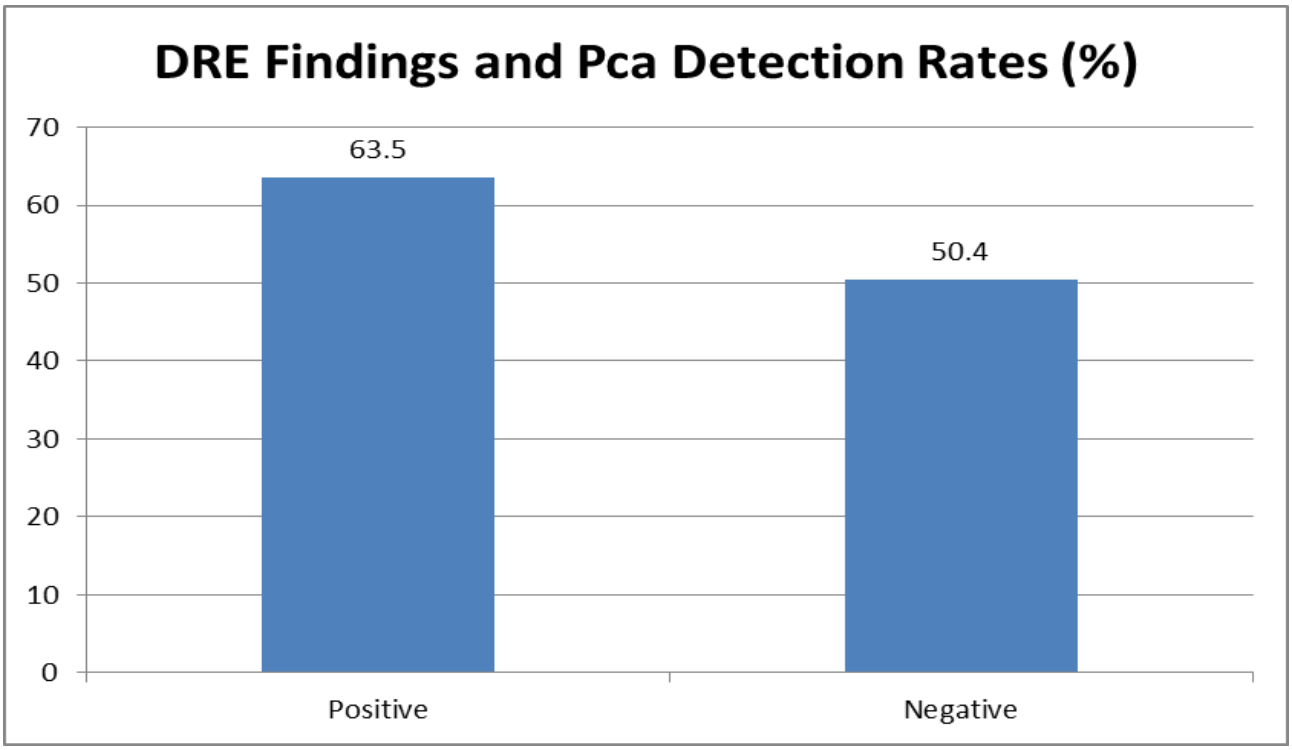

Figure 17: DRE Findings and Prostate Cancer Detection Rates.

Source: Field Data, 2023

Considering the DRE findings and the serum PSA levels, the cancer detection rates for the participants with negative DRE findings in the serum PSA ranges of < 4.0, 4.1-10.0, 10.1-20.0, 20.1-100.0, and >100.0 ng/ml were found to be 0, 28.3, 51.1, 80.0, and 100.0%, respectively.

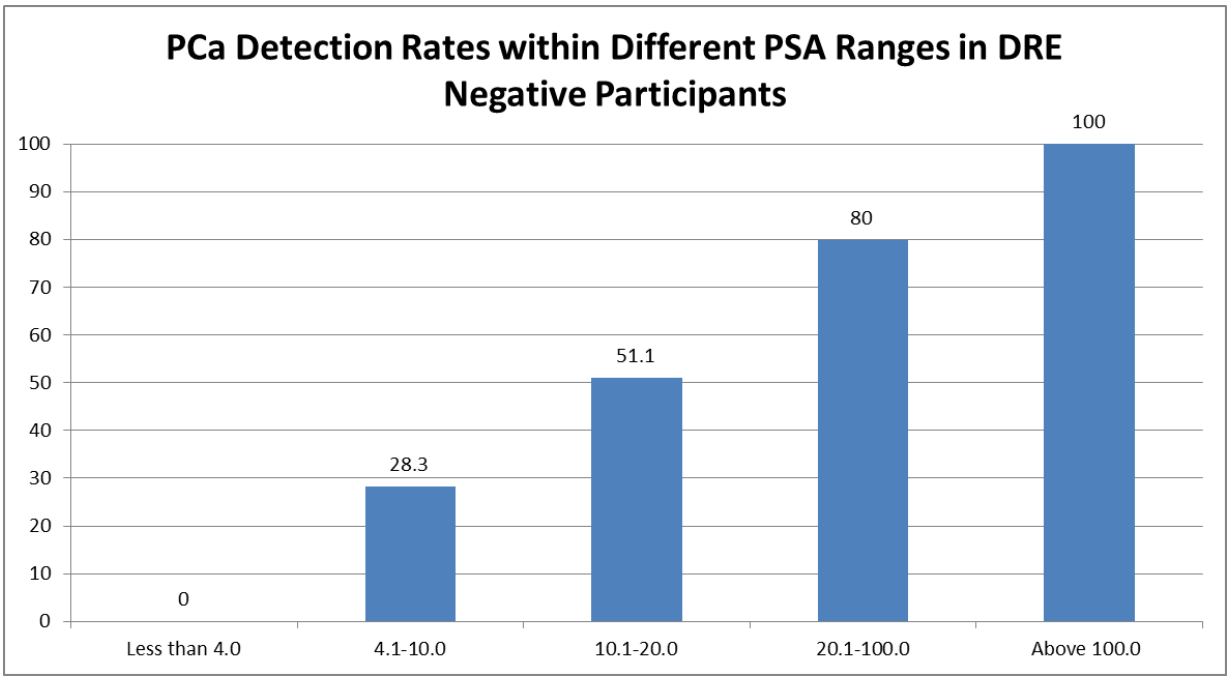

Figure 18: Prostate Cancer Detection Rates with Increasing PSA Level in Participants with Negative DRE Findings.

Source: Field Data, 2023.

Fifty-four out of the 85 study participants with positive DRE findings were diagnosed with prostate cancer giving a cancer detection rate of 63.5% among this group. The prostate cancer detection rates of the participants with positive DRE findings in the serum PSA ranges of < 4.0, 4.1-10.0, 10.1-20.0, 20.1-100.0, and >100.0 ng/ml were found to be 0, 28.6, 52.8, 88.5, and 100.0%, respectively.

