HISTOLOGICAL PATTERNS OF PROSTATE SPECIMENS ANALYZED AT JARAMOGI OGINGA ODINGA TEACHING AND REFERRAL HOSPITAL

BY

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A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN HUMAN ANATOMY

SCHOOL OF MEDICINE

MASENO UNIVERSITY

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DECLARATION

I declare that this thesis is my original work and has not been presented in any other university/institution for consideration of any certification. This thesis has been complemented by referenced sources duly acknowledged. Where text, data (including spoken words), graphics, pictures or tables have been borrowed from other sources, including the internet, these are specifically accredited and references cited using current APA system and in accordance with anti-plagiarism regulations.

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ACKNOWLEDGEMENT

I want to acknowledge the school of Medicine Maseno university for their guidance to this stage.

I also want to acknowledge Dr Dominic Marera, Dr Walter Adero, Dr Willis Ayieko, Dr Demba Norman and the entire M.Sc. class of 2020 for the concerted effort to completion of the course.

DEDICATION

I dedicate this work to Claire Katushabe, Carlton Moen, Genevieve Felister. I also want to dedicate this work to my family Antony Musungu, Brothers, Nelson Mukara, Moses Sechere and Fanuel Indongole. I also want to dedicate the work to my late Mum Alice Osimbo. The close interaction I had with you motivated me in working to completion of this work.

ABSTRACT

Prostate cancer is the fifth most prevalent cause of cancer-related death worldwide in men, accounting for an estimated 366,000 deaths and 6.3 million disability-adjusted life years. There is scarce information on prostate biology and histological characteristics of prostate tumors among men in western part of Kenya who are all exposed to factors that can alter the biology of prostate gland thus predisposing to prostate cancer variants that may be different from the conventional adenocarcinoma. Such scarcity of information could lead to assumptions that all prostate tumors are adenocarcinoma. While some prostate tumors are not aggressive, there are different types of prostate tumors and each prostate tumor type has unique clinical profile. Some prostate tumors have indolent course while others have aggressive course and therefore knowledge of tumor subtypes can help in clinical decision making based on patient profile. This purpose of the study was to investigate prostate histological patterns among patients whose prostate specimens were processed and reported at JOOTRH between 2017 and 2022 with a focus on improving prostate cancer diagnosis and histology reporting. The main objective was to determine histological patterns of prostate specimens at JOOTRH between 2017 and 2022. The specific objectives were to: find out the histomorphology of prostate specimens as reported at JOOTRH, to correlate the patient age and PSA level at the time of prostate specimen collection at JOOTRH and to determine the common prostate tumor type reported in men whose prostate specimens were analyzed at JOOTRH. This was a laboratory based cross sectional study design carried out in pathology laboratory at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) in Kisumu city. The target population in this study constituted prostate specimens which had PSA level, analyzed and reported at JOOTRH between 2017 and 2022. The study was carried out between December 2022 and February 2023. Using Yamane formula, the sample size was determined to be 80. Random sampling was used. A sampling frame consisted of pathology register of the histopathological reports of the prostate specimens analyzed at JOOTRH. Each name in the register was assigned serial numbers. All the numbers were fed in a computer program (randomizer application) to randomly sample 80 names. Data extraction form was used. The extraction form consisted of age of the patient, clinical notes (PSA and Age), macroscopic examination, microscopic examination of the prostate tissues and conclusion. Descriptive and inferential statistics was done by the SPSS version 29 for windows. The frequencies were tabulated in percentages, tables and graphs. Inferential statistics utilized chi-square, ANOVA, independent t test, one sample chi-square and linear regression. P value less than 0.05 was considered statistically significant. There was statistically significant variation (p 0.001) in prostate specimen color as reported in prostate histology at JOOTRH. The researcher could not demonstrate that the prostate specimen surfaces occur with equal changes ($p<0.05$, $X2=23.275$, $df=2$, 95% CI). The results reveal that there is no statistically significant difference in the prostate biopsy sizes in comparison to the mean ($p=0.984$, $t=0.020$, 95% CI). Prostate histology reports were divided into four groups based on the age of the patient (Group 1: 40–49 years, Group 2: 50–59 years, Group 3: 60–79 years, and Group 4: above 80 years). The ANOVA results suggest that the microscopic features of the groups did not differ significantly ($F2, 34 = 1.469$, $p = 0.244$, 95% CI). There is a statistically significant positive correlation between Gleason scores and PSA levels ($p = 0.004$, $r = 0.474$). The Pearson correlation between age and PSA levels was found to have a statistically significant positive correlation ($r = 0.236$, $p = 0.035$, 95% CI). Regarding the prostate tumor type, prostate adenocarcinoma was the predominant tumor type, accounting for all 100% of observed prostate cancer types. The tumor types reported were divided into four groups based on the age of the patient (Group 1: 40–49 years, Group 2: 50–59 years, Group 3: 60–79 years, and Group 4: above 80 years). The ANOVA results suggest that the types of prostate tumors in the groups did not differ significantly ($F3,76 = 1.300$, $p = 0.28$, 95% CI). Based on study results, the health workers should improve documentation of the prostate histology reporting to include core biopsies and gross morphological parameters like volume, description of cell details observed and Biopsies should be requested in cases where there is high likelihood of prostate cancer.

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LIST OF ABBREVIATIONS

BPH: Benign Prostatic Hypertrophy

CI: Confidence Interval

CZ: Central Zone

JOOTRH: Jaramogi Oginga Odinga Teaching and Referral Hospital

MPCA: Metastatic Prostate cancer

Ng: Nanogram

PCa: Prostate Carcinoma

PCSM: Prostate Cancer Specific mortality

PSA: Prostate Specific Antigen

PZ: Peripheral Zone

PIN: Prostatic Intraepithelial Neoplasia

SSA: Sub-Saharan Africa

TZ: Transition Zone

WHO: World Health Organization

OPERATIONAL DEFINITIONS OF TERMS

Biopsy: Tissue obtained from a prostate of a man whose PSA levels are more than 10ng/mL

Histopathology: Study of tissues under microscope to detect any abnormality such as cancer

Characterize: To group prostate tissues into various prostate cancer subtypes based on microscopic appearance

Gleason score: Gleason score refers to a scale the compares how cells under study deviates histologically from the normal cells. Numbers are assigned to represent the degree of variation from normal cells.

Histomorphometry: The quantitative measurement and characterization of microscopic images and involves measurements.

Epstein score: This refers to a revised version of the Gleason score which makes characterization of cells easier by grading cells.

Histomorphology: Refers to shape and appearance of the cells when viewed through a microscope

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CHAPTER ONE

INTRODUCTION

1.1 Introduction

The study was about histological patterns of prostate specimens analyzed at Jaramogi Oginga Odinga teaching and referral hospital Kisumu (JOOTRH) between 2017 and 2022. While some prostate tumors are not aggressive, there are different types of prostate tumors and each prostate tumor type has unique clinical profile. Some prostate tumors have indolent course while others have aggressive course and therefore knowledge of tumor subtypes can help in clinical decision making based on patient profile. This chapter covers background information, problem statement, objectives of the study, purpose of the study, scope of the study, significance of the study, study limitations and delimitations, study assumptions and operational definition of terms.

1.2 Background information

Prostate gland is regarded to be at risk of old age-related conditions such as benign prostatic hyperplasia (BPH) and prostate carcinoma (Pca) (Henry et al., 2018a; Murray, 2021). The stages of human prostatic development are as follows: (a) pre-bud urogenital sinus (UGS); (b) emergence of solid prostatic epithelial buds from urogenital sinus epithelium (UGE); (c) bud elongation and branching; (d) canalization of the solid epithelial cords; (e) differentiation of luminal and basal epithelial cells; and (f) secretory cytodifferentiation. The gross anatomy of the human fetal prostatic is included in this process (Hill M., 2023). The mainstay of therapy for prostate cancer is androgen suppression. Because of the loss of luminal cells, the typical gland involutes to around 90% of its initial size. When androgen is restored, the prostate regenerates, and stem cells are thought to play a role in this process (Karthaus et al., 2020).

Prostate cancer is the fifth most prevalent cause of cancer-related death worldwide, accounting for an estimated 366,000 deaths and 6.3 million disability-adjusted life years as of 2015. It is in the top five malignancies for both incidence and mortality globally (Pernar et al., 2018). According to estimates from the 2018 Global Cancer Statistics, men of African descent have a 60% higher chance of developing prostate cancer and a three times greater chance of dying from prostate cancer than men who are not of African descent. Prostate cancer is also the leading cause of death in sub-Saharan Africa accounting for 10.2 percent of all malignancies and 17.3 percent of cancers in Kenyan men (Okyere et al., 2023).

Benign Prostate Hyperplasia (BPH) is a non-malignant prostate enlargement due to hyperplasia of prostate tissue and is a common cause urine obstruction (Figure 1) leading to lower urinary tract symptoms in men as they age (Jepsen & Bruskewitz, 1998). Prostate cancer is a significant etiology of pathology in men globally (Murray, 2021).

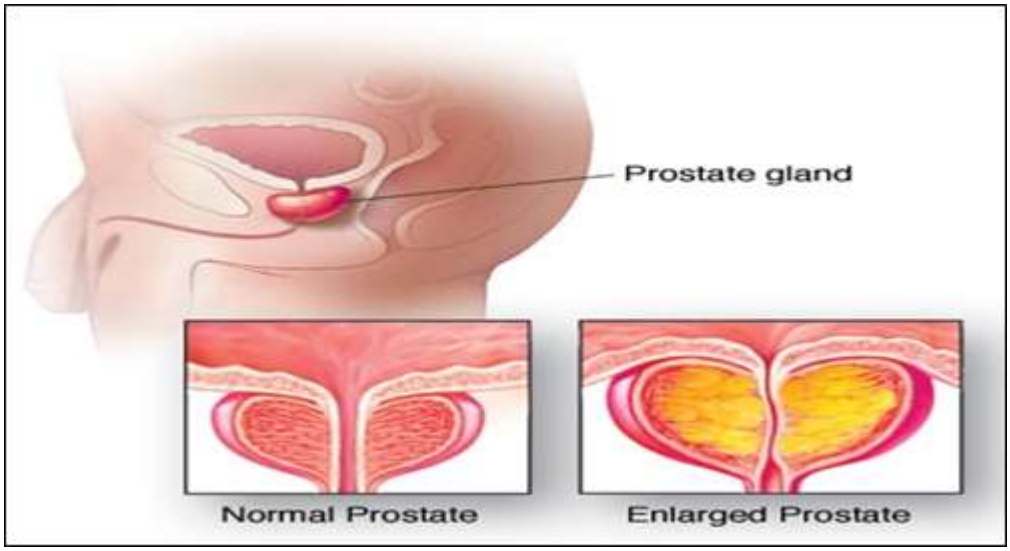

Figure 1: Diagram showing normal and enlarged prostate gland **(Gilbert et al., 2015a)**

BPH and Pca causes characteristic histologic and gross anatomical alterations to the prostate tissue architecture which can then be used to make a histological diagnosis. Histologically, BPH is characterized by the proliferation of stromal and epithelial cells in the transition zone of the prostate which surrounds the urethra thus narrowing the urethra causing bladder outlet obstruction (Figure 1) (BOO) and this leads to clinical manifestations similar to those of lower urinary tract infections (Jepsen & Bruskewitz, 1998). On the other side, prostate malignancy is characterized by the presence of large Golgi-like atrophic spaces parallel to the surface of the prostate represented by thin elongated tubular structures on hematoxylin and eosin slides. In contrast adenosis lacks acinar organization and therefore closely mimics low-grade prostate cancer although it is non-cancerous. High-grade prostatic intraepithelial neoplasia shows prominent intraluminal papillary protrusions while intraductal carcinoma consist mainly of spherical, ellipsoidal or scaly enlargements with confluent complex margins (Verhoef et al., 2019). Grossly, BPH and Pca exhibit alterations in color, size and surface. In prostate tumors, tan, white, yellow, and orange tumors made up 30%, 30%, 30%, and 24%, respectively, of those that can be definitively recognized. Orange color of tumors in the transition zone predominate (61%) compared to tan or whitish tumors in the peripheral zone (35% and 33%) (Lindh et al., 2018).

