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Risk factors for Prostate cancer in men of African descent aged 45 years and older in Gauteng province, South Africa 2017 – 2021: Case-control study

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2025

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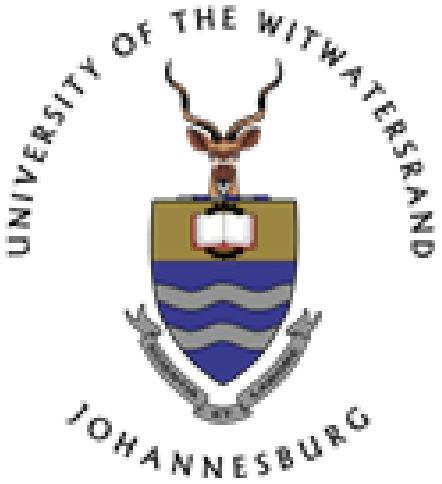
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Simelane, Thobile Sakhile. (2025). Risk factors for Prostate cancer in men of African descent aged 45 years and older in Gauteng province, South Africa 2017 – 2021: Case-control study [Master`s dissertation, University of the Witwatersrand, Johannesburg]. WIReDSpace. https://hdl.handle.net/10539/48039

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UNIVERSITY OF WITWATERSRAND



SCHOOL OF PUBLIC HEALTH

By

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Risk factors for Prostate cancer in men of African descent aged 45 years and older in Gauteng province, South Africa 2017 – 2021: Case-control study.

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Research report submitted for the degree of Master of Science in Epidemiology and Biostatistics

Declaration

I Thobile Sakhile Simelane, student number 2187697, declare that this research report is my work, unassisted except where otherwise stated. The report is being submitted for the fulfilment of a Degree of Master of Science in Epidemiology and Biostatistics at the University of Witwatersrand, Johannesburg. This is the first time it has been submitted.

Signature: T.S. Simelane

Date: 21 April 2025

Dedication

This thesis is dedicated to my God who has given me the strength to do this work, to Him be the Glory. To my beloved husband Ncamiso Mamba, your unwavering financial and emotional support has been invaluable. To my dear children, Divine and Dumolwakhe, thank you for your patience and for allowing me time to focus on this work. To my dear mother, your prayers and encouragement have been a source of strength. To my spiritual family, thank you for your prayers and support.

Abstract

Background

Prostate cancer (PCa) is the fifth leading cause of cancer-related deaths worldwide and the second most common cancer in men, with higher incidence among Black African men. In South Africa, PCa is a notifiable disease, yet risk factors among African men remain understudied. This study examines PCa risk factors in African men aged 45+ in Gauteng (2017–2021).

Methods

This study used data from the African Descent Prostate Cancer Study at Chris Hani Baragwanath Hospital, examining genetics and epidemiology in men aged 45+ (2017–2021). Data analysis in STATA 17 summarized continuous and categorical variables. Conditional logistic regression (age-matched) was preferred over Cox regression based on AIC values. Statistical significance was set at $p < 0.05$.

Results

The study analysed 2007 men aged 45 and older at Chris Hani Baragwanath Hospital (2017-2021). Among them, 1005 had prostate cancer (PCa), and 1002 served as controls. The average age was 65.5 years, with PCa patients being sufficiently older. Most participants were married (67.4%, had less than a high school education (80.5%), were retired (73.6%), and earned less than R5000 per month (94.3%).

Key findings

Married men had a 45% higher risk of PCa, while high school graduates had a 62% reduced risk. Employment nearly doubled the odds. Current alcohol consumers had a 59% higher risk, past drinkers twice the odds, and past smokers a 79% increase. A paternal history of PCa raised the risk 8.6 times, while diabetes reduced it by 48%.

Conclusion

Findings showed that alcohol consumption, smoking, and a family history of PCa were strong predictors. Targeted interventions should focus on raising awareness and promoting early screening, especially in hard-to-reach areas, to improve health-seeking behaviour and outcomes.

Keywords

Prostate cancer, men of African descent, risk factors.

Acknowledgements

The author wishes to express sincere gratitude to the Men of African Descent Cancer of the Prostate Department for granting access to their data, which was instrumental in the completion of this study. Appreciation is also extended to Dr. Welnong Carl Chen and Dr. Maureen Joffe for their assistance in providing the essential documents related to the primary study.

Special thanks are due to Professor Eustasius Musenge, Division of Biostatistics, School of Public Health, and Dr. Winston Padayachee of the Urology Department at Baragwanath Hospital, for their invaluable supervision and contributions throughout this research. Their commitment and dedication were fundamental to the success of this work.

The author is also grateful to colleagues whose steadfast support helped ease the demands of the academic journey.

Above all, heartfelt thanks are given to God for His continual strength, provision, and grace throughout this endeavour. Indeed, we are more than conquerors through Christ who gives us strength.

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Abbreviations and acronyms

AIC	Akaike Information Criterion
AR	Androgen Receptors
aOR	Adjusted Odds Ratio
ASIR	Age-Specific Incidence Rate
BMI	Body Mass Index
CDC	Centre For Disease Control
CHBAH	Chris Hani Baragwanath's Hospital
CI	Confidence interval
CLR	Conditional Logistic regression
COVID	Corona Virus Disease
CPGR	Centre for Proteomics and Genomics
DX	Diagnosis
DRE	Digital rectal examination
DHMS	Discovery Health Medical Scheme
DHT	Dihydrotestosterone
GLOBACON	Global Burden of Cancer Study
HIV	Human Immunodeficiency Virus
HR	Hazard rates
KM	Kaplan Meier
MADCAP	men of African Descent with Cancer of the Prostate
NCDs	Non-communicable Diseases
NCR	National Cancer Registry

NCSFSA	National Cancer Strategic Framework of South Africa
OR	Odds Ratio
PCa	prostate cancer
PSA	Prostate-specific Antigen
RR	Relative Risk
SA	South Africa
SD	standard deviation
SSA	Sub-Sahara Africa
STI	Sexually Transmitted Infections
TB	Tuberculosis
ULR	Unconditional Logistic regression
USA	United States of America
USD	United State Dollar

CHAPTER 1: INTRODUCTION

This chapter introduces the research by providing the global background about prostate cancer (PCa), and its incidence in Southern Africa. It also clearly states the problem statement, justification for doing the study, and outlines the research question, aims, and objectives of the study.