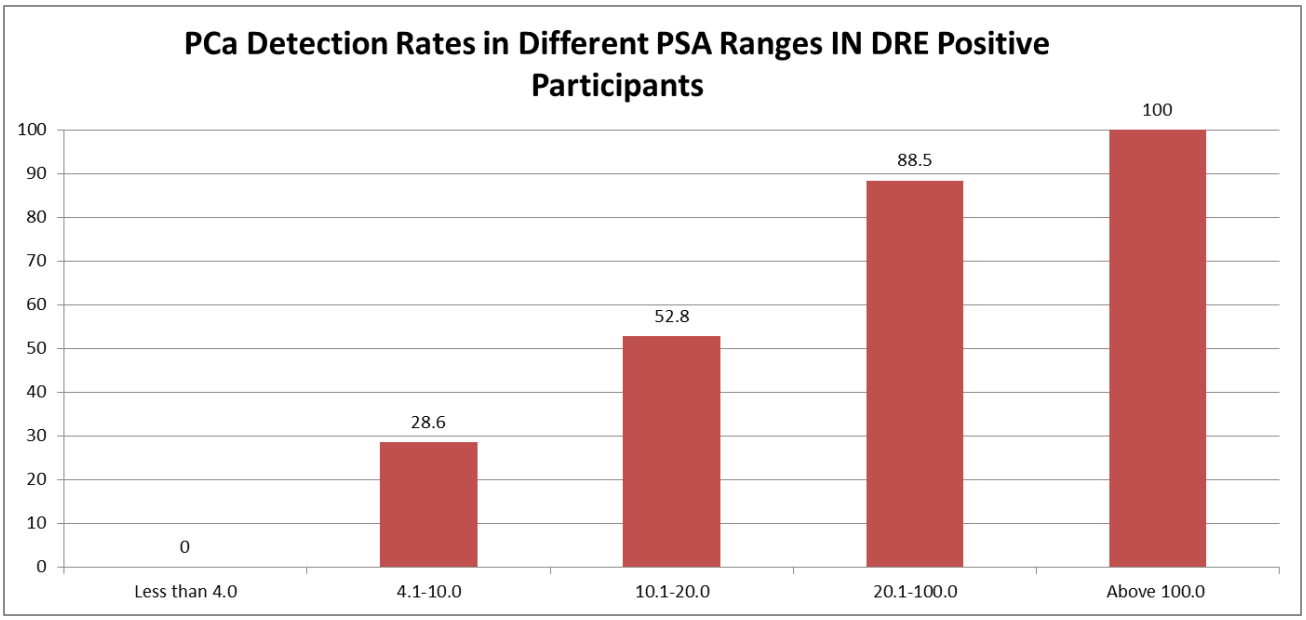

Figure 19: Prostate Cancer Detection Rates with Increasing PSA Level in Participants with Positive DRE Findings.

Source: Field Data, 2023.

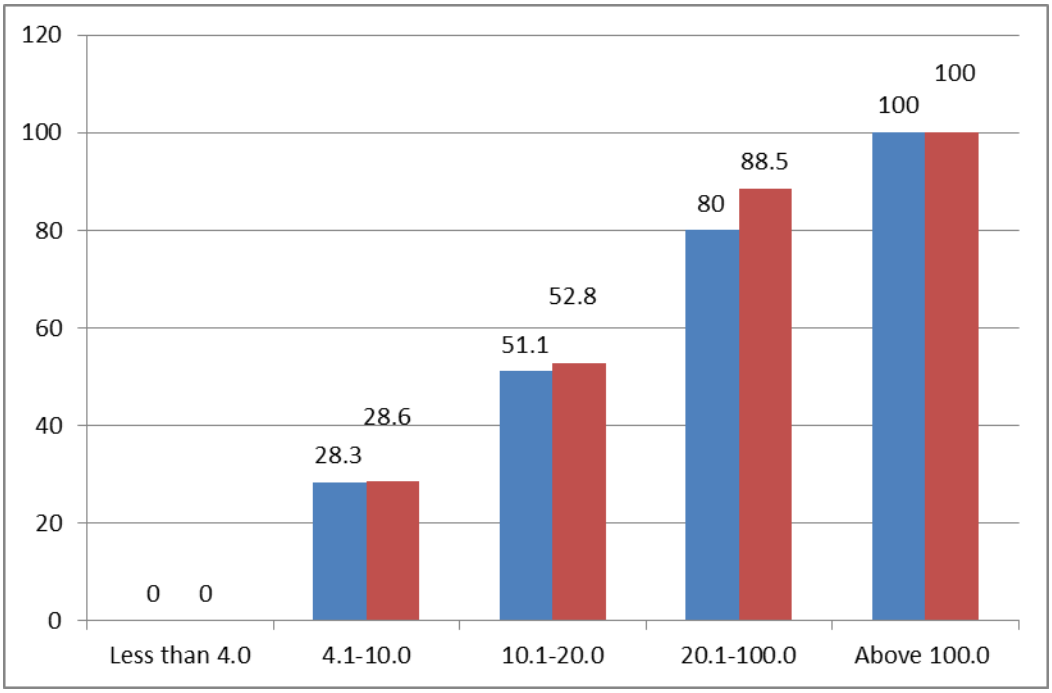

Figure 20: Prostate Cancer Detection Rates with Increasing PSA Level in Participants with Negative DRE Findings and Participants with Positive DRE Findings.

Source: Field Data, 2023

4.4.5 Sonographic Findings and Cancer Detection Rates

Ultrasound imaging studies of the prostate were done, along with an evaluation of the reports brought by the study participants. More than half (53.2%) of the study participants had suspicious findings on sonographic evaluation of the prostate gland. One hundred and ninety-two study participants (88.1%) had intact prostate capsules. The mean prostate volume of the study participants was 72.63 ml, while the mean volumes for those diagnosed with prostate cancer and those without prostate cancer were 60.59 ml and 78.19 ml, respectively.

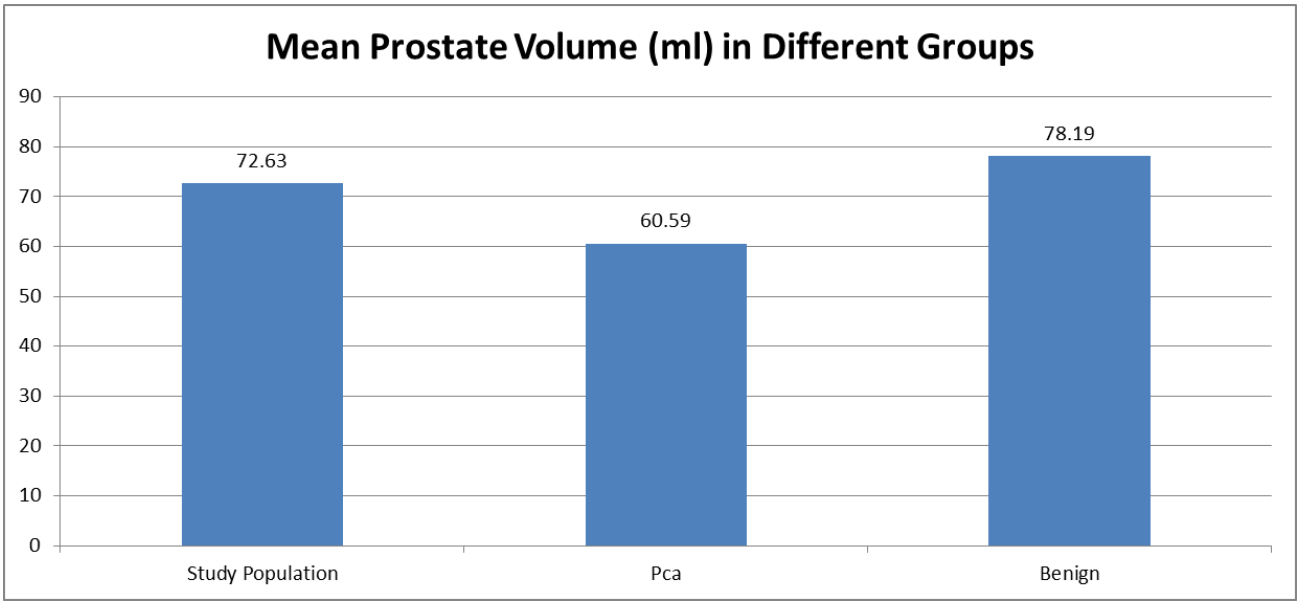

Figure 21: The mean Sonographic Prostate Volume and in Study population and Subcategories of Study Population.