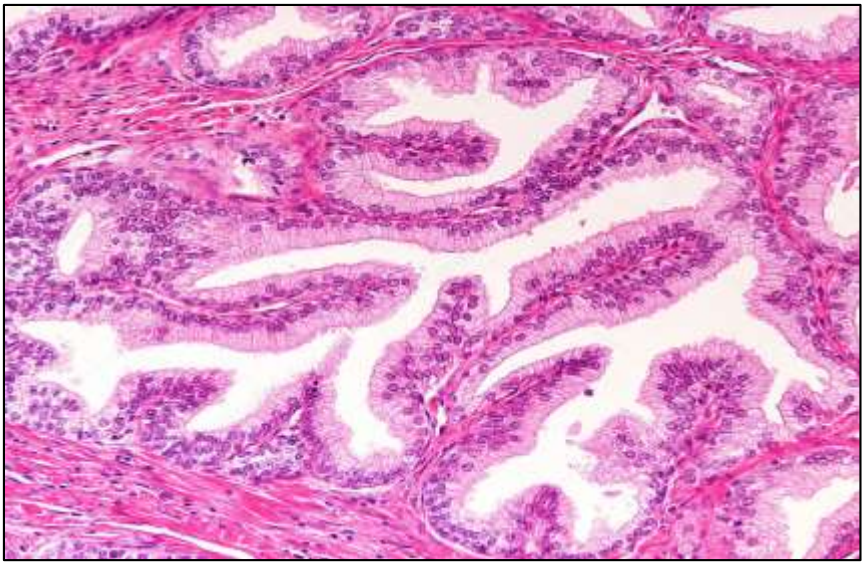

Figure 2: Photomicrograph of normal human prostate histology slide *(Divatia & Ro, 2016)*

The Gleason score of the patient is one element of the decision-making process that aims to improve quality treatment decision-making and promote risk communication. The idea of glandular dedifferentiation is the foundation of the Gleason scoring system (GSS) in which case primary and secondary histologic pattern are quantified by the method, and each pattern is rated from 1 to 5, with grades 1 and 2 being categorized as benign lesions. The total of the two patterns is then reported as the Gleason sum, for example, 3+3=6, 4+3=7. Globally speaking, Gleason sums of 6 and 7 are regarded as low risk, respectively, and those of 7 or greater as intermediate risk. (Tagai et al., 2019).

The prostate consists of glands and stroma both of which are tightly packed within the prostate capsule (Henry et al., 2018b). The prostate is located under the bladder in front of the ampulla part of the rectum. It surrounds the prostatic part of the urethra which is the passageway for urine from the bladder. A normal prostate weighs up to 20 grams and the seminal vesicles are located on either side of the base of the prostate and measure 4 cm x 3 cm x 2 cm. (Henry et al., 2018b).

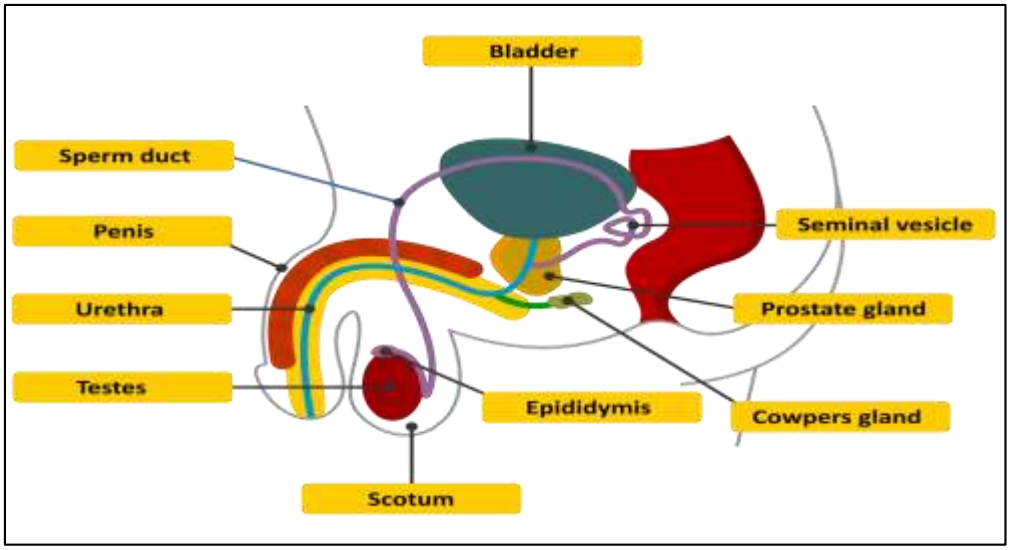

Figure 3: Anatomical location of prostate gland **(adapted from Abdelsayed et al., 2015)**

The prostate has unique anatomical architecture that make certain regions prone to BPH or Pca. Histologically the prostate consists of three tissues; fibrous, muscular and glandular and three main glandular regions that are histologically and biologically distinct; the peripheral zone, central zone and transition zone with each region of the prostate exhibiting distinct histological characteristics associated with susceptibility to various prostate pathologies (Bhavsar & Verma, 2014; Ittmann, 2018; McNeal, 1988). The central zone is resistant to prostate carcinoma and other prostatic lesions and the transition zone is largely affected by benign prostatic hyperplasia. In cross section the prostate is divided into two areas; the external and internal compartments separated by an internal fibrous capsule (surgical capsule) (Humphrey, 2017). Carcinoma affects the peripheral zone mostly because it is rich in glands and benign prostatic hypertrophy (BPH) affects the central region of the prostate (Gilbert et al., 2015). Cells of a prostate gland with BPH or Pca secrete prostate specific antigen (PSA) in large amounts above the normal levels of 0-4ng/ml and thus elevated PSA is biological marker for the diagnosis of prostate cancer therefore early diagnosis

using prostate-specific antigen (PSA) facilitates disease detection; the higher the level of PSA the higher the chance to have prostate cancer (Negahdary et al., 2020; Zhang & Sun, 2018).

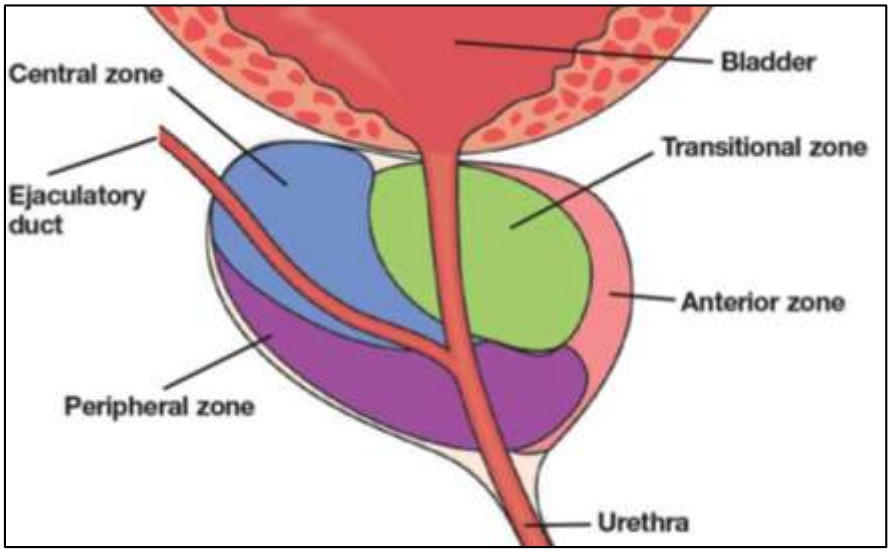

Figure 4: Diagram showing regions of the prostate gland **(adapted from Miyai et al., 2014)**

Although prostate adenocarcinoma is the most common subtype of prostate tumor, variations in histology occur due to geographical, racial and dietary factors among populations (Grignon, 2004). Age, genetic predisposition, and family history are risk factors for prostate cancer. Other variables might include things like nutrition, exercise, smoking, certain drugs, and work-related issues (Bergengren et al., 2023). Variation can result in rare Pca variants that are aggressive with poor clinical results thus knowledge of the histological differences in prostate cancer is important because different types of prostate cancer are associated with different clinical outcomes and may have different treatment options (Montironi et al., 2007). The aim of this study was to determine

histological patterns of prostate specimens as analyzed and reported at Jaramogi Oginga Odinga Teaching and referral hospital, Kisumu Kenya.

1.3 Problem statement

Prostate cancer is the second common cancer diagnosis made in men behind skin cancer. Globally, prostate cancer is the fifth leading cause of death and may be asymptomatic at the early stage with an indolent course (Rawla, 2019). Diagnosis of prostate malignancy is made on the underpinning of urinary tract symptoms and elevated PSA levels (>10ng/mL) which then prompts the need for biopsy to confirm the diagnosis through histological characterization. There has been global shift to genetically modified diet and generally people use high energy foods in form of fast foods which according to US National Cancer Institute (2018) can alter prostate molecules and be molecular determinants of prostate cancer variation. The molecular basis of carcinogenesis in the prostate cancer are emerging due to the fact that alterations in molecules that regulate the cell cycle and apoptosis contribute to the pathogenesis of prostate cancer. While studies done in the western world have demonstrated that acinar adenocarcinoma is common, variations due to changing lifestyle, fast foods and genetics among African men cannot be ignored. There is scarce information on prostate biology and histological characteristics of prostate tumors among men in western part of Kenya who are all exposed to factors that can alter the biology of prostate gland thus predisposing to prostate cancer variants that may be different from the conventional adenocarcinoma. Such scarcity of information could lead to assumptions that all prostate tumors are adenocarcinoma. Such assumptions can cause delayed decision making in care. In addition, geographical and racial factors are documented by American society of urology as independent risk factors for prostate tumors. Men in western part of Kenya could have different prostate histological characteristics given different geography and race. Such knowledge will guide the

aggressiveness in pursuit of treatment for patients whose prostate specimens are reported positive for cancer. The study sought to determine histological characteristics of prostate specimens from men in western part of Kenya that were processed at JOOTRH between 2017 and 2022.1.4 Purpose of the study

The purpose of the study was to investigate prostate histological patterns among patients whose prostate specimens were processed and reported at JOOTRH between 2017 and 2022 with a focus on improving prostate cancer diagnosis and histology reporting.