1.1 Background

Prostate cancer (PCa) is recorded as the 5th leading cause of death globally and the 2nd most common cancer in men (1,2). In 2018, it was estimated that 18.1 million people had cancer, and of these 9.6 million died globally (3). In 2020, the incidence of prostate cancer (PCa) was approximately 7.3% and it was the third most common cancer, with developed countries having higher incidence (1). According to Sung et al. (2020), a 70% rise in PCa incidence has been projected by the year 2030 in Africa compared to other continents (1). This increase could be due to demographic changes and urbanisation (1). Among African men, the incidence is higher compared to white men with 158.3 new cases per 100,000 African men and double the mortality compared with white men (1,4) (see appendix A). The PCa incidence is related to age, with the highest incidence having been reported in men above 65 years (1). A report from the NCR has also shown an increase in the number of PCa cases with increasing age among African men, and the majority presenting at an advanced stage of the disease (5). Report from the Discovery Health Medical Scheme (DHMS) have highlighted that 8.3% of its members were treated for PCa in 2018, and a majority (71%) were receiving active treatment (6). This has led to increased spending towards PCa in S.A. which is estimated at $27,000 compared to other African countries like Tunisia with a spending of $7500 (7). Screening programs using Prostate-specific Antigen (PSA) tests have been introduced (8,9). Limited studies on PCa risk factors among Men of African descent have been conducted in S.A. which may negatively

impact the awareness and prevention of the disease (10). Identifying the risk factors will assist in defining the target population for designing realistic and cost-effective prevention strategies. This will then inform policies and decision-making through the establishment of evidence base on which prevention, control, and treatment strategies are built (11). This study therefore aims to identify the risk factors for prostate cancer among men of African descent aged 45 years and older in Gauteng province between the years 2017 - 2021.

1.2 Incidence in Southern Africa

The PCa incidence in Southern Africa is 40.5 per 100,000 population per year with a mortality rate of 22.5 per 100,000 population per year(4,12). The increased incidence has been associated with increasing life expectancy and the assumption of a Westernized lifestyle (tobacco use, dietary habits, fertility, body weight, physical activity) (3,13). These increased rates could also be related to the changes in screening and testing procedures in the region (14).In South Africa (S.A), an increase in the incidence of PCa (26.3 per 100,000 population) was observed(15,16). The highest incidence was noted among African men compared to other ethnic groups (15,16).

1.3 Problem statement

It has been projected that by 2030 the global burden of PCa will be doubled (13). Prostate cancer is expected to be the most prevalent cancer among men in SA with increasing mortality in men aged 65 years and older (1). A notable difference in the incidence (2.4 times the rate of other ethnic groups) and mortality among men of African descent (17) has been stated by (Stern et al., 2021). By contrast, the incidence is lower among other ethnic groups and the reason for these differences is still unexplained (17). Between 2006 and 2016, a 44.9 -57.3 per 100,000 population increase in ASIR was observed in SA (13). In 2018 this increase has shown to be consistent with ASIR rising to 68.0 per 100,000 population (13). The highest cases were noted among African males (5) (see Appendix A). For long PCa was considered a condition for the

elderly but has emerged in young men (<50 years) with the risk observed mainly among black African men(18). This has affected the economy due to unavoidable extra costs associated with an inability to partake in workforce, treatment, recuperation and fatalities (6,7). The amount spent on PCa in SA is estimated to be ($27000) which is higher compared to other African countries like Tunisia ($7500) (7). The limited number of studies conducted in Gauteng on this subject has resulted in a lack of comprehensive evidence for the province, hindering a better understanding of the risk factors specific to PCa in South Africa.

1.4 Justification

Despite existing screening programs, limited evidence on prostate cancer (PCa) risk factors in South Africa hampers awareness and prevention efforts (10). Understanding these factors is crucial for defining target populations and developing cost effective prevention strategies. This evidence base can guide policy-making, reduce treatment costs, and improve productivity (13,19).

This study examines PCa risk factors in Johannesburg, Gauteng, focusing on men of African descent aged 45 and older. Findings will enhance service provision, contribute to existing knowledge, and encourage screening uptake by providing insight into risk factors that affect how men asses their likelihood of developing PCa (20). Identifying risk factors may also aid in early detection among asymptomatic individuals, especially in high-risk regions affected by industrialization and westernization (10).

Reducing PCa-related deaths, disabilities, and economic burdens is essential (21,22). Epidemiological data show that initial treatment costs per patient in South Africa average R161,540, covering surgery, radiation, and hormone therapy (7,13,22–25).

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1.5 Research question

What are the risk factors associated with prostate cancer among men of African descent aged 45 years and older in Gauteng province, South Africa between 2017 and 2021?

1.6 Aim

To determine the risk factors associated with prostate cancer among men of African descent aged 45 years and older in Gauteng province, South Africa.

1.7 Objectives

1. To describe the socio-demographic characteristics of men of African descent aged 45 years and older with prostate cancer in Gauteng province, South Africa between 2017 and 2021.

2. To determine the risk factors that are associated with prostate cancer in men of African descent aged 45 years and older in Gauteng province, South Africa between 2017 and 2021**.**

CHAPTER 2 LITERATURE REVIEW

2.0 Introduction

This Chapter gives current literature relevant to risk factors among men of African descent being diagnosed with PCa. The literature review involves the incidence in South Africa, non-modifiable risk factors, modifiable risk factors, social factors, enabling factors, healthcare facilities and insurance coverage.

2.1 Incidence in South Africa

Following the 2011 legislation, which improved access to healthcare and promoted cancer screening programs, the reported incidence of PCa increased (44.9 – 57.3 per 100,000 population. This rise may be attributed to enhanced early detection through expanded screening efforts rather than actual surge in cases (12). The policy changes likely led to more men undergoing screening, resulting in a higher number of diagnosed cases that might have previously gone undetected.

However, continued awareness campaigns ensured that more cases were detected overtime. Reports from the National Cancer Registry (NCR) indicates a rising incidence of prostate cancer (PCa) in South Africa, with African men experiencing the highest burden compared to other ethnic groups (16,18). In 2020, the highest incidence was from the private sector with 109.5 per 100,000 population compared to the public sector with 57.4 per 100,000 population (26). The Global Cancer Network (GLOBOCAN) 2020 further highlights that PCa remains underdiagnosed and underreported, contributing to delayed treatment and increased mortality rates (27).

According to the National Cancer Strategic Framework of South Africa 2017-2022 (NCSFSA), PCa is among the top five priority cancers in S.A(26). Measures have been put in place by the South African health system to screen men through yearly physical examination and PSA

serology for men who are aged 45 years and older (26). Despite the rising incidence of PCa in S.A, there are gaps in understanding the specific trends, risk factors, and disparities among different populations, particularly African men. While post-2011 healthcare policies improved access to screening, it remains unclear whether the continued increase in cases reflects a true rise in incidence, improved detection, or both. This study is necessary to analyze these incidence trends, assess contributing factors, and provide insight to inform targeted prevention and detection strategies.

. Among those diagnosed, 20% die from the disease (26). The increased mortality among African men has been attributed to delays in seeking medical treatment (10). These delays result from PCa risk factor unawareness, inaccessible healthcare facilities, low socio-economic status, and stigma associated with the disease (27).

PSA screening has been controversial in the early diagnosis of PCa and may result in overdiagnosis of low-grade disease that does not necessarily require treatment (28). Early identification of PCa risk factors is crucial in the aim of reducing the disease burden among men of African descent (28). However, it is uncertain whether the increased risk in African men is due to ethnicity alone or there are additional social and societal confounders (29).