Source: Field Data: 2023.

The prostate cancer detection rate among the group of study participants with normal (negative) sonographic findings was 51.0%, with the cancer detection rates for the serum PSA ranges < 4.0, 4.1–10.0, 10.1-20.0, 20.1–100.0, and >100.1 ng/ml being 25.0, 30.8, 40.5, 59.4, and 100%. While the prostate cancer detection rates among the group with suspicious (positive) sonographic findings was 59.5%, the prostate cancer detection rates for the serum PSA ranges < 4.0, 4.1–10.00, 10.1-20.0, 20.1–100.0, and >100.0 ng/ml were 0.0, 28.6, 57.7, 60.8, and 100.0%.

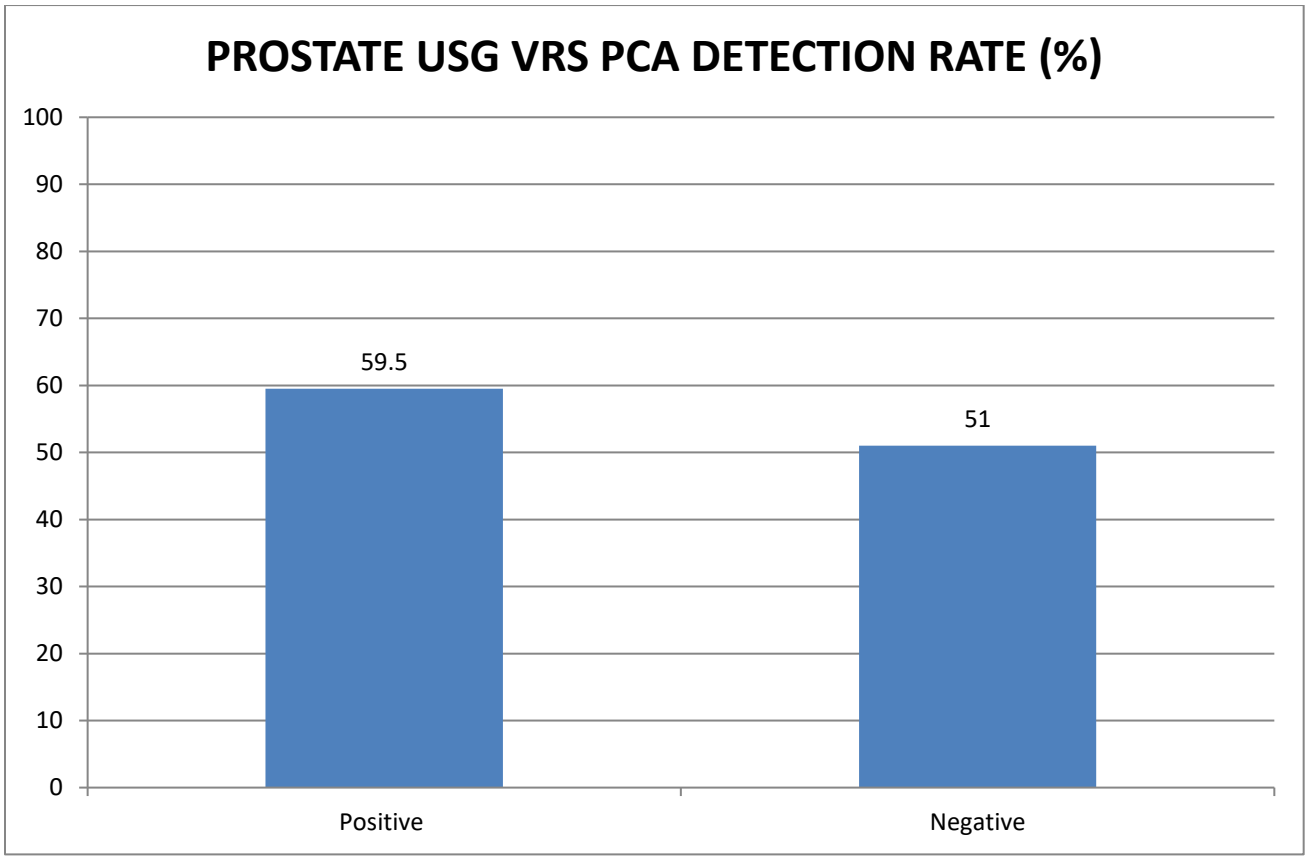

Figure 22: Prostate Cancer Detection Rates in Participants with Positive and Negative Sonographic Findings.

Source: Field Data, 2023.