1.4 Research Objectives

1.4.1 General objective

To determine histological patterns of prostate specimens analyzed at JOOTRH between 2017 and 2022

1.5.2 Specific objectives

a) To describe prostate specimen histomorphology as reported at JOOTRH

b) To correlate the patient age and PSA level at the time of prostate specimen collection at JOOTRH

c) To determine the common prostate tumor type reported in men whose prostate specimens were analyzed at JOOTRH

1.5 Research hypothesis

a) There is no variation in histomorphology in prostate specimens analyzed at JOOTRH

b) There is no relationship between PSA and patient age at the time of prostate biopsy at JOOTRH

c) There is no variation in prostate tumor in specimens analyzed at JOOTRH

1.6 Significance of the study

The findings of the study will benefit hospitals, healthcare workers and patients. There are various prostate tumor types with different characteristics. Some are aggressive while some are non-aggressive. Some are associated with elevated PSA while others occur in patients with normal PSA level. Therefore, knowledge of prostate tumor types and their characteristics will help healthcare workers design appropriate evidence-based intervention among men presenting for prostate symptom evaluation. This in turn will contribute to help hospitals improve quality of care in urological patients with prostate symptoms who seek care. The findings of this study may then generate information that can inform new strategies and corresponding resources to improve diagnosis based on histological patterns of prostate specimens analyzed at JOOTRH. Patients who present with elevated PSA levels will have better outcomes because the findings of this study will improve clinical decision making by doctors regarding histopathology reports from such patients. The knowledge of prevalence of specific prostate cancer subtype will help future researchers to investigate risk factors associated with specific prostate cancer subtypes in Western Kenya

1.7 Scope of the study

The study was conducted at JOOTRH because this is a regional referral hospital in western Kenya and therefore suitable because most of patients are referred to this hospital for biopsy and subsequent histopathological analysis. Secondly, JOOTRH has a well-equipped laboratory as well as human resource to analyze prostate specimens.

1.8 Study assumptions

The study worked on several assumptions. First, that histology reports are well documented at all time at JOOTRH pathology laboratory. Secondly, that all prostate specimens were adequate to draw a conclusion. Thirdly, that all histological reports describe prostate lesions in a way that can distinguish prostate cancer subtypes.

1.9 Limitations of the study

While JOOTRH is a western regional referral hospital, the researcher was not able to verify the geographical distribution of men whose prostate specimens analyzed confirmed prostate cancer. The proposed study utilized prostate histology reports done at JOOTRH and as such the findings may not be generalizable to Kenyan regions other than western Kenya.

1.10 Study delimitations

While there are other private hospitals that process prostate biopsies in western Kenya, the study included prostate biopsies analyzed at JOOTRH pathology laboratory only between 2017 and 2022.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

While some prostate tumors are not aggressive, there are different types of prostate tumors and each prostate tumor type has unique clinical profile. Some prostate tumors have indolent course while others have aggressive course and therefore knowledge of tumor subtypes can help in clinical decision making based on patient profile. This chapter presents general literature review and empirical literature review on histological characteristics of prostate specimens in relation to histomorphology, PSA and patient age and common prostate tumor types.

2.2 General literature review

Cancer causes more deaths globally than HIV, TB and malaria combined with more than 70% of the global cases occurring in the low- and middle-income countries (Magak, 2016). Magak further states that cancer is the 3rd highest cause of morbidity in Kenya after infectious and cardiovascular diseases and contributes to about 7% of deaths annually and majority (81.1%) of the malignancies occur in adults aged 30 years and above and prostate malignancy constitutes 9% of the total malignancies in Kisumu. (Wambalaba et al., 2019) states that most frequent age at diagnosis of cancers in females in Kenya is 52, and for men is age 62. (Wambalaba et al., 2019) observes that breast cancer is more prevalent in women in addition to cancer of the cervix, while for men carcinoma of prostate and esophagus are common. Wambalaba further indicates that people living in the rural areas are most vulnerable contrary to local perception that cancer affects mostly adults in urban areas.

Prostate cancer incidence is on the rise due to the interaction of many risk factors, including age, race, positive family history, vasectomy, and dietary fat consumption (Gandaglia et al., 2021;

Pienta, 1993). Using the available data, the best practices for diagnosing and treating prostate cancer were examined by (Litwin & Tan, 2017). The authors found that improvements in these areas have made it possible to better classify patients according to risk and enable medical professionals to suggest a course of treatment based on the prognosis and preferences of the patient.

Clinical and patient treatment are fundamentally impacted by the diagnosis of prostate cancer (PCa) and appropriate staging. Rectal examination and the prostate-specific antigen (PSA) blood test continue to be the mainstays of screening, and multiparametric magnetic resonance imaging is the gold standard for local staging despite significant advancements in biology and imaging (Descotes, 2019). Many studies have focused on risk factors for prostate cancer, prevalence of prostate cancers and techniques of diagnosis but there appear to be scanty literature on prostate histological changes associated with prostate pathologies.

2.3 Empirical literature review

2.3.1 Prostate histomorphology in prostate lesions at diagnosis

A thorough cellular anatomy of human prostate is crucial for explanation of cellular origins of benign prostatic hyperplasia and prostate cancer. The human prostate gland is a distinct gland with distinct histological regions. The peripheral zone surrounds the outside of the prostate and accounts for the majority of prostate cancers. Benign and malignant prostate diseases are limited to the proximal and distal end zones respectively. The peripheral zone makes up 70 percent of normal prostate tissue while the transitional zone is located near the prostatic urethra and it is invisible in young men and makes up five percent of the prostate. Benign prostatic hyperplasia in most elderly men significantly increases the area of metastasis and chronic prostate tumors occur at various stages of prostate cancer. (Henry et al., 2018b; Ittmann, 2018; Paner et al., 2012)

Prostate cancer means a malignant tumor of the prostate. Most malignant tumors originate from epithelial tissue and are called carcinomas (Humphrey, 2017). Humphrey also noted that ductal (intraductal) carcinoma develops when the tumors epithelial cells divide to fill the large ducts of the acini and prostate. Ductal prostate cancer represents an advanced stage of prostate cancer and is associated with advanced adenocarcinoma. Humphrey concluded that adenocarcinoma of the prostate shows an abnormal pattern of glandular structures with disruption of the benign epithelial-stromal junction.

Forty-one (29%) of patients with atypia had cancer diagnosed; 26 of the 41 (66%) had Gleason 6 cancer, 20% had Gleason 7 cancer, and 7% had Gleason 8 cancer (Gleason 6 not recorded). Age, race, family history, PSA, PSA density (PSAd), number of prior biopsies, and duration between previous and repeat biopsies did not significantly correlate with cancer diagnosis. Histological inflammation was connected to an 85% lower risk of malignancy on repeat biopsy in multivariate regression (Kopp et al., 2011). Compared to more common pathological prognostic indicators, the absence of HGPIN in RRP specimens indicates a considerably lower likelihood of tumor multifocality, perineural invasion, and eventually biochemical recurrence (Pierorazio et al., 2007). Korean men with clinical prostate cancer had the same prevalence of HGPIN as men from other parts of the world. A decreased prevalence of HGPIN was seen in Asian men who underwent cystoprostatectomy, as evidenced by prior research and our findings. The disparity in HGPIN prevalence between Asian and Western males with incidental prostate cancer raises the possibility that there are variables inhibiting the progression of the disease or that prostate cancer in Asian populations has different characteristics (Han et al., 2007).

There are two distinct intraductal lesions: high-grade prostatic intraepithelial neoplasia (HGPIN) and intraductal carcinoma of the prostate. HGPIN is regarded as a precancerous lesion, whereas

the intraductal carcinoma is frequently accompanied by invasive carcinoma and has an aggressive course. Atypical cribriform lesions (ACLs), which fall between intraductal prostate carcinoma and HGPIN morphologically but are not well described, are another type of lesion (Miyai et al., 2014).

The characteristic of intraductal prostate cancer that affects the ducts and/or acini is often accompanied with extra-prostatic extension and seminal vesicle invasion, as well as a high Gleason score, a significant tumor volume, and adverse prognostic markers. Poorer results are associated with the occurrence of intraductal carcinoma, which are atypical cribriform lesions of the prostate. This group of lesions also includes high-grade prostatic intraepithelial neoplasia among other intraductal proliferations (HGPIN) (Divatia & Ro, 2016). While there appear to be attempts to describe the changes associated with prostate histology by various authors, there still exists scanty literature on key parameters such as specimen colors, surfaces and texture that could correlate with disease severity.

2.3.2 Age and PSA levels in prostate cancers at diagnosis

There is a significant correlation between age and level prostate in the serum (Maciel et al., 2018) and the optimal starting age for initial PSA testing to rule out prostate malignancies should be 57.5 years (Liu et al., 2020). It has been observed that the mean and median ages of patients admitted for prostate cancer in countries like China is 70 and 63 years while among other ethnic groups was 73 and 71 years (Feng Wang et al., 2012). Wang adds that whereas Uygrs (ethnic group in China) had higher prostate cancer than Huns (ethnic group in China) in the age ranges of 50–59 and 60–69, the age at prostate cancer diagnosis in both study groups was 70–79 years.

Other study findings like (Bernard et al., 2020) indicate that those over 75 years of age had a mean prostate cancer-specific survival at 5 years that was 6.7 months shorter than those under that age (95% confidence interval, (5.5-7.8 months) and men aged more than 75 years have a 49 percent

increase in the rate of prostate cancer-specific mortality compared to those aged below 54 years. Bernard concludes that age is an independent predictor of mortality in men diagnosed with metastatic prostate cancer even with effective therapies and such patients presents with higher PSA levels. In other studies, (Kopp et al., 2011; Matti et al., 2022), it was noted that PSA reference limits increases with age and significant ethnic differences were present.

Prostate-specific antigen (PSA) blood tests and subsequent prostate biopsies, if PSA levels are elevated, are extensively used screening procedures for prostate cancer (Gilbert et al., 2015b). Gilbert adds that PSA testing is utilized for early detection since therapy can alter men's longevity and most prostate tumors found by screening have a low likelihood of progressing. Furthermore, PSA levels can predict metastatic bone disease. The likelihood of a positive bone scan increased to 50% if the PSA level was higher than 50 ng/L from 40% when it was between 20 and 50 ng/L (Gleave et al., 1996). Gleave also noted that a serum PSA level of less than 10 ng/L was a significant negative predictor of a positive bone scan in 290 patients with a PSA level of less than 10 ng/ml.

A PSA level more than 10 ng/ml is a strong predictor of prostate cancer in males with probable bone metastases, according to Gleaves findings, which are in agreement with Gilberts' findings. It is expected that men with BPH and Covid-19 would experience significant increases in PSA levels over the course of the disease due to SARS-CoV-2 infection. Similar findings were reported by (Cinislioglu et al., 2022) that the measurement of PSA values for use in the diagnosis, differential diagnosis, and follow-up of prostate diseases during the acute phase of infection with Covid and the initial phase of infection treatment may result in false evaluations that may affect the diagnosis and treatment steps of prostate diseases in these patients.