Some of the hospital-based studies conducted in SA focused on PCa incidence and survival among African men (13).A study conducted in the Eastern Cape reported that 99,8% of new cases were black Africans (14). To expand on this limited data in SA, a case-control study will be conducted to determine the risk factors associated with PCa among men of African descent in Johannesburg, Gauteng between 2017 and 2021. Gauteng province is the focus of this study because it houses a significant proportion of the South African population (26.1%) (30) and has the highest (24.1%) population of geriatrics (60 years and older) (30).

2.2 Risk factors of prostate cancer

Many hereditary and environmental risk factors may influence the incidence and mortality rate of cancers (31). These include sociodemographic, environmental, clinical, and behavioural factors (see Appendix A). The currently acknowledged PCa risk factors include family history, age, and race (e.g. African)(32,33). There have also been some factors that may influence PCa incidence such as occupation, increasing intake of red meat, high intake of animal fat, educational level, smoking habits, sexual behaviours, marital status, baldness, and other metabolic diseases (32). While age, family history, and being of African descent are well-established risk factors, the role of modifiable factors such as diet, smoking, and occupation remains less clear. It is worth noting that the African ethnic group has been reported to have an increasing risk of developing PCa disease (34). Although genetics have been stated as one of the risk factors of PCa among African men, there is still limited information on other contributing factors among African men, and thus no sufficient evidence yet on potential preventative measures(11,35).

2.3 **Non-modifiable risk factors**

2.3.1 Advancing age

Age is part of the acknowledged non-modifiable risk factors of PCa. The risk of developing PCa increases with an increase in age (36). The average age at diagnosis is reported to be 66 years (37,38). The Centre for Disease Control (CDC) has reported that African men are more likely to be diagnosed with PCa at a younger age (below 40 years) compared to other ethnic groups. In all population groups, the PCa incidence reveals that risk increases sharply after the age of 55 years and peaks at age 70-74 (39).

2.3.2 Family history

A family history of prostate cancer is one of the identified important risk factors. Current South African PCa guidelines recommend earlier screening (at 40 years) among those with a positive lineage of PCa (18). The greater the proximity of kinship, the higher the likelihood of diagnosis at an earlier age (37,39). The PCa risk is estimated at 12% for a man with a father who was diagnosed with PCa at ≥60 years (36,40). It further increases by up to 40% for a man with three or more affected male siblings, while it is reduced by 8% for a man without a family history of the disease (36,40). A family history of breast cancer has also been associated with increased PCa incidence (40). Identifying higher-risk individuals assists with subsequent management and follow-up to reduce morbidity and mortality.

2.3.3 African ancestry

Men of African descent face a significant higher risk of developing PCa compared to other ethnic groups(41). Black men are 1.7 times more likely to be diagnosed with PCa and 2.1 times more likely to die from the disease than White men(42). Genetic factors contribute to this increased risk. Studies have identified genetic variants that are either predominantly or exclusively found in men of African ancestry, which elevate the likelihood of developing prostate cancer(43–45).

2.4 Modifiable risk factors

2.4.1 Dietary factors

Dietary factors have been reported to influence the development of PCa in both black and white populations (46). Keeping up with the invention of different synthetic materials used in the food industry has been challenging (31). These materials have been assumed as potential sources of causes of cancer development (31). A study done in the United States has shown

that intake of animal products and animal fats has an association with PCa. Increased animal fat consumption was linked to PCa among black Americans but not in White Americans (47). This brought an assumption that the Black ethnic group has an increased risk of PCa with increased consumption of animal products.

A reduction in animal fat intake among Black Americans could reduce the incidence and mortality rate of PCa (46,48). Increased intake of fruits and vegetables has been associated with reduced incidences of developing PCa (49,50). Black individuals have been found to consume fewer fruits and vegetables compared to white individual. Although aforesaid studies indicate that nutritional practices modify the risk of PCa, case-control and cohort studies have provided varied conclusions on the dietary aetiology of PCa.

2.4.2 Alcohol consumption

Studies of alcohol consumption have reported alcohol consumption to be associated with PCa. However, conflicting results on the risk of alcohol consumption on PCa exist (33,35,51,52). Binge drinking is associated with carcinoma of the buccal cavity, liver, and digestive system (53). Some studies have reported an increased risk of pancreatic cancer and colon cancer with alcohol consumption (53).

Meta-analysis studies have depicted a positive relation between binge drinking and PCa(33,52). The risk is higher among those taking more than four drinks per day (33,52,54). However, most of these studies (51,54) did not assess the type of alcohol used. Vartolomei (2018) reported an increased risk with the consumption of moderate white wine (RR=1.25) while moderate red wine was reported to have a reduced effect (RR=0.88) (33). The conflicting findings on the association of PCa and alcohol consumption between studies may be due to the different study methods used and the type of alcohol used.

2.4.3 Smoking habits

Smoking is one of the important risk factors for many cancers, however, it remains uncertain whether there is an association between smoking and PCa (55,56). Cigarette smoking has been reported to affect various hormones, including testosterone (55,56). Sato (2020) has stated that current smoking is associated with not only an increased probability of biochemical failure post-surgery without hormone therapy but also an increased serum testosterone level among smokers compared to non-smokers(57–59). Furthermore, a possible negative outcome in smokers treated for advanced PCa has been reported (57,60,61). This hormone has been positively associated with PCa risks in other studies (35,43,59,62). In a study done in the Free State, smoking more than six cigarettes per day was associated with metastatic PCa thus signifying a positive association between smoking and PCa(57).

2.4.4 Comorbidities

Although the aetiology of PCa has been multifactorial, underlying metabolic syndrome and obesity could affect the incidence of PCa (63). Men presenting with diabetes mellitus have been reported to have lower risks of PCa among the Iranian population (32). Tande et al (64) reported that men with metabolic syndrome were more likely (RR-1.9) to develop PCa than those without.

Most notably, a dose-response relationship between the number of metabolic syndromes and PCa has been observed, with reduced risks among men with a combination of syndromes (60,65). The possible link between metabolic syndrome and PCa has been associated with altered androgen levels (9,64). Men with metabolic syndrome have been reported to have decreased testosterone levels which decrease the risk of PCa (60,65,66). Most of the literature searched (9,63,64,66) have produced contradictory results. Arbelaez et al (2023) reported that metabolic syndrome was associated (OR=7.5) with increased odds of PCa. Body Mass Index (BMI) >30kg/m2 had increased odds (OR=1.9) of PCa incidence (63).

2.4.5 Sexual habits and sexually transmitted infections

Epidemiological studies have suggested that sexual habits and sexually transmitted infections (STI) influence the chances of being diagnosed with PCa (62,67,68). Early Sexual engagement, multiple sexual partners, and previous infection with sexual diseases increase the relative risk of PCa (67). Self-reported history of having STIs was strongly associated with PCa regardless of the type of STI (60). Some studies state that males who reported having more than 2 sexual partners were most likely to have PCa (68,69).