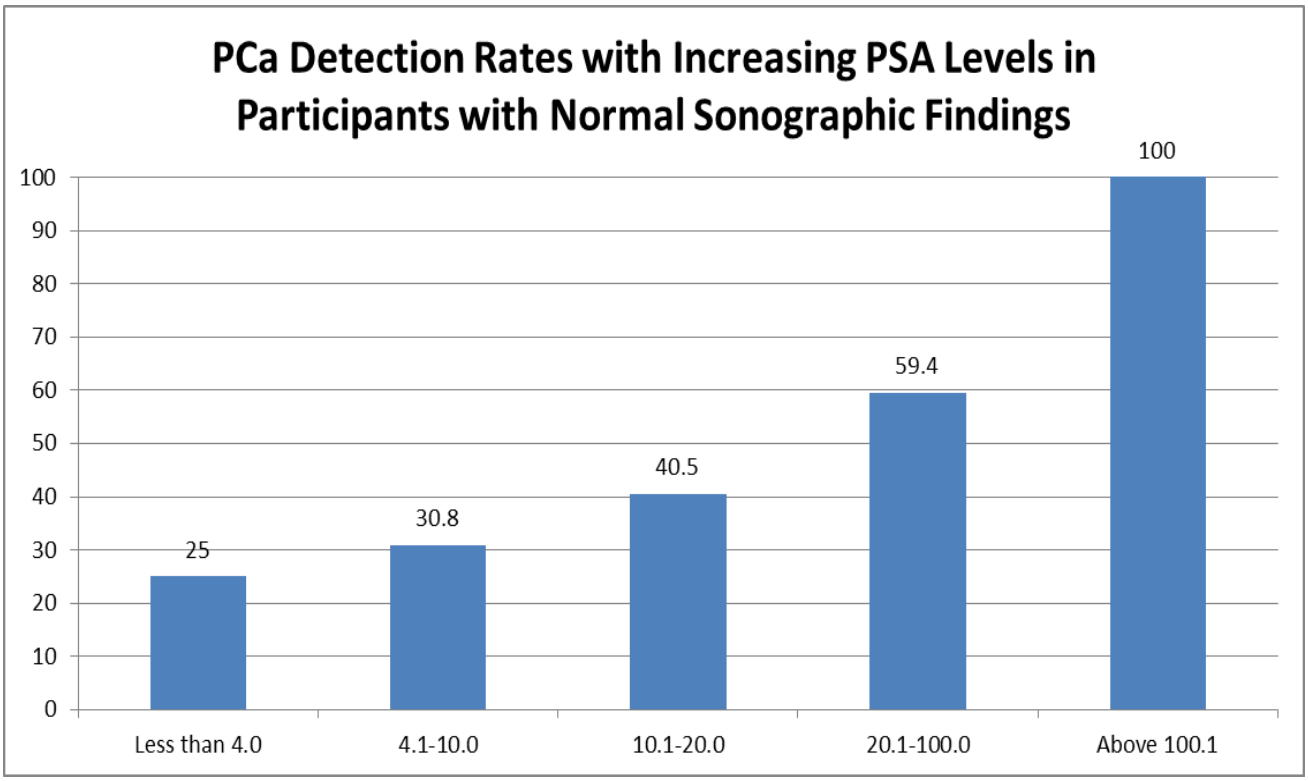

Figure 23: Prostate Cancer Detection Rates with Increasing Serum PSA Levels in Participants with Normal (Negative) Sonographic Findings.

Source: Field Data, 2023.

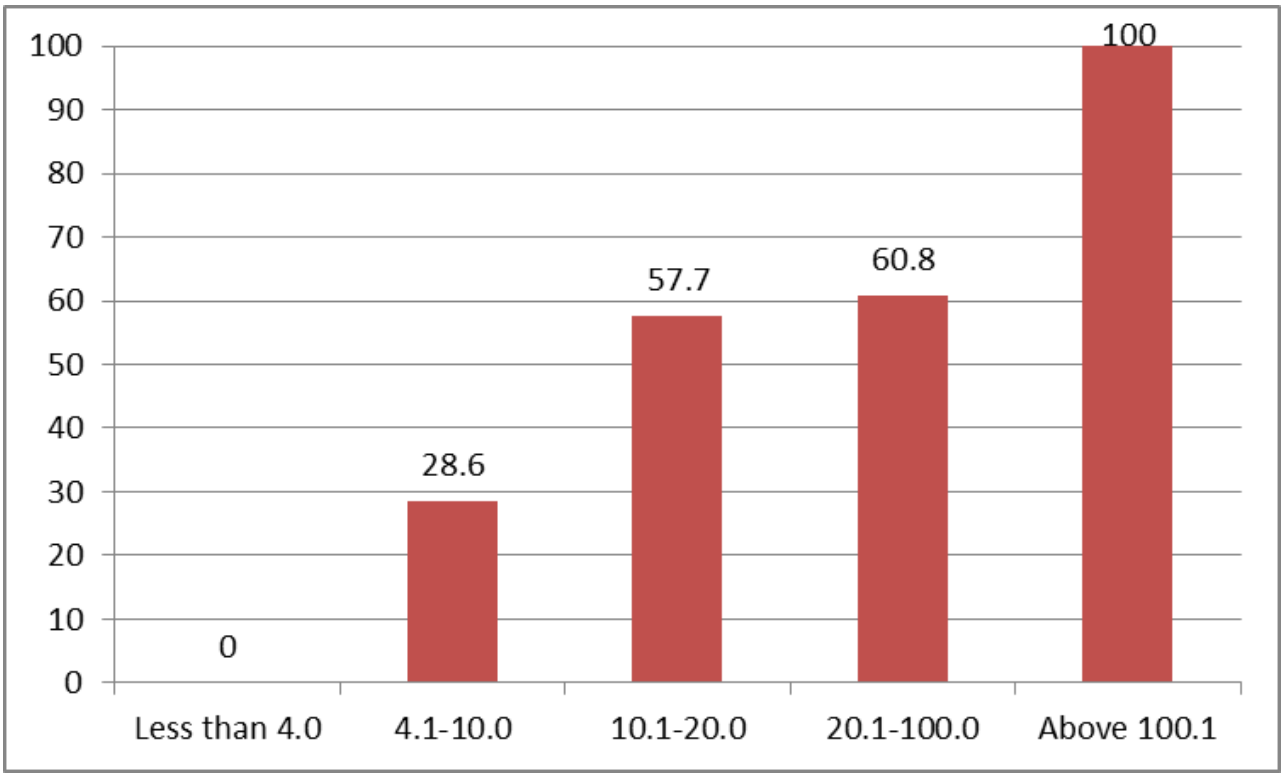

Figure 24: Prostate Cancer Detection Rates with Increasing Serum PSA Levels in Participants with Suspicious (Positive) Sonographic Findings.

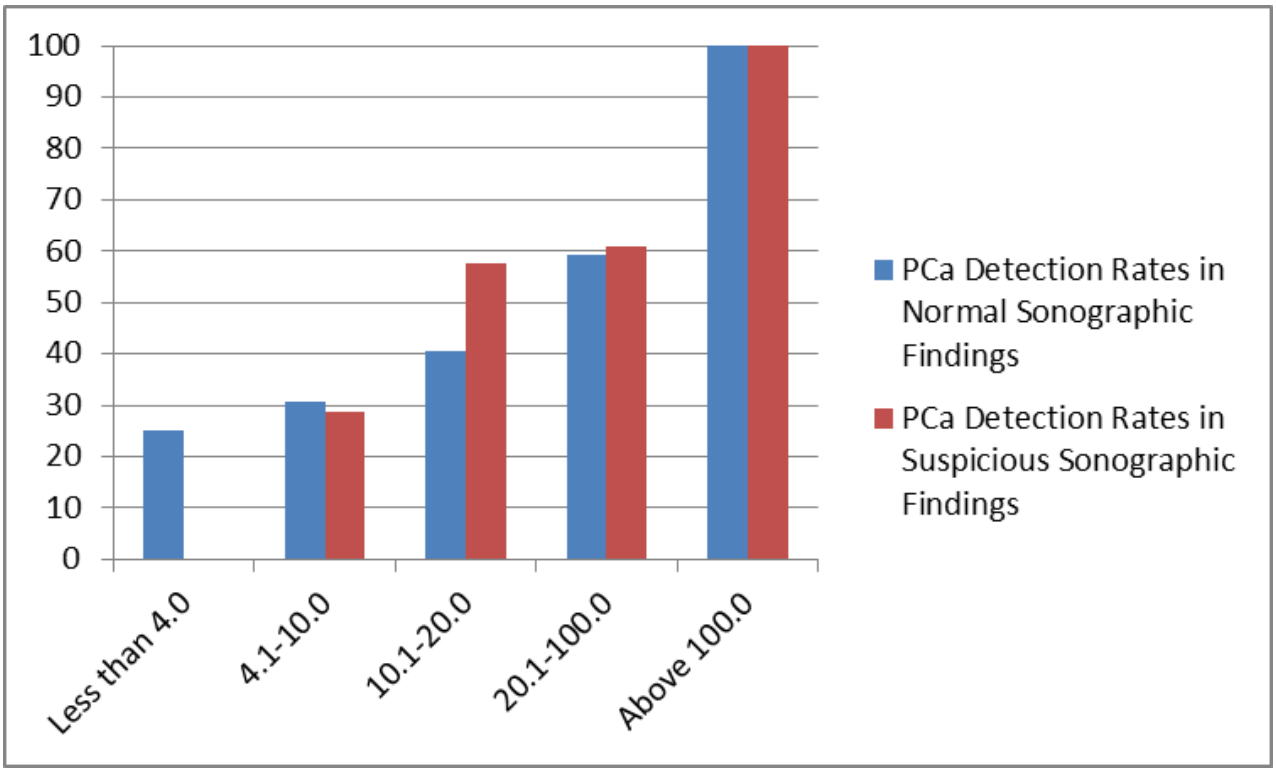

Figure 25: Prostate Cancer Detection Rates with Increasing Serum PSA Levels in Participants with Normal Sonographic Findings and those with Suspicious Sonographic Findings.