In a minority of people PSA levels (4-10 ng/ml) may indicate advanced prostate cancer. Patients with high-grade locally advanced prostate cancer and low PSA levels are associated with a greater risk of prostate disease progression but not with biochemical recurrence (Lu et al., 2021). Lu noted that serum PSA may not be a reliable marker for detecting prostate cancer progression in this unique population and therefore recommended the use of other biomarkers or imaging to monitor these patients. In such patients, PSA screening may have little or no effect on prostate cancer-related mortality (Ilic et al., 2018) and prostate-specific antigen (PSA) screening for prostate cancer can prevent some men from dying from the disease (Black, 2014). In some variants of prostate carcinoma such as neuroendocrine, patients present with low PSA level or normal PSA level may be regarded a poor prognostic indicator (Wang et al., 2019). While most authors indicate that PSA levels increase with age, there is not much in relation to prostate tumors presenting with normal PSA levels.

2.3.3 Types of prostate tumors

Males can acquire a variety of prostate cancer subtypes, including adenocarcinomas and neuroendocrine tumors, and adenocarcinomas account for the great majority of prostatic tumors that form in adult males (Grignon, 2004). Visceral metastases are more common in those with neuroendocrine prostate cancer (Zhou et al., 2022) which is an aggressive histologic subtype of prostate cancer that typically develops in advanced prostate cancer as a means of developing resistance to treatment and this is partly due to late diagnosis and a lack of efficient therapy options (Conteduca et al., 2019; Yamada & Beltran, 2021).

Adenocarcinoma has two main variants; acinar and non-acinar and most prostate cancers in males are acinar adenocarcinomas (Baig et al., 2015a; Humphrey, 2017). Non-acinar adenocarcinoma like basal squamous cell carcinoma, and other histological forms of prostate carcinoma like adeno-

squamous carcinoma and urothelial carcinoma are rare accounting 5-10% of prostate cancers yet more aggressive (Mazzucchelli et al., 2008). For prostate cancer, there are two significant subgroups. It is possible to make a morphological and immunohistochemical diagnosis of ductal and acinar prostate cancer and a high pathological grade will be observed in ductal adenocarcinomas. When ductal adenocarcinomas are compared to acinar adenocarcinomas, data imply a more aggressive natural history (Baig et al., 2015a). Therefore, knowing such histological differences in prostate tumor types is important since different types of prostate tumors are associated with different clinical outcomes and may have different treatment options (Randolph et al., 1997).

Ductal and acinar prostate cancer can be distinguished histologically using immunohistochemical and pathological techniques. In contrast to acinar tumors, the majority of patients with ductal prostate tumor type are likely to be younger than 60 years old at the time of diagnosis and that substantial elevations in blood PSA levels tend to be identified in most patients with both prostate cancer subtypes. The majority of ductal adenocarcinomas are much more aggressive than the rest (Baig et al., 2015b). In addition to the common acinar morphology observed in most prostate adenocarcinomas there are a range of morphological variants and subtypes of prostate cancer (Fine, 2012). Fine elaborates that those unusual entities include cancer forms that arise from the differentiation of prostate acinar or basal duct cells and associated prostate tissues with unique clinical features or therapeutic approaches to normal prostate adenocarcinoma that may lead to Gleason grading difficulties.

While foam gland and conventional cell types varied in patients with adenocarcinoma, ductal ring and sarcomatoid cell types had aggressive growth patterns and high scores, atrophic and pseudohyperplastic cell types had mild growth patterns, and pseudohyperplastic cell types had low

scores. Prostate adenocarcinoma's histological type and the employed staging system are thought to be compatible (PĂnuŞ et al., 2020). The 2022 WHO classification recognizes sarcomatoid cell-like carcinoma of the prostate prostatic intraepithelial neoplasia (PIN)-like carcinoma and pleomorphic giant cell adenocarcinoma of the prostate as true subtypes of acinar PCa. Abnormal histological pattern that includes atrophic foam cells microcystic pseudohyperplasia and mucous membranes. Non-cynic forms of prostate cancer include other ductal adenocarcinomas adenoidal PCa and therapy-related neuroendocrine carcinomas and adenosquamous squamous cell carcinomas non-adenoid PCa and adenoidal (basal) cystic carcinomas of the prostate (PĂnuŞ et al., 2020; Wasinger et al., 2022). Prostate adenocarcinoma has extensively been reviewed but there is no extensive information on the other forms of prostate carcinoma from many authors.

2.3.4 Prostate cancer staging and diagnosis technique

Given the enormous number of men receiving a prostate cancer diagnosis, it is preferable to accurately stratify individuals based on their risk in order to prevent overtreatment and needless biopsies in low-risk patients and to inform treatment decisions for high-risk patients. The provided biomarkers are helpful supplementary precision medicine tools that help guide treatment decisions and facilitate collaborative decision-making (Uhr et al., 2020).

Prostate cancer can be staged in two different ways: clinically and pathologically. The outcomes of a digital rectal exam (DRE), prostate-specific antigen (PSA) testing, and the Gleason score—which is used to grade prostate cancer—are used to determine clinical staging. The information discovered during surgery and the laboratory results of the prostate tissue extracted after surgery are the foundations for pathologic staging (Prostate Cancer: Stages and Grades | Cancer.Net, n.d.).

In patients following radical prostatectomy, the Gleason score can predict the mortality specific to prostate cancer with a very high degree of accuracy. Therefore, to forecast the mortality specific

to prostate cancer, nomograms should place greater weight on the Gleason score (Mithal et al., 2015).

2.3.5 Summary of information gaps

There seems to be little research on the changes in prostate histology linked to prostate diseases, despite the fact that several studies have concentrated on risk factors for prostate cancer, the frequency of prostate malignancies, and detection methods. Prostate adenocarcinoma has been explored in great detail; however other kinds of prostate cancer have not been thoroughly discussed by several writers. There is little information on prostate cancers presenting with normal PSA levels, despite the majority of writers' assertion that PSA levels rise with age. There is currently a dearth of research on important characteristics including specimen colors, surfaces, and textures that may be correlated with the severity of the illness, despite the authors' apparent attempts to characterize the alterations related to prostate histology.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

While some prostate tumors are not aggressive, there are different types of prostate tumors, and each prostate tumor type has a unique clinical profile. Some prostate tumors have an indolent course while others have an aggressive course, and therefore knowledge of tumor subtypes can help in clinical decision-making based on patient profiles. This chapter includes the following: research approach, research design, location of the study, target and study populations, sampling procedures, research instruments, validity and reliability of research tools, data collection methods, ethical considerations, and data analysis.

3.2Research Approach

To address the key research objectives, the research used quantitative methods and secondary sources from the histopathological reports.

3.3 Research design

The study was a analytical and descriptive cross sectional retrospective study design between 2017 and 2022.

3.4 Location of the study

Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) is a level five hospital located in Kisumu Kenya and has a well-established pathology laboratory with adequate staffing and necessary equipment to analyze histology specimens.

3.5 Target specimens

The samples in this study constituted prostate specimens which had PSA level at the time of reporting.

3.5.1Inclusion criteria

All Histology reports with PSA values indicated.

3.5.2 Exclusion criteria

Prostate specimens analyzed as follow up to treatment were excluded. Histology reports without PSA values were excluded.

3.6 Sample size

The formula below (Yamane Taro, 1967) was used because the study utilized a small sample.

$n=N/(1+ N(e)^2)$

In the formular above;

n is the required sample size from the population under study

N is the whole population that is under study (100)

e is the precision or sampling error (0.05)

The total number of prostate samples with PSA at JOOTRH in the study period was 100. Using Yamane formula, the sample size is 80

3.7 Sampling procedures and techniques

Random sampling was used. A sampling frame consisted of pathology register of the histopathological reports of the prostate specimens analyzed at JOOTRH. Each name in the register was assigned serial numbers. All the numbers were fed in a computer program (randomizer application) to randomly sample 80 names out of those so that each had an equal chance of getting selected.

3.8 Research instruments

Data extraction forms were used (appendix I). The extraction form consists of age of the patient, clinical notes (PSA and Age), macroscopic examination, microscopic examination of the prostate tissues and conclusion.

3.9 Validity and reliability

All instruments were reviewed by the researcher's supervisor against the objectives of the proposed study. Each section of the data form was evaluated to determine how relevant the information collected is to the proposed objective. The data extraction forms were pretested by giving them to one staff member at the JOOTRH pathology lab, who collected pre-test data by collecting data from the pathology registers. The information gathered was then evaluated to check for consistency.

3.10 Data collection methods and procedures

The researcher collected the data from JOOTRH pathology with the help of two research assistants who were laboratory technicians working in the pathology laboratory and conversant with retrieving soft copy data from the storage site. The data from each prostate pathology report was then transferred into each data extraction form for each patient profile: the age, clinical notes including PSA levels, microscopic and macroscopic examination, and conclusion will be extracted and recorded in the research data extraction form (Appendix I). Photographs of slides mounted on a microscope were also taken for prostate tissues with prostate cancer and with benign prostatic hypertrophy.

Procedures for tissue processing using hematoxylin and eosin at JOOTRH is as follows (Wick, 2019):

a) Biopsy (either core biopsy or prostatectomy specimen)

b) Tissue fixation achieved by immersing the biopsy tissue in formalin 2%

c) Tissue processing: once the fixed tissue reaches the pathology lab it processed via a series of steps as follows:

i. Dehydration of tissue achieved by immersing the tissue in varying degrees of alcohol to remove water.

ii. Clearing achieved by immersing dehydrated tissues in xylene so that alcohol is removed from tissue.

iii. Waxing in which the cleared tissue is waxed at 56^0 C temperature.

iv. Blocking in which a block of wax is made by cooling the wax

v. Microtomy where the block with tissue is sliced using a microtome into thin slices that can be mount on a slide after staining

vi. Staining in which the slices are stained with eosin and hematoxylin. This stain makes the nucleus blue and cytoplasm and other organelles pink.

d) Reading through microscope and interpretation of any abnormality the reporting.

3.11 Data analysis and dissemination

Descriptive and inferential statistics were done with SPSS version 29 for Windows. For objective 1, one sample chi-square was used to test the hypothesis that there is no variation in specimen colour and surface. One sample t test was used to assess if the specimen size differed significantly from the mean. ANOVA was used to check whether microscopic features differed significantly. A post hoc analysis based on the Levine statistic was achieved by Dunnett's 3 analysis to check which group contributed to differences. The Pearson statistic was used to assess the relationship

between Gleason scores and PSA levels. For objective 2, Pearson correlation was used to assess the relationship between PSA levels and the age of the patient at the time of the biopsy. For objective 3, an ANOVA was used to test the hypothesis that there were significant differences between the prostate tumours observed. The frequencies were tabulated in percentages, tables, and graphs. P value of less than 0.05 was considered significant.

3.12 Ethical considerations.

This study was approved by Maseno University School of graduate studies (Appendix II). The study was licensed by the National Commission of Science, Technology, and Innovation (NACOSTI) under license number NACOSTI/P/23/22845 (Appendix V). The study was approved by the JOOTRH ethics committee via letter reference number ISERC/JOOTRH/659/22 (Appendix III). The data collection was allowed by the JOOTRH hospital CEO via letter reference number GEN/21A (Appendix IV). No patient identifiers were collected during the study. Data collected was anonymized to ensure identity protection.

CHAPTER FOUR

RESULTS

4.1 Introduction

This section contains study findings on the histological patterns of prostate specimens analyzed and reported at JOOTRH between 2017 and 2022. This section includes the response rate and presentation of study findings categorized as descriptive analysis and statistical analysis in tandem with study objectives.