According to Oliver (2001), many men diagnosed with Chlamydia at STI clinics in the Carletonville mines of South Africa exhibited elevated prostate specific antigen (PSA) levels. This observation suggested a possible link between chlamydia and PCa. However, high PSA levels do not necessarily indicate PCa, as infections can compromise the membranes that separate the prostate from the bloodstream, making them more permeable(66).

A case-control study conducted in the Unites State among both Black and White men found that individuals with a history of both syphilis and gonorrhoea had over three times the relative risk of developing PCa compared to those with no record of sexually transmitted infections(68). Furthermore, the lack of condom use was identified as a contributing factor to increase PCa risk(63,67). These findings are consistent with other research (58,60,65,66,68), reinforcing the idea that sexual behaviours and exposure to STI may heighten susceptibility to PCa. However, research exploring the connection between sexual behaviour and prostate cancer remains limited in South Africa.

2.5 Enabling factors.

2.5.1 Place of residence

Adeola 2017 stated that despite SA being developed in terms of diagnostic capability, a high rate of African men still present with advanced PCa (28). This could result from a lack of access

to medical aid among men of African descent compared to whites (16). Poor screening and lack of information about the symptoms and signs of PCa have contributed to delays in seeking treatment (70).

A study by Tindal (2014) has shown that black South African men present with higher PSA values compared with Black Americans. The majority of South African men who have PCa are from rural areas (34). The incidence could have been a result of the higher case-finding rate in the private sector due to better access screening for those on medical schemes (29). Babb (2014) reports a variation in the trends of PCa in the Eastern Cape Province with low incidence in the Southern Region (11.5 per 100, 000) compared to the Northern region (53.4 per 100, 000) (12). The observed variation has been linked to poor screening in the region and poor access to facilities (27,71).

2.5.2 Baldness patterns

Baldness patterns have been acknowledged among contributing risk factors of PCa (72–74), nevertheless, studies on baldness are scarce in South Africa. Recently performed studies (72–74) based in the United States of America (USA) observed an association between vertex baldness two folds increased risk among men with PCa (73). In contrast, frontal baldness modified the risk by lowering the risk of PCa (73). High DHT levels with elevated androgen receptors (AR) are some of the presented indicators of bald scalp (72,74). The binding of the androgen gene to androgen receptors have shown a positive risk for prostate cancer (21,75). Studies exploring the relationship between baldness and PCa have been inconclusive, with a majority of investigations focusing on the European population (21,35).

CHAPTER 3 METHODS

3.0 Introduction

This chapter outlines the research methods used and gives an overview of the study. It includes details about the study design, setting, population, inclusion and exclusion criteria, sampling, and data collection. It also provides additional information on data extraction, study variables, data management, analysis, and ethical consideration.

3.1 Study Overview

The primary study was a multicenter research conducted among men of African descent across five centres in Sub – Saharan Africa, including South Africa(9). It aimed to investigate prostate cancer (PCa) by collecting comprehensive data on socio-demographics, environmental and behavioral factors, as well as clinical characteristics. Trained staff were responsible for data collection, ensuring standardised procedures, and informed consent was obtained from all participants prior to their inclusion in the study (16)

This study focused on newly diagnosed PCa cases among men aged 45 years and older, residing in Soweto, Gauteng Province, between 2017 and 2021. Eligible participants had confirmed histological diagnoses of PCa, regardless of stage, grade, or pathological classification. However, individuals with a prior diagnosis of any other cancer from a different medical center were excluded. For comparison, control participants were selected from St John's Eye Hospital and included patient-caregivers without any prior cancer diagnosis(9).

3.2 Study design, study setting, and study population

This study employs a case-control design using a quantitative approach. It is a secondary data analysis derived from a primary study investigating the prevalence of prostate cancer (PCa) among men of African descent. The study was conducted at Chris Hani Baragwanath Hospital (CHBAH) in Johannesburg, Gauteng Province, South Africa. CHBAH is one of the study centres that participated in the broader multicenter study. The study population consist of men aged 45 years and older who were enrolled at CHBAH between 2017 and 2021. Eligible cases included men diagnosed with PCa and identified as black. Controls were patient-caregivers without a prior cancer diagnosis (9).

Johannesburg is chosen deliberately because it houses 26.1% of the national population and has the highest inflow of migrants from different places who come to seek jobs in the mines(30). CHBAH is one of the major government hospitals (third world largest) and attends to the black urban population in Johannesburg(30). About 200 patients are seen per day at the urology clinic referred from primary and secondary facilities around Soweto and are mostly of African descent(9). The majority of standard PCa treatment options exist at CHBAH such as prostatic brachytherapy, external beam radiation, radical surgery, and hormonal therapy (9,16).

3.3 Inclusion and exclusion criteria

This study focuses on men of African descent aged 45 years and older. It excludes those who are below 45 years of age. The lower bound for inclusion is based on the 2017 South African prostate cancer guidelines, which recommend screening for all men from the age of 45 years. Only patients who were newly diagnosed with PCa at the start of the primary study were included. Cases included only those with confirmed pathology, while individuals previously diagnosed with PCa more than six months prior to the hospital visit, as well as those diagnosed based on clinical factors, were excluded. Cases were defined as men aged 45 years and older

who were referred to the urology department with newly confirmed diagnoses. Controls were either participants identified at the St John's Eye Hospital or patient-caregivers who had no previous cancer diagnosis.

3.4 Sampling

Pathology results were used as the method of selection. Cases were those with confirmed positive pathology results presenting at the urology clinic. Controls were participants identified either at the St John's Eye Hospital or were patient-caregivers without any prior diagnosis of cancer.

Controls were matched with cases by age. Matching was done using age as a continuous variable. Age was used since it is a well-documented and known confounding factor for PCa (14,37,76). A 1:1 matching was done adopting a matching procedure called CC-Match by Cooks (74). Observations that were found matched were 836, and 335 could not find matches (see Figure 3). Those observations with no matches were excluded from the matched analysis.

Power of the study

Power calculation was done using 836 cases and 836 controls. According to a study by Cassim (2021), 39% of black Africans had PCa from biopsy results. Usual past residence was stated as a risk factor that had the highest odds ratio(OR=4.09) (35). Using Stata 17, power was computed based on the above parameters (prevalence =39%, OR=4.09). A power of 1.00 was obtained, which means that the study is powered enough to show if a difference exists since it is above 0.80**.**

3.5 Data collection

Data for this study was obtained from a primary study conducted at CHBAH among men of African descent presenting at urology clinic. Structured interviews and medical records review were used as to obtain primary data. Collected data was entered into an electronic database and

password protected. Data deidentification was also completed. Data access and use were obtained from the MADCAP team. The data was received in a Stata format.

3.6 Study Variables

3.6.1 Outcome Variable

The outcome variable Prostate cancer was confirmed by a positive pathology result. Prostate cancer is binary, coded 1 for someone with PCa and 0 for someone without PCa.