Source: Field Data, 2023.

CHAPTER FIVE

Discussion

5.0 Introduction

Prostate cancer is a very common disease affecting sub-Saharan African men with devastating consequences. According to Globocan 2020, it is the most common cancer in Ghanaian men by incidence, with an incidence rate of 31.0 per 100,000 populations per year. [1]

It is diagnosed through a TRUS-guided prostate biopsy, which is done when there is an elevated or abnormal serum PSA level, a suspicious digital rectal examination finding, or a clinical suspicion of the presence of prostate cancer. There are very few studies evaluating this indispensable diagnostic modality in our environment.

5.1 Overall Prostate Cancer Detection

In this study, 218 men who were undergoing TRUS-guided prostate biopsy were recruited for prospective evaluation and follow-up. Of these, 128 men were diagnosed with prostate cancer, giving an overall cancer detection rate of 55.5%. This is consistent with the overall cancer detection rate in a similar study by Abrahams et al. at the Korle Bu Teaching Hospital, who reported a rate of 52.7% from their study. [99] This, however, is less than the detection rate of 67.7% that Arthur et al. reported from a similar study at the Cape Coast Teaching Hospital that they carried out. [98] A similar study by Ogbetere et al. in Nigeria, a neighbouring West African country with a healthcare setup similar to ours, reported an overall prostate cancer detection rate of 65%. [93] These rates of cancer detection are generally higher than those reported in populations of other geographical locations and among different racial populations. Jia et al. reported an overall cancer detection rate of 42.8% among the Han Chinese population in Northern China, while Narayanaswamy et al. from a study in Kuwait reported a rate of 27.4%. [33, 92] The significantly higher rates of prostate cancer detection reported from this study and from Nigeria by Ogbetere et al. as compared to the lower rates reported by other researchers in different racial populations support the observation that prostate cancer is more common in Africans and people of African descent. [92, 93]

5.2 The Indications for TRUS-Guided Biopsy

This study has shown that the main indication for TRUS-guided prostate biopsy in our population is abnormal serum PSA level. About 2 out of every three people (134, 61.5%) who undergoes biopsy being on this account. The mean serum PSA of the study participants for men in the age brackets of < 50, 50–59, 60–69, 70–79, and >80 years were 100, 59.19 ± 46.87, 36.25 ± 34.58, 48.93 ± 45.45, and 96.65 ± 25.80 ng/ml, respectively. This shows the patients were referred with very high serum PSA, which may indicate advanced disease before referral for TRUS-guided biopsy. This observation points to the fact that, prostate cancer patients in our environment present generally late for diagnostic workup and management. This may be because of poor health seeking behavior and infrequent screening for prostate cancer which allows early detection of the disease in our population.

5.3 Age and Prostate Cancer Detection

The results of this study demonstrate that prostate cancer is primarily a disease of the elderly. In this study, the mean age of the study participants was 69.84 ± 8.10, with a range of 45–89 years. The majority of the patients (174, 80.7%) were within the age bracket of 60–79 years. This is consistent with the findings from a similar study by Arthur et al., who reported the mean age of patients who underwent TRUS-guided prostate biopsy at their hospital to be 68.3 years (range of 34–89 years), with the majority of the patients (49, 79.1%) aged between 60 and 79 years, while Abraham et al. reported a similar finding with a mean age of 67.7 ± 8.6 years (range of 46–85 years) and with the majority of the patients (110, 73.4%) aged between 60 and 79 years. [98,99]

The age distribution of patients in this study suggests a trend towards older individuals being more commonly affected by this condition. From the study, the cancer detection rates for the age brackets <50, 50-59, 60-69, 70-79, and > 80 years were found to be 0.0, 55.0, 47.1, 61.8, and 66.7%, respectively. This shows increasing prostate cancer detection rates with advancing age. This trend is similarly observed in the reported findings of other studies in different populations at various geographical locations.

Ogbetere et al. reported, from their study in Nigeria, that the cancer detection rate for the age brackets of 50–59, 60–69, 70–79, 80–89, and 90–100 years was 75, 46.7, 72.3, 85.7, and 100%, respectively. [93] In their study in Northern China, Jia et al. found the cancer detection rates for the age brackets of < 50 years, 51–60 years, 61–70 years, 71–80 years, and > 80 years to be 7.1, 28.1, 33.3, 48.7, and 62.2%, respectively. 33 While Narayanaswamy et al. reported, for the age brackets of <55, 56-65, 66–75, and >76 years,

detection rates were 16.7, 17.6, 33.3, and 40.7%, respectively. [33,92,93] This shows the incidence (and prevalence) of prostate cancer increases with increasing age.

The rising incidence of prostate cancer across the world is explained by the demographic shift in population structure globally over the past decade. With increasing life expectancy across the world, people are living longer into their old ages. These ageing populations have increasingly larger proportions of elderly men, who have a higher incidence of prostate cancer. This increasingly larger pool of patients most at risk of prostate cancer in a population with one of the highest risks of the disease because of our African racial background is a potential public health crisis in the making.

5.4 Serum PSA Level and Cancer Detection

In this study, the cancer detection rates for the PSA ranges of < 4.0, 4.0-10.0, 10.1-20.0, 20.1-100.0, and >100.1 ng/ml were detected to be 0, 23.3, 54.2, 85.2, and 100.0%, respectively. This shows an increasing cancer detection rate with increasing serum PSA levels. This observation indicates a steady rise in the risk of being diagnosed with prostate cancer with rising levels of serum PSA. This risk rises from negligible for a serum PSA range of < 4.0 ng/ml or less, through 23.3% for a serum PSA range of 4.1–10.0 ng/ml, 54.2% for a serum PSA level of 10.1-20.0 ng/ml, and 85.2% for a serum PSA range of 20.1–100.0 ng/ml, to the highest of 100% for a serum PSA level of >100.0 ng/ml.

This finding is consistent with the reported findings of other studies in different populations and geographical locations. In the study by Ogbetere et al. in our neighbouring West African country, Nigeria, the prostate cancer detection rate rose from a low of 25% for a serum PSA level of 4–10 ng/ml, through 54.7 for a serum PSA range of 10.1-20.0 ng/ml, 67.4% for a SPA range of 20.1–50.0 ng/ml, and a peak of 100% for a SPA range of >50.1 g/ml. 85 This trend is also observed in the study by Jia et al. in the Han population in China in Eastern Asia (Far East) and by Narayanaswamy et al. in the Arab population of Kuwait in the Middle East. [33,92]

It may also be inferred from these findings that the increasing rates of prostate cancer detection on TRUS-guided biopsy with increasing serum PSA may point to an increasing size of the tumour in the prostate gland with increasing serum PSA levels. This is because TRUS-guided biopsy is only an organ-targeting biopsy but not a lesion-targeting procedure, and the increasing cancer yield rate on such biopsies may point to the higher propensity to hit the malignancy with each drive of the biopsy needle into the gland.