4.2 Response rate

This was a retrospective study that reviewed 80 prostate histology reports between 2017 and 2022 at JOOTRH. All the extraction reports were filled thus the response rate was 100%.

4.3 Histomorphology of prostate specimens

4.3.1 Specimen color

A total of 80 prostate histology reports for prostate specimens were retrieved. The prostate specimen colors reported were categorized as white, tan/white, tan/brown, and tan/grey. Prostate color was not reported in eight reports. Of the 72 specimens observed, 50 (69.4%) were reported to be white, 12 (16.7%) were reported to be tan/white, 9 (12.5%) were tan brown, and 1 (1.4%) was tan grey (Table 1).

Table 1: Prostate tissue color

		Frequency	**Percent**
Valid	White	50	62.5
	Tan/white	12	15.0
	Tan/Brown	9	11.3
	Tan/grey	1	1.3
	No colour reported	8	10.0
Total		**80**	**100.0**

Figure 5: Image of prostate colors

Key: A=Tan brown, B=Tan Grey, C=White

One sample chi-square was used to test the hypothesis that the categories of prostate specimen color occur with equal chances. One sample Chi-square statistic was used to examine this hypothesis. There was statistically significant variation (p 0.001) in prostate specimen color as reported in prostate histology at JOOTRH (Figure 5).

4.3.2 Specimen surface

The surface of prostate specimens was described in clinical categories: coarse, shrunken, or nodular (Figure 6). Of the 80 specimens, 47 (58.75%) had prostate biopsy surfaces that were coarse, followed by nodulated surfaces (16; 20.00%) and shrunken surfaces (17; 21.25%); Figure 7. The study sought to establish whether the texture reported was due to chance.

Table 2: Chi-square test of fitness output

Test Statistics	
	Surface texture
Chi-Square	23.275[a]
df	2
Asymp. Sig.	.000

One sample chi-square test of fitness was used to test the hypothesis that prostate surfaces as reported occurred by chance. The researcher could not demonstrate that the prostate specimen surfaces occur with equal changes ($p<0.05$, $X^2=23.275$, df=2, 95% CI) (Table 2). Hence H1 was supported.

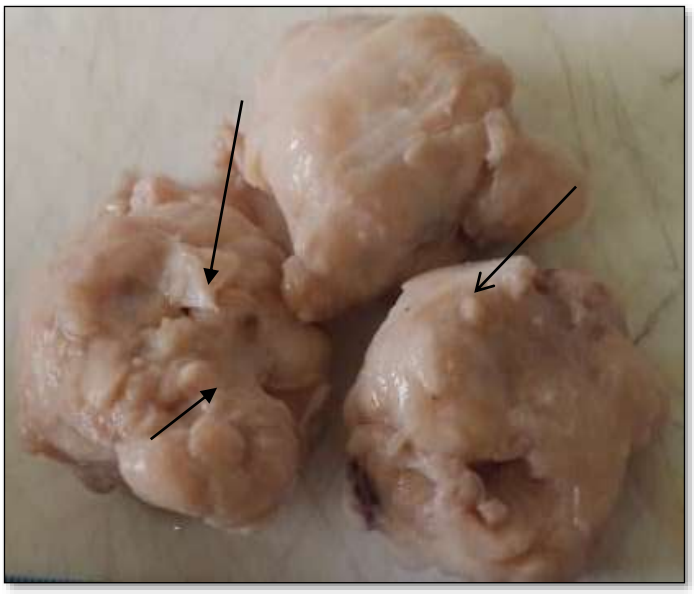

Figure 6: Photograph of nodulated prostate gland (arrow indicate specific nodules)

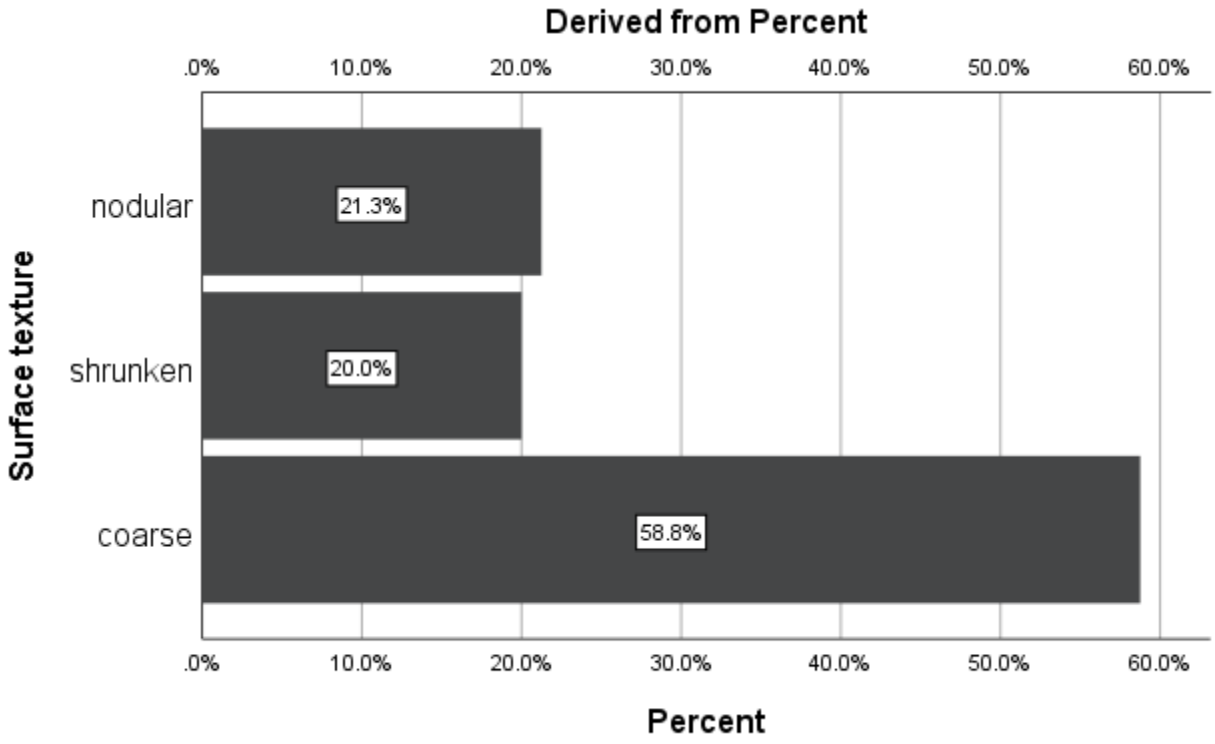

Figure 7: Frequency distribution of Prostate surface texture

4.3.3 Specimen size

Majority of the biopsy specimens 55 (68.8%) measured between 0-29 mm, 12 (15%) measured 30-59 mm, 7 (8.8%) measured 60-89, 3 (3.8%) measured 90-119, 2 (2.5%) measured >150 mm and 1 (1.3%) measured 120-149 mm (Figure 8).

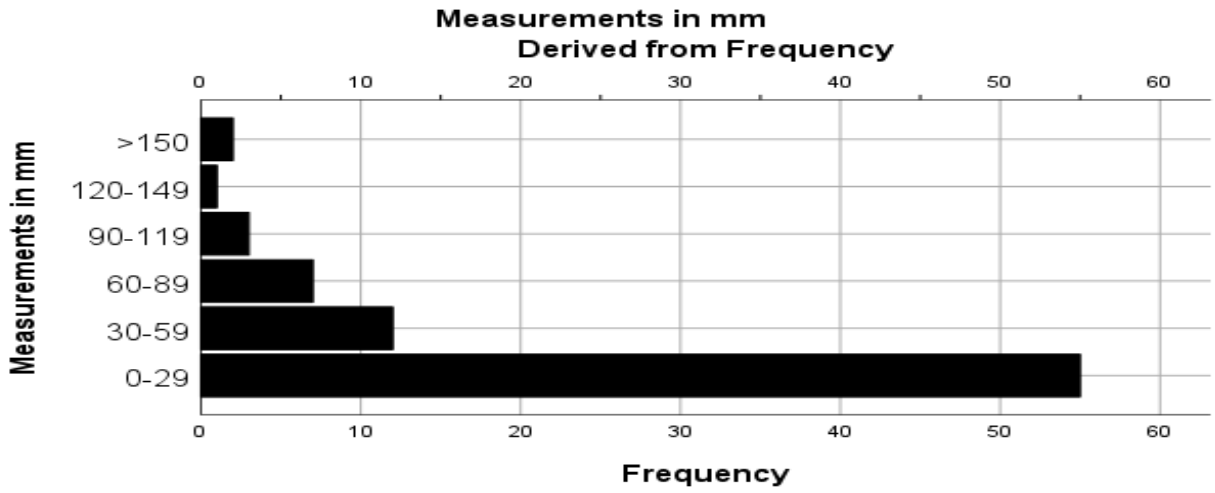

Figure 8: Prostate specimen measurements

Table 3: One sample t test on specimen measurement in mm

One-Sample Test						
	Test Value = 1.61					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
Measurements in mm	.020	79	.984	.002	-.25	.26

One sample t test was run to assess if the specimen sizes differed significantly in comparison to the mean prostate biopsy size. The descriptive statistics showed that prostate biopsy size had a mean of 1.61, with a standard deviation of 1.142. The results reveal that there is no statistically significant difference in the prostate biopsy sizes in comparison to the mean (p=0.984, t=0.020, 95% CI) (Table 3).

4.4 Microscopic morphology

The study sought to establish the microscopic features of prostate specimens as reported in JOOTRH. The microscopic features of the prostate were reported as either having atypical findings, high grade prostatic intraepithelial neoplasia (HGPIN), or prostate cancer. The majority of specimens analyzed were labelled as having prostate cancer in 20 (25%), followed by those labelled as atypical in 15 (18.75%), and high-grade PIN in at least 2 (2.5%) (Figure 9). The specimens that were marked as having prostate cancer were further characterized in terms of Gleason or group scores (Table 4). The hypothesis tested if the microscopic features differed across different age groups. Prostate histology reports were divided into four groups based on the age of the patient (Group 1: 40–49 years, Group 2: 50–59 years, Group 3: 60–79 years, and Group 4: above 80 years) (Figure 10). The ANOVA results suggest that the microscopic features of the groups did not differ significantly (F2, 34 = 1.469, p = 0.244, 95% CI). Since Levine's statistic for the mean is significant (p 0.001), an equal variance was not assumed. To check for individual

differences between groups, post-hoc comparisons were assessed using Dunnett's T3. The test indicated that the mean microscopic features for ages 50–59 years (M = 1.00, SD = 0.000) were significantly different from those for ages 60–79 years (M = 2.19, SD = 0.981). The mean differences were significant at the 0.05 level. However, no significant differences were detected between the other groups.