3.6.2 Explanatory variables included (see figure 1 below)

Figure 1 presents a conceptual framework outlining the risk factors for prostate cancer. It serves as a visual presentation of the key variables examined in this study, illustrating their potential interactions and contributions to prostate cancer risk. This framework provides context for the study and helps to conceptualize how various factors, such as lifestyle behaviours, infections, and biological influences, may be associated with prostate cancer development.

1. *Biological factors*: These are non-modifiable factors which are: age in years used as a continuous variable, family history of having a father who was diagnosed with PCa coded yes for someone with a father who had prostate cancer, or no for someone whose father did not have PCa. Family history of having a biological brother who had PCa coded yes or no.
2. *Behavioural factors*: smoking status was categorized as never smoked, current smoker, or past smoker. Alcohol consumption was classified based on individual responses as never consumed alcohol, currently drinking, or previously consumed alcohol. The presence of sexually transmitted infections (STIs) was recorded as either yes or no. Due to limited sample size in certain categories, gonorrhea, syphilis, and herpes were collectively recorded as “yes” if present. Circumcision status was also documented and classified as either circumcised or not.

3. *Social factors*: income level was used as an explanatory variable to gauge the social economic class. Income was measured in Rands and recorded as less than R5000 per month, between R5000 to R10,000 per month, and Above R10,000 per month. Marital status was also used which was coded single (separated and divorced included), married, and widowed. Education status was coded less than high school, high school graduate, and more than high school.
4. *Comorbidities:* Diabetes mellitus was also used as an explanatory variable coded yes for someone already diagnosed and on treatment, and no for someone not diagnosed with the disease. High cholesterol level was also used which was coded no for someone with a total cholesterol level of less than 3.0 mmol/L, and yes for someone with a total cholesterol level above 5.5 mmol/L. BMI was recorded as underweight (BMI<18.49), healthy weight (BMI>18.5 <24.99), overweight (BMI >25.0 <29.99), and obese (BMI >30.0 <52.0) according to the World Health Organization (WHO) categories (19,77).
5. *Enabling factors:* some of the enabling factors for PCa include access to health care, and medical insurance cover which influences health-seeking behaviour (24,76,78).
6. *Confounders*: age and a positive family history of PCa are known confounders(44,76,79).

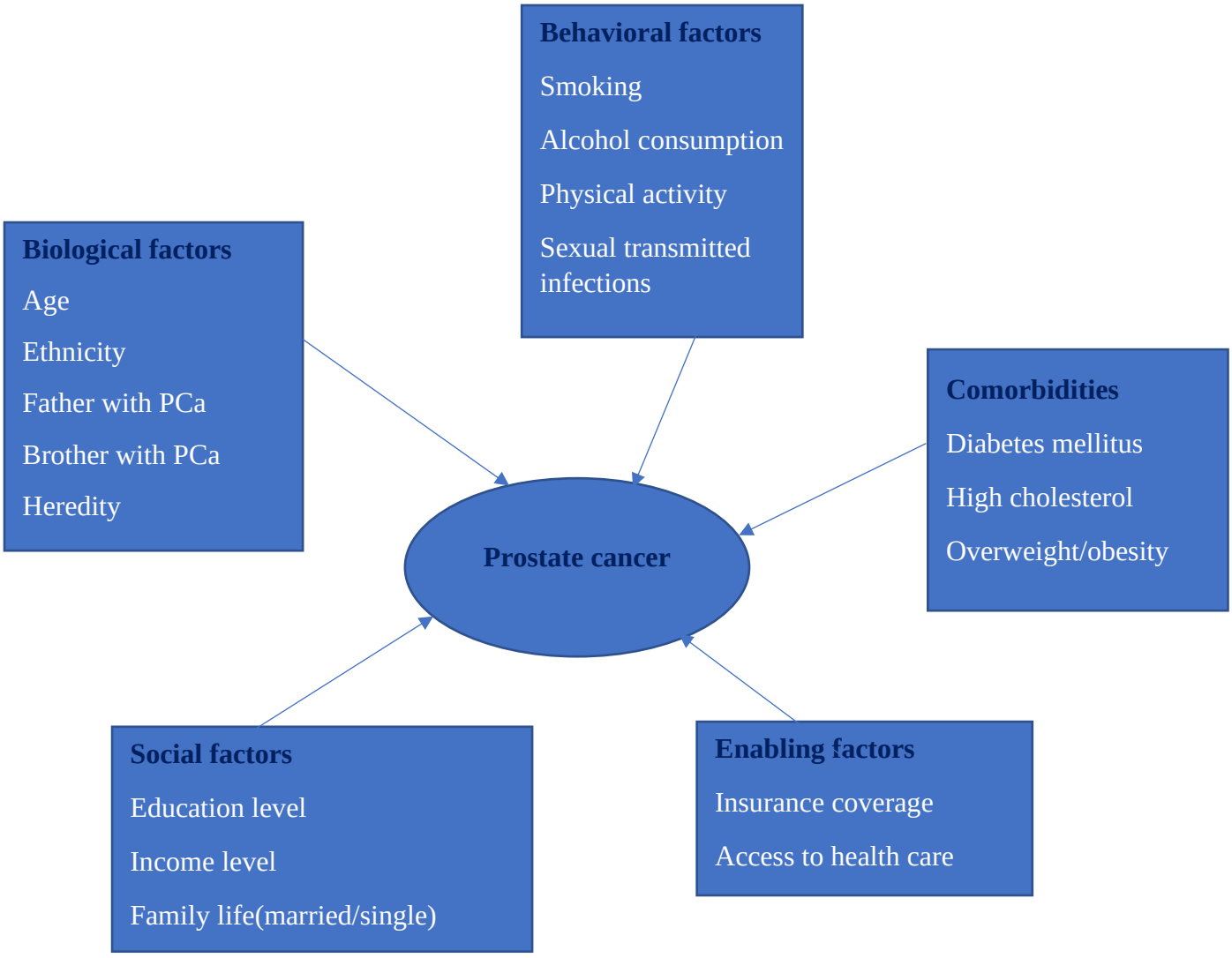


Figure 1: Conceptual framework of risk factors for prostate cancer

3.7 Data management

Data was received through a password-protected email and then imported to STATA 17 for analysis. A password-protected computer was used for data storage. Datasets were received separately for cases and controls. Variable age in years was created for both cases and controls. For controls, date of birth and date of interview were used to create the new variable age. For

cases, date of birth and date of diagnosis were used to create the new variable age since there was no variable for the date of interview among the cases. The two datasets were appended. Completeness and consistency of data was done using STATA 17prior to the analysis. The controls had two observations with missing values on key parameters such as age, PCa status, as well as income. These missing observations were excluded in the analysis. The outcome variable prostate cancer had no missing values. Variable age in years was checked for missing values. Participants with missing ages were excluded from the analysis. Continuous variable BMI was categorized. All categorical variables were coded. Variable renaming, recoding, and labelling was done.