5.5 DRE Findings and Prostate Cancer Detection

In this study, eighty-five study participants who had suspicious DRE findings were diagnosed with prostate cancer. This gives a positive predictive value of DRE for prostate cancer in this study to be 63.5%, which is lower than the 82.4% that Ogbetere et al. reported from their study in Nigeria. Since DRE is useful in detecting clinically advanced prostate cancer, these high predictive values may mean most prostate cancer patients in Ghana and Nigeria present late with clinically advanced disease and may not benefit from curative treatment. [93] Far lower DRE positive predictive values are reported from studies by researchers in other locations. [33, 92] This indicates that prostate cancer patients in other environments were detected or reported earlier in the natural history of the disease compared to our population. This may be due to the low level of awareness of prostate cancer among our population, poor health-seeking behaviour among our people, relatively poor access to specialised urology consultations, poor access to appropriate diagnostic services for prompt diagnosis of prostate cancer, and a higher propensity for our people to develop more aggressive prostate cancer that progresses rapidly, which is therefore more likely to be detected at an advanced stage.

5.6 Prostate Volume and Prostate Cancer Detection Rates

The mean prostate volume for the study participants who were diagnosed with prostate cancer was 60.59 ml, compared to a mean prostate volume of 78.19 ml for those without prostate cancer. The findings from this study show patients with smaller prostates are more likely to be detected to have prostate cancer than those with larger prostates. This finding is similar to that made by Narayanaswamy et al. in their study in Kuwait, but contrary to the findings from similar studies by Ogbetere et al. in their studies in Nigeria and by Jia et al. in their studies in China reporting a larger mean prostate volume for the prostate cancer group as compared to those with no prostate cancer. [33,92,93]

The lower cancer detection rate among study participants with larger prostate volumes may be because of sampling error since TRUS-guided prostate biopsies are essentially organ-targeting but not lesion-targeting procedures as used in MRI-guided or fusion-image-guided prostate biopsies of the prostate gland.

CHAPTER SIX

Conclusions and Recommendations

6.0 Conclusions

The indications for referral for a TRUS-guided biopsy of the prostate gland in this study were elevated serum PSA levels, suspicious DRE findings, or a combination of both. The commonest indication for the prostate biopsy was elevated serum PSA levels, accounting for 61.5% of the referrals.

From the study, the overall prostate cancer detection rate among men undergoing TRUS-guided biopsy of the prostate gland was found to be 55.5%. In our settings, the TRUS-guided prostate biopsy detects more prostate cancer cases than benign conditions, detecting about 6 cancer cases out of every 10 patients who are referred for a prostate biopsy using the TRUS-guided biopsy as having prostate cancer. This also implies that about 4 out of 10 patients referred for prostate biopsy may not need to undergo the procedure.

Prostate cancer is a disease of elderly men. Men who undergo TRUS-guided prostate biopsy and are diagnosed with prostate cancer at KATH have a mean age of 72.35 $\pm$ 8.02 years, as compared to 66.72 $\pm$ 7.07 years for those diagnosed with benign conditions ($P < 0.001$). Prostate cancer prevalence increases with advancing age, as shown by the increasing prostate cancer detection rates with the increasing age of the study participants. The risk of prostate cancer increases with increasing serum PSA levels. Increasing prostate cancer detection rates with increasing serum PSA levels, as reported in this study and prostate cancer detection rates, are proof of this. The risk of prostate cancer rises from being almost negligible at a serum PSA level of less than 4.0 ng/ml to almost certainty at a serum PSA level of 100 ng/ml or more.

DRE is a poor screening tool for early prostate cancer when used alone. It is useful in detecting locally advanced prostate cancer. DRE had a high positive predictive value for prostate cancer among the study population. This shows that patients with prostate cancer in our environment present late with clinically advanced disease.

6.1 Recommendations

The findings and inferences made from the data of this study offer insight for recommendations.

1. **Education on Prostate Cancer**

Blacks and people of African descent are at very high risk of developing prostate cancer as compared to the other races. There is therefore a need for targeted education to increase awareness among our population about prostate cancer. This will help our men to be aware of the disease and become aware of the fact that it is common in our population because of our racial and genetic background and that every man is at risk of it. This will help demystify the knowledge about the disease and improve the health-seeking behaviour of men as they become more responsible for their health when armed with the right set of knowledge on prostate cancer.

2. **Voluntary and Targeted Prostate Cancer Screening Programs**

Because of our racial background, all Ghanaian men are at risk of prostate cancer. It would be prudent to institute a screening programme for prostate cancer consisting of two arms: a voluntary annual screening arm and targeted screening arms.

The voluntary screening programme will be for all men with average risk, such as black men with no family history of breast or prostate cancer. By this, Ghanaian men would be encouraged to start screening at the age of 50 with annual PSA checks and DRE, while the targeted screening will be for men with a higher-than-average risk for prostate cancer, such as men with a family history of prostate or breast cancer.

There is a need to put in place a targeted screening programme for prostate cancer across the country for the early detection, diagnosis, and management of prostate cancer.

3. **Replication of Study in Other Centers**

There is also the need to replicate this study in more centres across the country for our population. The findings from multi-centre studies with a larger sample size will enable the making of better and more accurate projections and inferences. This may help us make discoveries that will aid in better utilising our limited resources in the screening, diagnosis, and management of prostate cancer in our environment.

6.2 Limitations of the Study

a. The study could not recruit the needed 246 study participants into the study.

b. The serum PSA values presented by the study participants were from different laboratories. This may be a possible source of error in the study data.

c. The prostate biopsies, the digital rectal examination, and the trans-rectal ultrasound measuring the prostate volume were performed by different doctors, not the principal investigator alone. Despite strict adherence to established protocols, it is still expected that there will be some interpersonal variations which may also be a source of error.

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APPENDICES

APPENDIX A: QUESTIONNAIRE

A STUDY OF PROSTATE CANCER DETECTION RATES IN MEN UNDERGOING TRANS-RECTAL ULTRASOUND-GUIDED PROSTATE BIOPSY AT KATH, KUMASI

Study number: Date:

Section A: Demographics

1. Age: ……years
2. Ethnicity:
3. Residence: [a] Rural [b] Peri-urban [c] Urban [d] other: …….
4. Educational background: [a] None [b] basic [c] secondary [d] tertiary [e] other:
5. Occupation: [a] managerial [b] professional [c] clerical [d] technical/craft [e] manual/service

6. Marital status: [a] Single [b] Married [c] divorced [d] widowed
7. Number of children: [a] 0-3 [b] 4-6 [c] >6
8. Health Insurance (NHIS or any other): [a] Yes [b] No

Section B: Clinical features

History

9. Which of the following symptoms do you have?

Frequency	[ ]	Dysuria	[ ]
Urgency	[ ]	Dizziness	[ ]
Nocturia	[ ]	Scalp swelling	[ ]
Weak urine flow	[ ]	Painful ejaculation	[ ]
Intermittency	[ ]	Unexplained Weight loss	[ ]
Straining	[ ]	Incomplete bladder emptying	[ ]
Easy fatigability	[ ]	Pains in the back, hips, waist, or pelvis	[ ]
Hemospermia	[ ]	Erectile dysfunction of recent onset	[ ]
Hematuria	[ ]	Weakness in any lower limb of recent onset	[ ]
Pathological fracture	[ ]	Acute urine retention within the past 3 months	[ ]