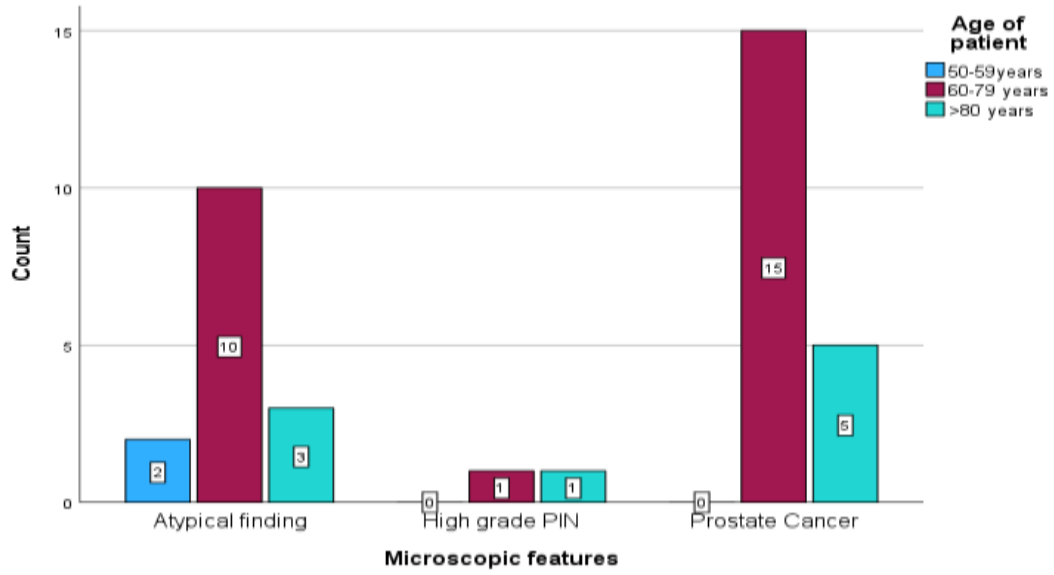

Figure 9: Microscopic features

4.5 Gleason score

Majority 6 (28.6%) of patients who presented with PSA levels greater than 100 ng/ml contributed most to group 2 Gleason score (25%) (Table 4). The study sought to establish the association between Gleason scores and PSA levels.

Table 4: Gleason scores, PSA crosstabulation

		PSA (ng/ml)					Total
		0-4	5-10	11-49	50-99	>100	
Gleason Scores	Gleason<6/Group 1	0	2	3	2	1	8
		0.0%	66.7%	60.0%	33.3%	4.8%	22.2%
	Gleason 7/Group 2	1	0	1	1	6	9
		100.0%	0.0%	20.0%	16.7%	28.6%	25.0%
	Gleason 7/Group 3	0	1	1	1	5	8
		0.0%	33.3%	20.0%	16.7%	23.8%	22.2%
	Gleason 8/Group 4	0	0	0	2	4	6
		0.0%	0.0%	0.0%	33.3%	19.0%	16.7%
	Gleason 9or10/Group 5	0	0	0	0	5	5
		0.0%	0.0%	0.0%	0.0%	23.8%	13.9%
Total		1	3	5	6	21	36
		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 5: Pearson PSA and Gleason scores correlation

Correlations

		PSA (ng/ml)	Gleason Scores
PSA (ng/ml)	Pearson Correlation	1	.474**
	Sig. (2-tailed)		.004
	N	80	36
Gleason Scores	Pearson Correlation	.474**	1
	Sig. (2-tailed)	.004	
	N	36	36

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

Chi-square statistics were used to examine null hypothesis that there is no association between Gleason's scores and PSA levels. There is a statistically significant positive correlation between Gleason scores and PSA levels ($p = 0.004$, $r = 0.474$) (Table 5). Therefore, the null hypothesis was not supported.

4.6 PSA and patient age

Majority 55 (65%) of patients who presented with high PSA levels (>4 ng/ml) were aged between 60 and 79 years old, followed by >80 years at 15 (18.75%) and 50 to 59 years at 10 (10%) (Figure 10). Age group 40–49 did not have any patients with elevated PSA. The study tested hypothesis that there is no correlation between age and PSA level. The study sought to establish the correlation between age and PSA level. The mean age at which patients presented with elevated PSA was 62.25 (60–79) years.

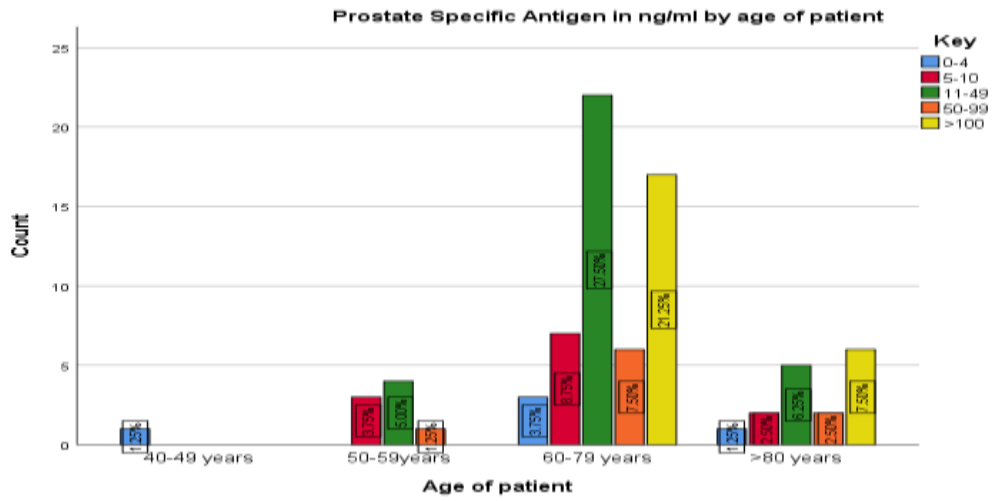

Figure 10: Prostate Specific Antigen levels by age

Table 6: Patient Age and PSA Pearson correlation

Correlations			
		PSA (ng/ml)	Age of patient
PSA (ng/ml)	Pearson Correlation	1	.236*
	Sig. (2-tailed)		.035
	N	80	80
Age of patient	Pearson Correlation	.236*	1
	Sig. (2-tailed)	.035	
	N	80	80
*. Correlation is significant at the 0.05 level (2-tailed).			

The Pearson correlation between age and PSA levels was found to have a statistically significant positive correlation (r = 0.236, p = 0.035, 95% CI) (Table 6). Hence, H1 was supported. This shows that an increase in age would lead to an increase in PSA levels, and a high PSA level is likely to be observed in men older than 60 who may test positive for prostate cancer on a prostate biopsy.

4.7 Prostate tumor type

Majority 52 (65%) of the prostate specimens that were analyzed at JOOTRH were labelled as benign prostatic hypertrophy, while only 28 (35%) were positive for prostate cancer (Figure 11). Slides of the histological pattern for BPH showed solid nests (Figure 12). Regarding the prostate tumor type, prostate adenocarcinoma was the predominant tumor type, accounting for all 28 (100%) observed prostate cancer types. Histologically, prostate adenocarcinoma was characterized by large, prominent nucleoli and micronodular infiltration (Figure 11). The study sought to establish the common prostate tumor type reported at JOOTRH between 2017 and 2022. The tumor types were categorized as adenocarcinoma, transitional cell carcinoma, neuroendocrine, and BPH.

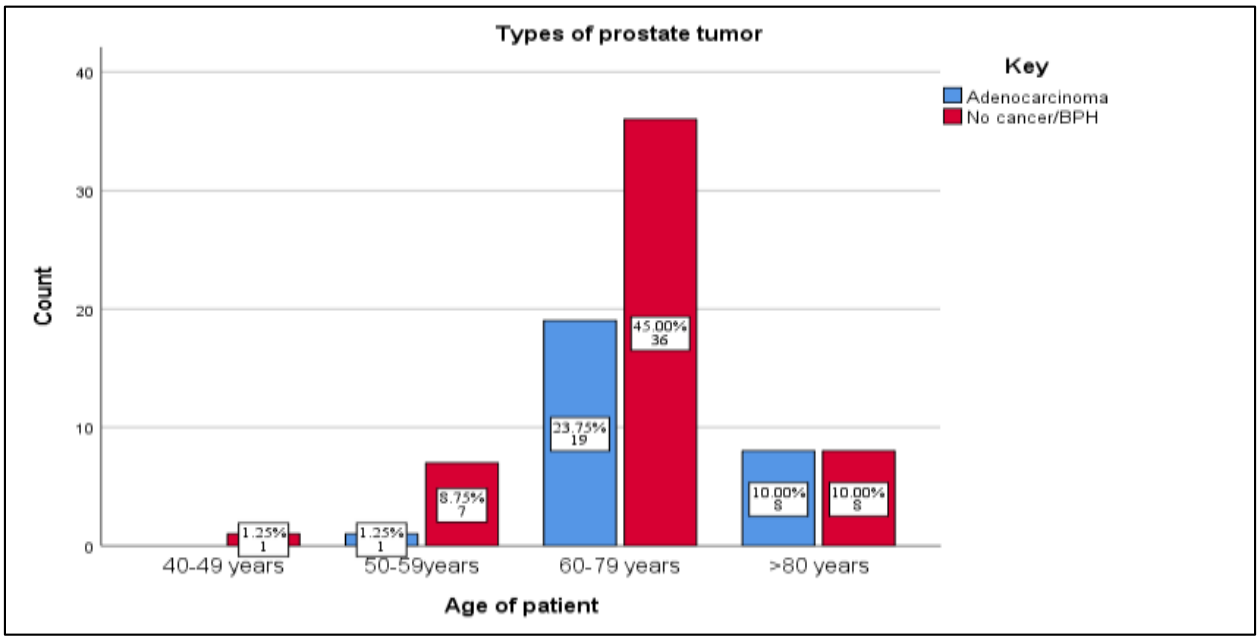

Figure 11: Prostate tumor type by age

Table 7: ANOVA out for prostate tumor types across ages

ANOVA					
Type prostate tumor					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	14.218	3	4.739	1.300	.281
Within Groups	276.982	76	3.644		
Total	291.200	79			

The hypothesis tested if tumor types differed across different age groups. The tumor types reported were divided into four groups based on the age of the patient (Group 1: 40–49 years, Group 2: 50–59 years, Group 3: 60–79 years, and Group 4: above 80 years). The ANOVA results suggest that the types of prostate tumors in the groups did not differ significantly (F3,76 = 1.300, p = 0.28, 95% CI) (Table 7).

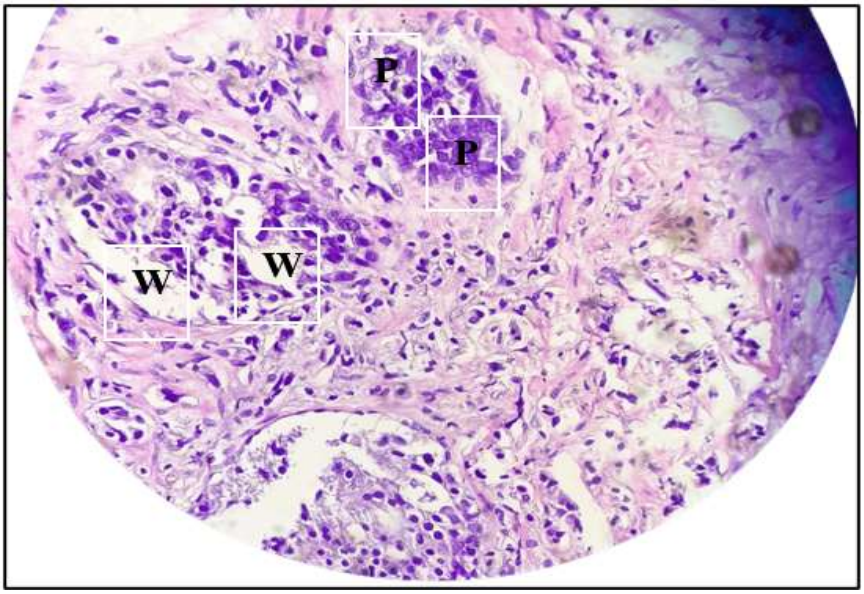

Figure 12: Prostate adenocarcinoma. Photomicrograph showing large nuclear, prominent nucleoli and collagenous micronodules infiltration.