Of the 2139 participants who were involved in the study, 1095 were cases and 1044 were controls. Among the controls, two were loss to follow-up and they were excluded Among the cases, seven were below 45 years of age and 37 among the controls were below 45 years. These were excluded as they did not meet the inclusion criteria. All participants who were recruited before the year 2017 or after 2021 (86 participants) were excluded from the analysis. Only 2007 participants remained for the analysis (cases=1005 cases, controls=1002). (See figure2 below)

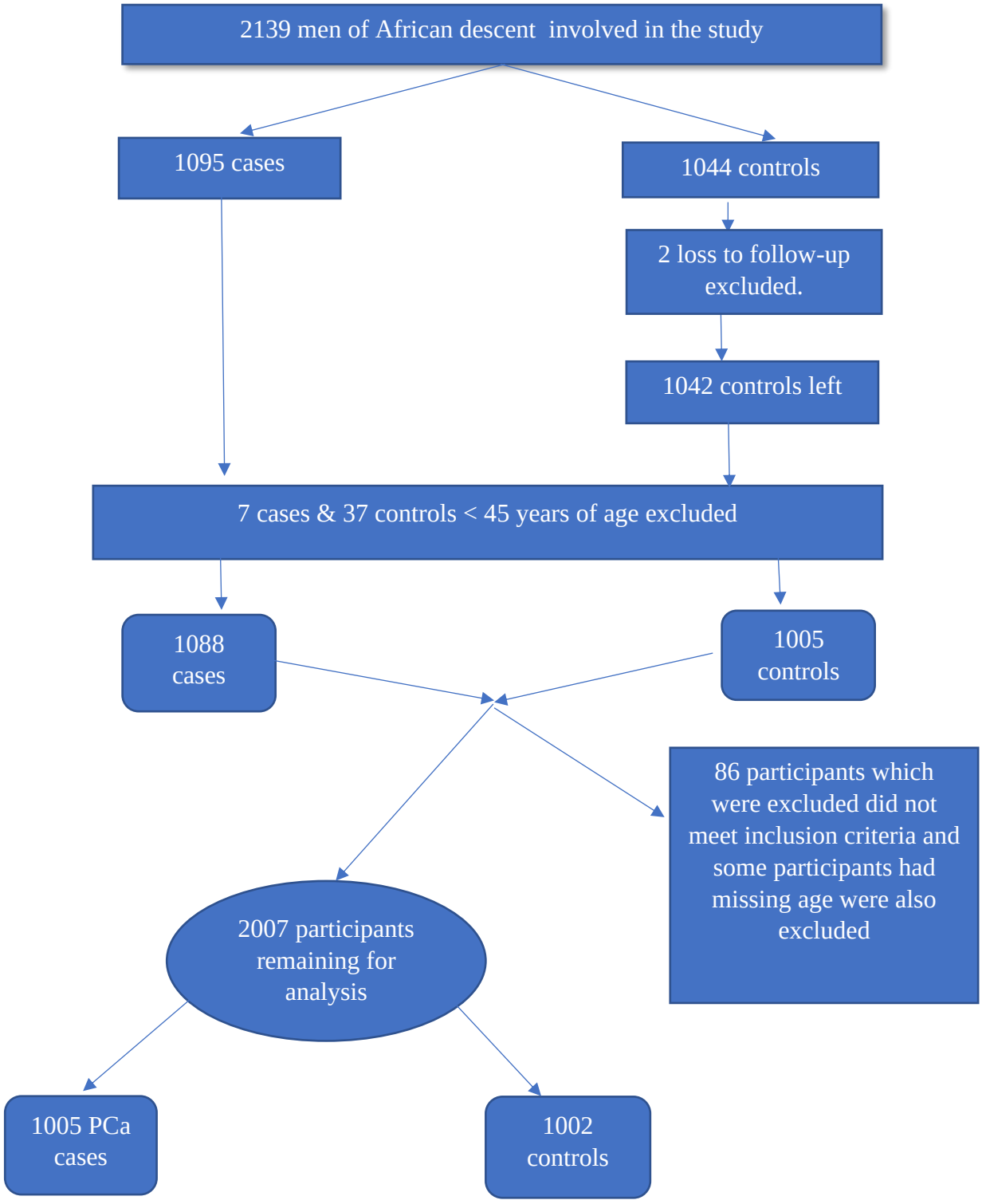


Figure 2: Sampling diagram of men included in the study as cases and controls, 2017 -2021

3.8 Data analysis

Data analysis was conducted using STATA 17.

3.8.1 Descriptive statistics

The assumption of normality for variable age in years was tested graphically using a histogram and was met. Means and standard deviation (SD) were reported. Descriptive statistics using proportions and frequencies for categorical variables such as marriage status, education level, income, and family history of PCa were used to summarize the sociodemographic characteristics of the participants. Pearson chi-square test was used for categorical variables.

3.8.2 Logistic regression analysis

To determine the risk factors for PCa, a logistic regression method was used for unmatched data. This method is one of the generalized linear models. It is used for the classification of binary outcomes based on multiple categorical or continuous factors (80). This model utilizes maximum likelihood methods which enables adjusting for multiple confounders (81). The probability of an event (in this case prostate cancer) ranges between 0 and 1 where 0 indicates no event (no prostate cancer) and 1 indicates the occurrence of an event (have prostate cancer) (80). The logistic regression utilizes the formulae below (82).

$$\frac{e^{(bo+b1X)}}{1+e^{(bo+b1X)}} \qquad \text{[Equation 1]}$$

Where:

X= independent variables

Y = Predicted outcome which is Prostate cancer

b0 = intercept

b1 = coefficient for independent variable(X)

The independent variables (X) are combined to predict the outcome (Y), binary prostate cancer. This model takes the assumption that the response variable (Y) is binary, and the predictor variables (X) are independent of each other (83). Exposure variables which were used in the model include age in years, marital status, education status, employment status, income level, etc. Univariate logistic regression was done first for each exposure variable and the odds ratios (OR), p-values and 95% confidence interval (CI) were reported.

3.8.3 Stepwise regression variable selection

A stepwise logistic regression was used to select the best potential predictors for PCa. Stepwise regression is a procedure that adds or removes variables based on their statistical significance and predictive power (84). A stepwise backward selection was used which starts with all predictors in the model and then removes variables one at a time based on a criterion (82). A cut-off p-value of < 0.20 was used for the selection of the predictor variable. Variables which remain in the backward selection were then included in the multiple logistic regression model.

3.8.4 Multiple logistic regression

A multivariable logistic regression analysis was conducted using variables selected from the stepwise backward selection and those which were significant in univariate regression. Variables which were included in the multiple analysis were age in years, marital status, education status, employment status, income level, family history of a father who was diagnosed with PCa, family history of a biological brother who was ever diagnosed with PCa, and high cholesterol. A p-value of < 0.05 was considered statistically significant. Adjusted Odds ratios (aOR), p-values and 95% CI were reported.