10. Do you have a Family history of prostate cancer?

    Yes [ ] No [ ] Do not know [ ]

11. Who in your family has been diagnosed with prostate ca?

Father	[ ]	Maternal uncle	[ ]	Maternal grandfather	[ ]	Maternal cousin	[ ]
Brother	[ ]	Paternal uncle	[ ]	Paternal grandfather	[ ]	Paternal cousin	[ ]

12. Do you have a family history of breast cancer?

    Yes [ ] No [ ] Do not know [ ]

13. Who in your family has been diagnosed with breast cancer?

Mother	[ ]	Maternal auntie	[ ]	Maternal grandmother	[ ]	Maternal cousin	[ ]
Sister	[ ]	Paternal auntie	[ ]	Paternal grandmother	[ ]	Paternal cousin	[ ]

14. Do you have a history of smoking cigarettes?

    Yes [ ] No [ ]

15. If yes, for how long (in pack years)? ……years
16. Do you take alcohol?

Yes [ ] No [ ]

17. If yes, then averagely how many units of alcohol per a week?

……

18. How long have you been taking alcohol? ……Years

Physical Examination

19. Which of the following is present on Physical exam?

Pallor [ ] Scalp swelling [ ] Pedal swelling [ ]

Jaundice [ ] Hepatomegaly [ ]

20. Does patient have suprapubic catheter?

Yes [ ] No [ ]

21. DRE findings on the prostate:

Size: Normal [ ] Enlarged [ ]

Surface: Smooth [ ] Rough [ ]

Median sulcus: Present [ ] Obliterated [ ]

Rectal mucosa: Adherent [ ] Mobile [ ]

Consistency: Rubbery [ ] Hard [ ]

22. Overall feature of prostate gland

Normal [ ] Suspicious [ ]

Investigations

23. What is the serum PSA level? ng/ml

24. What is the size of the prostate gland measured sonographically?.....

25. What is homogeneity of the prostate gland?

[a] Homogenous [b] Heterogeneous

26. Is the prostate capsule sonographically intact?

Yes [ ] No [ ]

27. What is the post-void residual urine volume?

……ml

28. What is the indication for the prostate biopsy?

[a] Suspicious DRE findings

[b] Abnormal serum PSA

[c] Suspicious prostate USG

[d] Other. State:……

Histopathology report:

Please provide the following details from the prostate biopsy histopathology report:

29. Histological diagnosis:
30. Gleason score:
31. Gleason grade group:
32. Perineural invasion: [a] Present [b] Absent
33. Number of cores examined: …..
34. Number of cores with cancer present:
35. Percentage of biopsy material constituted by cancer:
36. Length of shortest core:
37. Length of longest core:

APPENDIX B

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

INFORMATION SHEET

Title of Research:

A STUDY OF PROSTATE CANCER DETECTION RATES IN MEN UNDERGOING TRANS-RECTAL ULTRASOUND GUIDED PROSTATE BIOPSY AT KATH, KUMASI.

Name(s) and affiliation(s) of researcher(s):

This study is being conducted by **Dr Dominic Annor Mintah**, supervised by **Dr Kwaku Addai Appiah Arhin** and **Dr George Amoah**, all of the Urology Unit of the Directorate of Surgery, Komfo Anokye Teaching Hospital.

Background:

Prostate cancer is the second most common malignancy affecting men worldwide with ethnic and geographical variations in incidence. Africans and people of African descent are affected disproportionally with more aggressive forms of the disease and present late for treatment.

Prostate cancer is diagnosed by taking a piece of the prostate (a prostate biopsy) for histological investigation which can confirm the presence or otherwise of the disease. The common and standard method of obtaining a biopsy of the prostate for the investigation is by driving a small needed (biopsy needle) under ultrasound guidance through the rectum (back passage) into the prostate to obtain small pieces of it in a process called Trans-Rectal Ultrasound-Guided (TRUS-Guided) biopsy of the prostate. There have not been a lot of studies on this investigative procedure in our people unlike what has been done in other populations. This study will provide more insight into this investigative tool, expanding our pool of knowledge on it. This will help us make better choices deciding when to request a person suspected of having prostate cancer to undergo this test.

Purpose(s) of research (why is the study being done?):

The study aims to determine how often prostate cancer is detected when men have small pieces of their prostate taken for investigations with a special needle through the back passage when their doctor think a cancer may be present at the Urology Unit of Komfo Anokye teaching hospital (KATH), Kumasi.

This study will help us find the reason where doctors request for the investigation, how useful it is, in which age group it offers more useful information when done, when not to do it and any other useful new insight it may provide. The insight the research will offer will help doctors make better decision when taking care of people suspected of haven prostate cancer.

Selection of participants (Who will be part of the study and why am I being asked to be part of the study?):

This study involves men aged 40 years and above in whom the possible presence of prostate cancer is considered significant and have therefore been requested by their doctors who are taking care of them to undergo evaluation of their prostate glands by having small pieces of the prostate taken as a biopsy under ultrasound guidance at the Urology Unit of KATH for investigation to confirm the presence or otherwise of prostate cancer. Participation in the study is voluntary.

You are being asked to join since you meet this criterion and you may therefore voluntarily join. Participation in this study is voluntary and you will suffer no disadvantage and will receive the same level of care and attention should you decide not to join this study.

The procedure of the research, what shall be required of the participant, and the approximate total number of participants that would be involved in the research:

This study plans to recruit 271 men who will be reporting to the Urology Procedure room to undergo a biopsy of their prostate for investigation at the request of their attending doctors. When you join the study, you will undergo an interview to obtain personal information to fill a form before you undergo the procedure. After the procedure, some additional details would be provided by the doctor who performed the procedure on his findings. We will arrange and meet you when you come to pick up the report of the investigation to present to your doctor 2-3 weeks after the procedure. This will allow us to obtain information from your report to complete the questionnaire we will be filling on you.

Risk(s) (What harm could possibly come to me if I take part in the study?):

The harm that can possibly come to you for taking part in this study includes:

1. The possible loss of privacy your privacy.
2. Possible breaches of confidentiality.
3. You may suffer some personal discomfort.
4. You may experience some delay in service delivery.

The following measures would be put in place to prevent or minimize the effect of these possible harms you may suffer:

1. All communications with you or with the doctor who will perform the test to obtain your personal or medical details will be conducted in absolute privacy and with your expressed consent.
2. You will be given a study number which will be used to represent you in the study. No document in the study will bear your name, telephone number, or any information that can be used to identify you. All documents on you in the study will bear only the number and only the principal

investigator can trace the study number to you. No one can therefore trace any information or findings to you as a study participant. This will protect your personal and medical information.

3. Efforts would be made to prevent or minimize any personal discomfort the study may cause.
4. You will be given prompt attention and care as a study participant when you report for the biopsy and collection of your report.

Benefit(s) (What do I hope to gain from the study? What will society gain from the study?):
There will be no direct potential benefit to you

Confidentiality:
The information needed from the study participants in this study would be obtained through interviews with the participants, by taking with the doctors who conduct the prostate biopsy with the consent of the participant right after the procedure to obtain his examination findings and directly from the report of the biopsy when the participant picks up the report when it is ready.