KEY: P Prominent nucleoli, W collagenous micronodules infiltration

From figure 12 prominent nucleoli and micronodule infiltration is notable which is tandem with prostate adenocarcinoma. Histological characteristics of prostate cancer requires any of the three: the presence of circumferential perineural infiltration, collagenous micronodules and glomerulation. In low power, architectural atypia consists of haphazard or infiltration of glands, glandular crowding and darker glands. In high power, prostate cancer (Pca) is characterised by nuclear enlargement, hyperchromasia and prominent nucleoli. These features are grouped into major and minor features. The major features include architectural infiltration pattern, loss of basal cells and nuclear atypia (nuclear enlargement, prominent nucleoli and hyperchromasia). The minor features include amphophilic cytoplasm, crystalloids, adjacent HGPIN, pink amorphous secretions and intraluminal blue mucin.

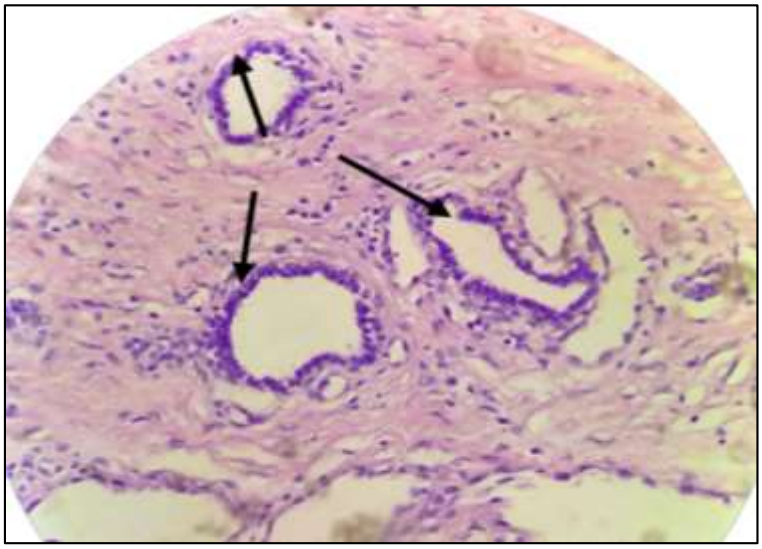

Figure 13: Benign Prostate Hyperplasia. Photomicrograph showing solid nests. ***Arrow points to nested cells***

In Figure 13 the arrow shows nested cells in two layers of epithelial cells which is characteristic of benign prostatic hyperplasia. Benign prostatic hyperplasia is characterized by infoldings, two layers of epithelial tissues giving it a nested cells appearance (arrows). It is also characterized by hyperplasia of smooth muscles of prostate, enlarged glands and enlarged fibrous tissue.

CHAPTER FIVE

DISCUSSIONS

5.1 Introduction

The results of the current finding were critically assessed and compared with other related findings from previous literature. The emphasis on significant correlations and differences was noted, and reasons where outcomes differed from other peers were given in line with each objective of the study.

5.2 Prostate histomorphology

The results from the current study suggest that there is significant variation in prostate specimen color, with the majority being white (50%), tan/white (12%), tan/brown (9%) and tan gray (1%) (Table 1). It should be kept in mind that a normal prostate gland appears white on gross examination and therefore one possible interpretation of results shown in Table 1 is that color variation (Figure 5) occurs due to pathologic changes or biopsy technique. Lindh et al. (2018), found that white, tan, yellow, and orange tumors made up the majority of those that could be definitively diagnosed as prostate tumor. In the current study, there was no documentation of color as yellow or orange, a major contradiction from findings by Lindh et al. (2018). This could be because of variation in pathologist coding of colors due to non-standardization of prostate color reporting. Another possible explanation could be that stage of prostate disease may distort the gross prostate histologic features to induce gross changes in prostate appearance.

The current study revealed that there is no difference ($p = 0.984$) in the prostate biopsy sizes in comparison to the mean of 14 mm. These findings shown in Figure 8 are similar to that of Obek

et al. (2012) who indicated that mean prostate core biopsy size is 12 mm and Fiset et al. (2013) who found biopsy size to be 13 mm. One possible interpretation of these results is that needle core length could be an important morphometric parameter of transrectal prostate biopsies that directly influences the biopsy size and thus the cancer detection rate. The results of the current study agree with other authors (Fiset et al., 2013; Öbek et al., 2012) and this could be explained by the fact that there could be guidelines on the standard prostate biopsy technique in which core biopsy needle is used. It could also be argued that perhaps core biopsies are the common technique of sample collection for prostate specimens.

The current study found that prostate microscopic features of the groups differ significantly with age and that microscopic features for age 50 – 59 years was significantly different from 60 - 79 years with majority of the pathological changes (HGPIN and prostate cancer) observed more in age bracket 60-79 (Figure 10) compared to atypical changes at 50-59 years. The results shown in Figure 10 are in agreement with other authors (Kopp et al., 2011; Liu et al., 2020) whose data suggest that patients aged 60-79 have increased likelihood for BPH and prostate cancer. One possible explanation of the results could be that perhaps alterations in prostate histological profile are pronounced at 60-79 years. The current study found that prostate atypical findings were mainly observed in ages 50-59 which agrees with (Matti et al., 2022; Miyai et al., 2014). The implications of this finding are that men aged 50-59 need screening for prostate diseases possibly because they have an increased risk for prostate disease.

In the current study, 40.5% of patients whose samples were analyzed had atypical findings (Figure 9), compared to 30.6% and 25% in Yanez & So (2015) and Kopp et al. (2011), respectively. These findings suggest that most biopsies are done among patients aged 50–59, the only age at which most of the prostate pathology demonstrates atypical findings (Figure 9). It should be noted

however that the Yanez & So (2015) study was a 2-year prospective study carried out in the Philippines, which is a different geographical region, and thus racial differences could be an explanation of the variation, indicating that perhaps atypical prostate findings are more prevalent among Kenyan men aged 50-59 in western countries compared to other parts of the world. Another possible interpretation is that most men present for prostate evaluation at ages 50-59 in western region of Kenya.

The current study found that 5.4% of the samples analyzed had high-grade intraepithelial neoplasia which is in contradiction to studies such as Han et al.'s (2007) 70.4% and Pierorazio et al.'s (2007) 88.4%. However, the current study findings agree with (Wael Sakr et al., 2000) that the reported prevalence of HGPIN varies significantly, with a range of 0.8-23.9 percent, especially in needle biopsy specimens. The significant variation could suggest that either reporting at JOOTRH for HGPIN is inadequately reported. Another possible interpretation could be that given the studies by Fitet et al. (2013) and Pierorazio et al. (2007) were done in developed countries where an aging population forms a larger proportion of the population, it is more likely to have prostate pathologies reported compared to Kenya, where there are fewer aged men likely to present for evaluation of prostate disease. It is also possible that economic implications can make fewer men present for prostate evaluation in Kenyan hospitals.

The current study found a statistically significant association between Gleason scores and PSA levels ($p = 0.004$, $r = 0.474$) (Table 5). The current study results agree with Cihan et al.'s (2019) finding that the ISUP grade (based on Gleason scores) of patients was significantly and positively correlated with age and PSA levels. It should be noted, however, that although the findings agree, Cihan et al. (2019) carried out a prospective study, and their reporting would likely have been better compared to a retrospective study. Similarly, Gündodu et al. (2020) found that Gleason

scores correlate positively with PSA levels in a prospective study of patients who underwent radical prostatectomy. The current findings, however, are in contradiction with Sanli et al. (2017). This could perhaps be due to the fact that Sanli et al. (2017) focused on patients who were on treatment follow-up, and therefore the relationship could have been confounded by treatment.

The histology reports analyzed were all from the JOOTRH pathology laboratory computer data base, and this study did not establish whether there were any errors in data entry. The prostate biopsies performed as a follow-up on treatment were not included in this study. More research in this area is required.

5.3 Prostate specific antigen and Age

The results of the current study indicate that PSA levels rise with age, and males aged 60 and older were likely to have higher PSA levels ranging from 11 ng/ml to greater than 100 ng/ml, and that 25% and 18% of such patients turned out positive for prostate cancer and benign prostatic hypertrophy, respectively (Figure 10). The current study findings agree with Liu et al. (2020; Maciel et al. (2018), whose studies found that the PSA levels start to rise at 58 years, compared to Cihan et al. (2019), who found that the median age at which PSA levels start increasing is 63 years. The findings in the current study agree with (Cinislioglu et al., 2022; Gilbert et al., 2015a) that 30% (compared to the current 25%) of patients with high PSA test positive for cancer of prostate. The age differences in different studies (Cihan *et al.,* 2019; Liu *et al.,* 2020; Maciel *et al.,* 2018) at the time PSA started rising may be an indication that race plays an important role in the PSA levels among males in relation to prostate pathology.

Although the findings of the current study agree with those of Cihan et al. (2019); Cinislioglu et al. (2022); and Gilbert et al. (2015b), it is important to note that Cihan et al. (2019) carried out a

prospective descriptive study in which a decision to undergo prostate biopsy was made due to complaints of decreased urinary tract symptoms and elevated PSA between July 2019 and December 2019. These findings, however are in contrast with those of Wang et al. (2019), who found that some of the patients with low PSA levels (0–4 ng/dL) tested positive for prostate cancer. These findings could be interpreted to mean that patients with advanced prostate disease can present with low PSA levels when the function of the prostate is diminished.

The current study findings indicate that 25% of those who presented with high PSA tested positive for prostate cancer. These findings agree with Zhang and Sun (2018), and perhaps this would suggest that an increase in age would lead to an increase in PSA levels, and a high PSA level is likely to be observed in men older than 60 years who may test positive for prostate cancer on a prostate biopsy. The findings of the current study agree with Maciel et al. (2018) who found that age groups 60–69 and 70–80 show a significant association between free PSA and total PSA ($p = 0.008$). The current study findings are in agreement with other studies (Maciel *et al.,* 2018; Matti *et al.,* 2022; Zhang & Sun, 2018), implying that perhaps PSA is indeed an important variable that changes positively as age advances. Another explanation could be that other studies also employed retrospective cross-sectional studies similar to the current study except for variations in the study population.

Overall, the study findings suggest that age and PSA have a positive correlation ($r = 0.283$) and higher PSA levels are likely to be observed in males aged 60 years and older who may have prostate cancer or benign prostate hyperplasia in order of occurrence. The current study findings, alongside other research findings (Cinislioglu *et al.,* 2022; Kim *et al.,* 2021; Matti *et al.,* 2022; Negahdary *et al.,* 2020; Zhang & Sun, 2018), point to the potential value of routine prostate evaluation in males older than 60 years who present with urinary symptoms so as to detect prostate

lesions early enough. It should be kept in mind that the current study was a retrospective study that reviewed only prostate reports as opposed to prospective studies such as those by Cinislioglu et al. (2022). Further research is therefore needed to determine the extent of prostate lesions in patients who present with an elevated PSA level.