3.8.5 Matching cases and controls

In a case-control study, matching can be done to account for known confounders (82). After conducting an unmatched analysis in this study, matching was done using age as a continuous

variable. Age was used since it is a well-documented and known confounding factor for PCa (14,37,76). Matching helps to build control by incorporating the known knowledge into the design of the study (82). A 1:1 matching was done adopting a matching procedure called CC-Match by Cooks (74). The CC-Match is used to randomly match cases and controls based on specified criteria. The matching variable (age) was specified following the CC-Match command in STATA 17. The CC-Match command indicates that the matching is for cases and controls which are of the same age as indicated by the matching variable (85). Observations that found matched were 836, and 335 could not find matches (see Figure 3). Those observations with no matches were excluded from the matched analysis. A conditional logistic regression analysis accounting for the matching variable was then conducted to compare the effects matching had on the results (86).

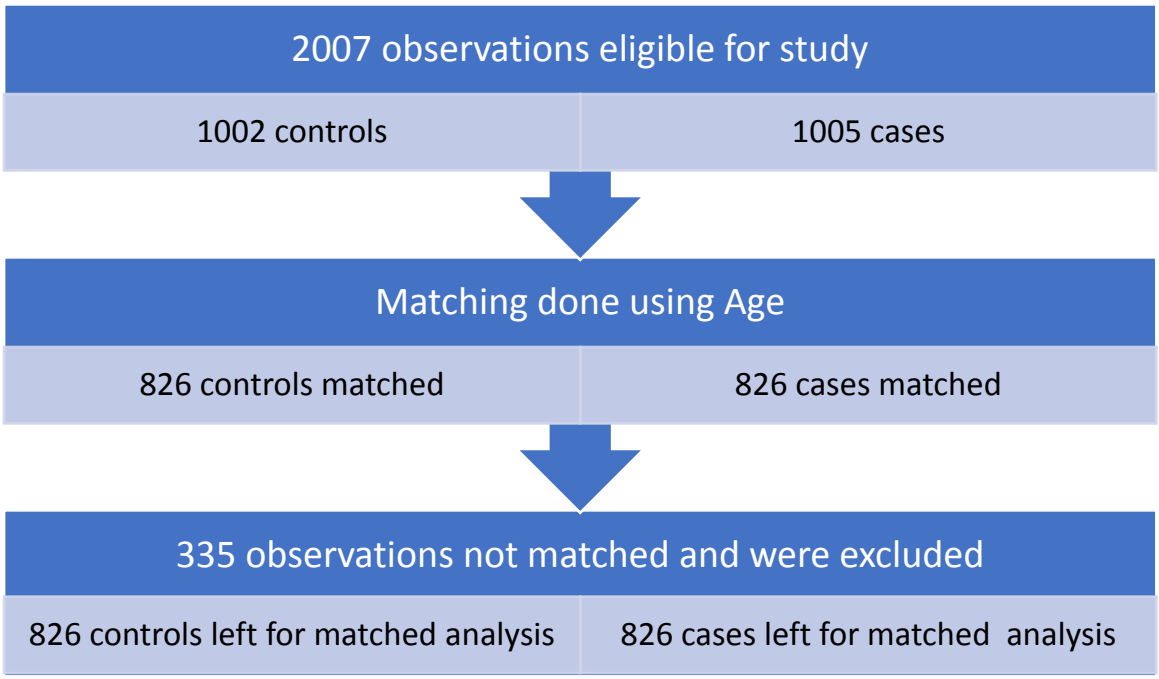


Figure 3A: Flow diagram for the matching procedure

3.8.6 Conditional logistic regression

A conditional logistic regression analysis was used for the matched observations. This is because cases and controls within matched sets are sampled together based on shared values of

the matching variable (age in this case), thus the structure of the overall sample differs from that of an unmatched study (82,86). The conditional logistic regression is based on a modification of the maximum-likelihood estimation approach used for the conventional logistic regression model (82). This model avoids estimating parameters accounting for the matching via conditioning. In this method, we conduct analysis the same way as in the standard logistic model except that variables used in matching are controlled for automatically and are not used directly in modelling (86). The conditional logistic regression is presented as

$$\text{logit}\{p_j(x_{1ij}, x_{2ij}, \ldots x_{kij})\} = \alpha_j + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \ldots + \beta_k x_{kij} \quad \text{----} \quad \text{[equation 2]}$$

where;

$\alpha_j =$ sum up the impact of matching variables on the odds of disease.

$P_j(X1_{ij}, X2_{ij} \ldots Xk_{ij}) =$ the odds that the ith individual in the jth matched set has the condition.

$X1_{ij}, X2_{ij} \ldots Xk_{ij}$ = the values of the k predictor variables

i = individuals

j = matched set

3.8.7 Survival analysis

In this research, we also assessed the association between time to diagnosis of PCa with sociodemographic factors. Kaplan-Meier (KM) nonparametric curves were conducted to determine the cumulative likelihood of PCa diagnosis from birth and those who had no PCa were censored on the last day of the follow-up study. The KM curves were conducted for different categorical covariates. The log-rank test was used to assess the equality of PCa probability among patients between different possible categorical risk factors. Since the KM method cannot provide effect estimates or related confidence intervals to compare survival in different groups, a Cox proportional hazards regression model was also used (87).

The Cox regression assessed the association between time to diagnosis of PCa with socio-demographic factors. Cox regression is a semiparametric method which has no assumption on survival time distribution but assumes that the effect of different covariates on survival is constant over time(80,87). The Cox regression model is based on the hazard function and is written as follows.

$$H(t) = H_O(t) * \exp[b_1x_1 + b_2x_2 + \ldots\ldots b_k x_{k.}] \quad \text{[Equation 3]}$$

where x_1 = the predictor variable

$H_0(t)$ = the baseline hazard at time t, which is the hazard of an individual having the predictors set to zero.

H(t) = the hazard rate as a function of time.

i = elapsed time to the event of interest for each observation

bi = the coefficient for each predictor variable i

3.8.8 Study time

In this study, we estimated the study time from birth to diagnosis using the date of diagnosis available on the cases and their date of birth. The controls were censored on the last day of the follow-up study (88). Age (in years) at the time of PCa diagnosis was used as a time variable. Results were reported as hazard ratios (HRs), 95% CI and p-values.

3.8.9 Model Analysis

A test of the overall statistical significance of the models was done using the Hosmer and Lemeshow test. This test is a goodness of fit test for logistic regression especially for risk prediction models (82,89). This test informs you how well your data fits the model. It can be used only for binary response variables. In this method, the likelihood chi-square statistics is

computed by comparing the deviance of a final model with a model comprising all covariates specified (87). The test brings a Chi-square value and a p-value. Small p-values (<0.05) indicate a poor fit whereas a large p-value(>0.05) indicates that there is a lack of evidence to say the model is not a good fit (90).

For the Cox regression model diagnosis, we used a Schoenfeld residual hazard assumption test. The Schoenfeld residual is one way of assessing the proportionality of the hazards. It does this by computing residuals for each subject and each covariate (90,91).