Every study participant will be given a study number which will be used to represent the person in the study. No document in the study will bear the name, telephone number, or any information that can be used to identify any study participant. All documents on study participants will bear only their study number and the study numbers can only be matched against the identity of their respective owner in a master book kept with only the principal investigator. Only the principal investigator can therefore trace the study number to the study participant. This will protect the personal and medical information of the study participants.
No name or identifier will be used in any publication or report from this study.

Voluntariness:
Taking part in this study should be out of your own free will. You are not under obligation to.
Participation in research is entirely voluntary.

Alternatives to participation:
You will suffer no disadvantage and will receive the same level of care and attention should you decide not to join this study.

Withdrawal from the research:
You may choose to withdraw from the research at any time without having to explain yourself. You may also choose not to answer any question you find uncomfortable or private.

Consequence of Withdrawal:

There will be no consequence, loss of benefit or care to you if you choose to withdraw from the study. This will not affect your treatment in this hospital/institution in any way.) Please note however, that if you withdraw at the time that some of the information that may have been obtained from you without identifiers (name etc), may have been modified or used in analysis reports and publications, these cannot be removed anymore. We do promise to make all the effort to comply with your wishes as much as practicable.

Costs/Compensation:

There will be no compensation for participation in the study.

Contacts:

In case you have any question(s) concerning this study, please do not hesitate to contact Dr Dominic Annor Mintah, the Principal investigator on this phone 0206 300 207.

Further, if you have any concerns about the conduct of this study, your welfare, or your rights as a research participant, you may contact:

The Office of the Chairman,
Komfo Anokye Teaching Hospital Institutional Review Board (KATH-IRB),
Research and Development Unit, Kumasi.
Tel: +233 3220 00617.
Email address: kathirb@kathhsp.org or kathirb25@gmail.com

INFORMED CONSENT FORM

Title of the research: A STUDY OF PROSTATE CANCER DETECTION RATES IN MEN UNDERGOING TRANS-RECTAL ULTRASOUND GUIDED PROSTATE BIOPSY AT KATH, KUMASI.

Name(s) and affiliation(s) of researcher(s) of applicant(s): This study is being conducted by **Dr Dominic Annor Mintah** and supervised by **Dr Kwaku Addai Appiah Arhin** and **Dr George Amoah** all of the Department of Surgery, Komfo Anokye Teaching Hospital.

Purpose(s) of research:

The study aims to evaluate the detection rates of prostate cancer on TRUS-guided prostate biopsy and analyze its characteristics among the men undergoing prostate biopsy at KATH, Kumasi.

This study is for my dissertation in part fulfilment of the Fellowship in Surgery (Urology) by the Ghana College of Surgeons.

Procedure of the research, what shall be required of each participant and appropriate total number of participants that would be involved in the research:

As a patient undergoing trans-rectal ultrasound-guided prostate biopsy to confirm the presence or otherwise of prostate cancer, you will be asked a few routine questions about the disease and your health. The information obtained together with report of the biopsy would be anonymized and fed into the study database and analyzed to generate the findings.

Risk(s) and Benefits:

You will not be subject to any additional risks beyond the risk inherent in the biopsy procedure you have been directed by your doctor to undergo already, as a participant in this study. The risk inherent in the TRUS-guided prostate biopsy procedure are hematuria, rectal bleeding, acute urine retention and infection.

Benefit(s):

You will help in the gaining of knowledge about the disease in Komfo Anokye Teaching Hospital and that will contribute to better treatment options, development of standardized treatment protocol for our local settings and also in the development of prevention programs.

Confidentiality:

All information collected in this study will be given code numbers. This cannot be linked to you in any way and your name or any identifier will not be used in the final dissertation of this study.

Voluntariness:

Your participation in this research is entirely voluntary.

Alternatives to participation:

If you choose not to participate, this will not affect your medical care in this hospital in any way.

Consequences of participants' decision to withdraw from research and procedure for orderly termination of participation:

You can also choose to withdraw from the research at any time. Please note that some of the information that has been obtained about you before you chose to withdraw may have been modified or used in the dissertation. These cannot be removed anymore. However, the researcher promises to make good efforts to comply with your wishes as much as practicable.

LETTERS OF APPROVAL

GHANA COLLEGE OF PHYSICIANS AND SURGEONS

OUR REF: BA.100.001.52
Cell: 0243-690073
Email: exams@gcps.edu.gh

P. O. Box MB 429
Ministries-Accra
Ghana

15th June 2023

The Head
Department of Surgery
KATH
Kumasi

Dear Sir/Madam,

REQUEST FOR ETHICAL APPROVAL

Dr. Dominic Annor Mintah, a Senior Resident in Surgery, Ghana College of Physicians and Surgeons has submitted the revised Research Proposal for his Dissertation. Comments by the College Dissertation Review Committee have been duly addressed.

Kindly arrange for this Research Proposal to be submitted to the Research and Ethics Committee of the Komfo Anokye Teaching Hospital for ethical approval to enable him to start his research work which is a requirement for the award of the Fellowship of the College.

Enclosed is a copy of the Research Proposal.

Counting on your usual cooperation.

Yours sincerely,

Prof. Richard M. K. Adanu
RECTOR

cc: Dr. Dominic Annor Mintah

KOMFO ANOKYE
TEACHING HOSPITAL

P. O. Box 1934
Kumasi-Ghana
Tel: +233-3200-22301-4
Fax: +233-3220-24654 / 24624
Website: www.kathhsp.org

Our Ref. No: *KATH IRB AP/ 160/ 23*

Your Ref. No:.....

Komfo Anokye Teaching Hospital Institutional Review Board

12th September 2023

Dr. Dominic Annor Mintah
Komfo Anokye Teaching Hospital
Department of Surgery
P. O. Box SE 1728,
Kumasi.

Dear Dr. Annor Mintah,

Ethics Approval

Protocol title:	A Study of Prostate Cancer Detection Rates in Men Undergoing Transrectal Ultrasound-Guided Prostate Biopsy at KATH, Kumasi
Study site:	Urology Unit of the Directorate of Surgery of the Komfo Anokye Teaching Hospital, Kumasi
Sponsor:	Self-funded

We write in response to your correspondence of 8th August 2023 requesting the Komfo Anokye Teaching Hospital Institutional Review Board (KATH IRB) to review the research study referenced above.

The proposed research study went through the Board review of 5th September 2023 and we are pleased to inform you that KATH IRB has given approval for the following study documents:

- *Protocol version 2.0 last updated 8th August 2023*
- *Informed consent form, version 2 last updated 8th August 2023*
- *Case report form version 2.0 last updated 8th August 2023*

Approval for the study is in effect until **11th September 2024** and it is the responsibility of the Principal Investigator to maintain the study in good standing at the Komfo Anokye Teaching Hospital. The Board anticipates to be notified of the actual start date of your project.

Prior to the expiration of the study approval, you must submit to the KATH IRB an "Application for Continuing Review" along with provision of "Annual Report" when the study is ongoing, or a "Termination Report" if the research has been completed.
You must hastily report to the KATH IRB should a modification to the research be proposed, and without delay if an unanticipated development occurs before the next required review.

Regulations do not permit you to modify conduct of the study in its present form prior to ethics approval; except where urgent action is required to eliminate an apparent immediate hazard to a study subject or other person. It is of utmost importance data generated from this study must be used for the intended purposes only.

Thank you.

Sincerely,

Prof. Kwabena Antwi Danso, BSc, MB ChB, FWACS, FGCS, FACOG
Chairman, KATH IRB