The current study found that prostate adenocarcinoma was the predominant tumor, accounting for 35% of all prostate diseases (Figure 11). The current study findings agree with Conteduca et al. (2019) and Seraphin et al. (2021) on the trend analysis of the incidence of prostate cancer, who reported that adenocarcinoma was found to be more common in sub-Saharan Africa, accounting for 27% of prostate diseases. Similarly, Onwuasoanya et al. (2022; PĂnuŞ *et al.,* 2020; Wasinger *et al.,* 2022) found that the most prevalent histological pattern of prostatic tumor was adenocarcinoma presenting with a Gleason score of 9, and the peak age of occurrence is 60–69 years. One possible interpretation of the current study results is that men aged 60 and older could be exposed to similar risk factors for prostate adenocarcinoma compared to other prostate tumors.

The current study has similar findings to those of Onwuasoanya et al. (2022), which indicate that approximately 24% of males who presented with PSA levels greater than 100 ng/ml had a Gleason score of 9 at the time of diagnosis of a prostate tumor. Montironi et al. (2007) note, however, that before progression to adenocarcinoma, almost all known information points to high-grade prostatic intraepithelial neoplasia (HGPIN) as the most likely precursor of prostatic cancer in 4% of men. The current study found that 2% of patients whose prostate specimens were reported had HGPIN (Figure 9), characterized by nuclear and nucleolar enlargements (Figure 12) similar to those found in prostate cancer. Even though the current study findings are in agreement, it should be noted that

(Humphrey, 2017b) reviewed prostate histological patterns as a follow-up to treatment in a prospective study, which may be more accurate than the current retrospective study.

Similar findings were reported by Grignon et al. (2004), Verhoef et al. (2019), and Wasinger et al. (2022): distinct prostate epithelial lesions may appear to be cancerous, yet their three-dimensional architecture is acinar and obviously different from the tubular structure of prostate cancer. The non-acinar (ductal type) of prostate accounts for 1% of cases (Grignon, 2004). While the current study found that adenocarcinoma is common, it should be kept in mind that the current study did not explore the subtypes of adenocarcinoma, and further research should be considered.

In contrast, other studies, such as Mazzucchelli et al. (2008) and Montironi et al. (2007), it was found that other types of prostate tumors, such as neuroendocrine and carcinoid, are surprisingly common. It should however be noted that such findings were observed among Italians, whose genetic variation could be a possible explanation of the observation. These findings may then suggest that, unless otherwise stated, prostate adenocarcinoma remains the most common tumor type among patients with prostate cancer in sub-Saharan Africa. Overall, the findings of this study, just like those of other studies (Grignon, 2004; Onwuasoanya, 2022; Verhoef *et al.*, 2019; Wasinger *et al.*, 2022), suggest that prostate adenocarcinoma is the most common prostate tumor.

CHAPTER SIX

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 SUMMARY

This study aimed to determine the histological patterns of prostate specimens analyzed at JOOTRH between 2017 and 2022. Specifically, the study sought to establish prostate histomorphology, examine the relationship between patient age and PSA level, and determine the most common prostate tumor type. Based on the findings of the current study, it is clear that an increase in age is associated with an increase in PSA level, and high PSA levels could be an indicator of prostate malignancy or benign prostatic hyperplasia. The findings of this study suggest that prostate adenocarcinoma is the most common prostate tumor among males in the western region whose prostate specimens were analyzed at JOOTRH between 2017 and 2022. The findings of this study point to a likely overdiagnosis with unnecessary biopsies recommended in older males who may not necessarily have prostate carcinoma.

The current study did not seek to establish the subtypes of prostate adenocarcinoma, hence the need for further research to establish the subtypes of prostate adenocarcinoma. The findings of this study suggest that age and PSA have a weak positive correlation ($r = 0.283$) and higher PSA levels are likely to be observed in males aged 60 years and older who may have prostate cancer or benign prostate hyperplasia in order of occurrence. The research also points to the potential value of routine prostate evaluation in males aged 50-59 years who present with urinary symptoms so as to detect prostate lesions early enough. It should be kept in mind that this study was a retrospective study that reviewed only prostate reports. Further research is therefore needed to determine the extent of prostate lesions in patients who present with an elevated PSA level.

These results suggest that there is significant variation in prostate biopsy specimen color in different men, but the majority of prostate specimens are white. Variations in colors such as tan and yellow could signify the effect of a disease process on the prostate that induces color alterations. The study found no association between Gleason scores and PSA levels, implying that high Gleason scores are not necessarily associated with high PSA levels. Patients whose prostate specimens were reported to have HGPIN or atypical findings need a repeat histology as soon as possible since these are premalignant findings or lesions that mimic prostate carcinoma. While the current study clearly illustrates that an increase in PSA is correlated with age, it also raises concerns about unnecessary biopsies that are carried out based on the PSA level among men who present with urinary symptoms.

Based on these conclusions, the following recommendations are made

1. There is significant variation in histomorphology of prostate specimens in relation to color and surface. Therefore, pathologists need to correlate the specimen color with extend of disease using tools such as Gleason scores.
2. Most men aged 50-59 are likely to have atypical findings on histology and therefore there is need to focus mass screening among men in this age bracket. Those with atypical findings need to have their histology repeated soon
3. Since there is a correlation between age and PSA, men aged 50-60 presenting with urinary symptoms needs routine PSA and biopsy where PSA levels are elevated or suspected cases where prostate tumors occur with normal PSA level
4. Prostate adenocarcinoma is the most common prostate tumor among men whose prostate specimen were analyzed at JOOTRH. Therefore, there is need for further research to distinguish subtypes of prostate adenocarcinoma since it has treatment outcome implications

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APPENDICES

APPENDIX I: DATA EXTRACTION FORM

Serial Number: _____

SECTION A: AGE AND PSA LEVEL

1. Age: |_____|
2. PSA level (ng/dl): |_____|

SECTION B: PROSTATE HISTOMORPHOLOGY

1. Macroscopic Morphology
   a. Color |_____|
   b. Surfaces |_____|
   c. Specimen measurements (mm) |_____|

2. Microscopic Morphology
   a. Atypical finding |_____|
   b. High-grade PIN |_____|
   c. Prostate cancer |_____|

3. Gleason score/Epstein grade grouping
   i. Gleason ≤ 6/Grade group 1 |_____|
   ii. Gleason 7/Grade group 2 |_____|
   iii. Gleason 7/Grade group 3 |_____|
   iv. Gleason 8/Grade group 4 |_____|
   v. Gleason 9 or10/Grade group 5 |_____|

SECTION C: PROSTATE TUMOR TYPE

a. Adenocarcinoma |_____|

b. Transitional cell carcinoma |_____|

c. Squamous cell prostate carcinoma |_____|

d. Neuroendocrine carcinoma |_____|

e. No cancer/BPH |_____|

APPENDIX II: LETTER FROM GRADUATE SCHOOL

MASENO UNIVERSITY
SCHOOL OF GRADUATE STUDIES

Office of the Dean

Our Ref: MSC/SM/00009/020

Private Bag, MASENO, KENYA
Tel:(057)351 22/351008/351011
FAX: 254-057-351153/351221
Email: sgs@maseno.ac.ke

Date: 07th October 2022

TO WHOM IT MAY CONCERN

RE: PROPOSAL APPROVAL FOR MUSUNGU VINCENT SECHERE — MSC/SM/00009/020

The above named is registered in the Master of Science in Human Anatomy programme in the School of Medicine, Maseno University. This is to confirm that his research proposal titled "Histological Characterization of Prostate Analyzed at Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu County" has been approved for conduct of research subject to obtaining all other permissions/clearances that may be required beforehand.

Prof. J.O. Agure
DEAN, SCHOOL OF GRADUATE STUDIES

APPENDIX III: ETHICAL APPROVAL LETTER

COUNTY GOVERNMENT OF KISUMU
DEPARTMENT OF HEALTH

Telephone: 057-2020801/2020803/2020321
Fax: 057-2024337
E-mail: ercjootrh@gmail.com
Website: www.jootrh.go.ke
When replying please quote

JARAMOGI OGINGA ODINGA TEACHING & REFERRAL HOSPITAL
P.O. BOX 849
KISUMU

Ref: ISERC/JOOTRH/659/22

Date: 15th December, 2022

RE: APPROVAL: STUDY TITLE
HISTOLOGICAL PATTERNS OF PROSTATE SPECIMENS BASED ON HISTOLOGY REPORTS AT JARAMOGI OGINGA ODINGA TEACHING AND REFERRAL HOSPITAL.

REF: ISERC/JOOTRH/659/22

To: Vincent Musungu Sechere

Dear Vincent,

RE: STUDY TITLE

This is to inform you that JOOTRH ISERC has reviewed and approved your above research proposal. Your application approval number is ***ISERC/JOOTRH/659/22.*** The approval period is ***15th December, 2022 to 15th December, 2023.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by JOOTRH ISERC
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to JOOTRH ISERC within 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to JOOTRH ISERC within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.

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APPENDIX IV: PERMISSION TO COLLECT DATA

COUNTY GOVERNMENT OF KISUMU
DEPARTMENT OF HEALTH

Telephone: 057-2020801/2020803/2020321
Fax: 057-2024337
E-mail: medsuptnpgh@yahoo.com
ceo@jaramogireferral.go.ke
Website: www.jaramogireferral.go.ke
When replying please quote
GEN/21A
Ref: .....

JARAMOGI OGINGA ODINGA TEACHING & REFERRAL HOSPITAL
P.O. BOX 849-40100
KISUMU

15th December, 2022
Date .....

To: Vincent Musungu Sechere

Dear Vincent,

RE: PERMISSION TO COLLECT DATA

Following approval of protocol titled "Histological Patterns on Prostate Specimens Based on Histology Reports at Jaramogi Oginga Odinga Teaching and Referral Hospital - Kisumu", you are hereby permitted to proceed with the activity.

Yours sincerely.

CHIEF EXECUTIVE OFFICER
JARAMOGI OGINGA ODINGA TEACHING & REFERRAL HOSPITAL(JOOTRH)
P.O. BOX 849-40100, KISUMU
DATE.....

DR. GEORGE RAE
CHIEF EXECUTIVE OFFICER
JOOTRH – KISUMU

APPENDIX V: NACOSTI LICENSE

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **801360**

Date of Issue: **17/January/2023**

RESEARCH LICENSE

This is to Certify that Dr.. Vincent Musungu Sechere of Maseno University, has been licensed to conduct research as per the provision of the Science, Technology and Innovation Act, 2013 (Rev.2014) in Kisumu on the topic: HISTOLOGICAL PATTERNS OF PROSTATE SPECIMENS BASED ON HISTOLOGY REPORTS AT JARAMOGI OGINGA ODINGA TEACHING AND REFERRAL HOSPITAL for the period ending : 17/January/2024.

License No: **NACOSTI/P/23/22845**

801360

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

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See overleaf for conditions