3.9 Ethical Consideration

Study endorsement was acquired from the Witwatersrand Human Research Ethics Committee (Medical) (clearance certificate number: M230312) (see Appendix B). Approval to utilize the dataset was obtained from the MADCAP network Wits Health Consortium (see Appendix C). The primary study obtained approval from both international and Local bodies namely the United States (US) Department of Health and Human Services Federal Wide Assurance. Coding was done for anonymity. The dataset was shared through Google Drive with the supervisors for confidentiality. All study material related to the dataset will be password-protected in the drive. Findings of this study will be disseminated through presentations to relevant stakeholders, and publication.

CHAPTER 4 RESULTS

4.0 Introduction

This chapter reports the results analysed using descriptive statistics, logistic regression, and Cox regression. The factors associated with PCa from the matched group and the unmatched group were determined. The results are shown in different subheadings. First, descriptive statistics using Pearson's Chi-square for categorical, T-test for continuous variables and Kaplan Meier curves for time to diagnosis stratified by different baseline characteristics. The findings are also presented from univariate and multiple logistic regression for matched and unmatched groups. A subgroup analysis of Cox regression is also presented.

Figure 3B below provides a schematic illustration of the fitted models and the selection process for identifying the best-fitting model. This visual representation complements the analysis by outlining the modelling approach, highlighting key comparisons, and demonstrating the criteria used to determine the most suitable model for the data.

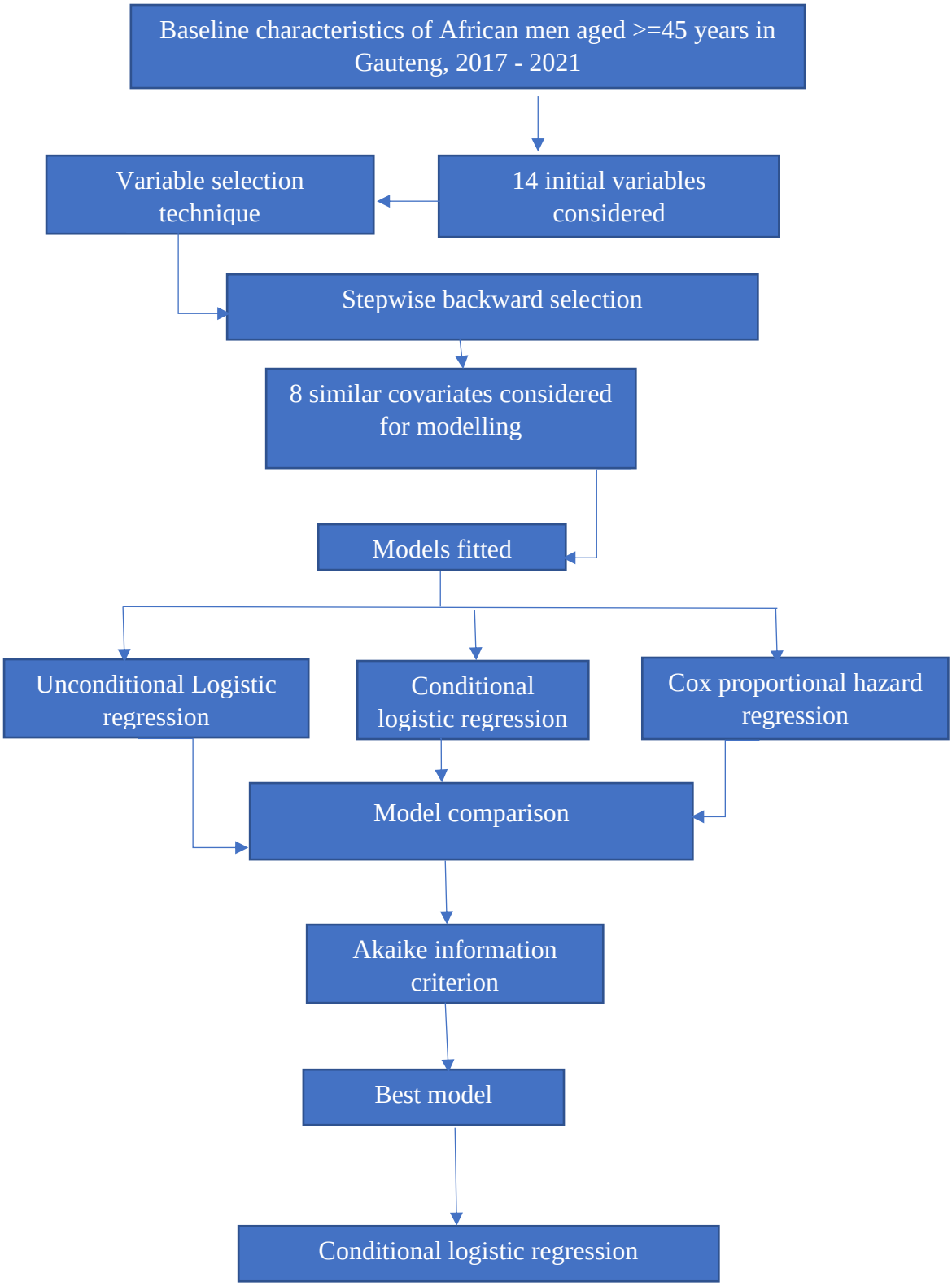


Figure3B: Schematic illustration of fitted models and selection of best fitting model.

4.1 Descriptive Statistics -Unmatched Data

4.1.1 Participants' baseline characteristics

The study had 2007 men who were seen between the years 2017 to 2021 and were 45 years and older based on unmatched data as illustrated in Table 1 below. Of these, 1005 were cases that had positive pathology results of PCa and 1002 were controls with no history of PCa. The overall participant's mean age was 65.5 ± 8.09 years. Those with PCa were older than those without PCa and this was statistically significant, p-value<0.05. The age range was 45-94 years. Most of the participants were married (n=1,353 (67.41%)); had attended less than high school (n=1,615 (80.47%)), were retired (n=1,477 (73.59%)) and had an income of less than R5000 per month (1,701 (94.34%)). A significant association (p-value<0.05) between having PCa and level of education, marital status and unemployment was observed. Regarding the lifestyle of the participants, (n=860 (42.85%)), were currently taking alcohol and (n=741 (36.92%)) had never smoked cigarettes. Most of the controls had never smoked (n=412 (41.12%)) while most of the PCa cases had a history of smoking (n=397 (39.50%)). Alcohol intake and smoking were significantly associated with PCa, p-value<0.05.

Most prostate cancer patients had a healthy weight, with 37.61% having a BMI between 18.5 and 24.99. additionally, 85.55% of the patients did not have diabetes mellitus (85.55%). Most PCa patients had high blood cholesterol (11.94%) as compared to the controls (4.89%). STIs appear to be higher among cases (40.10%) and most cases were not circumcised. Among the study participants, a majority (96%) reported that their fathers were never diagnosed with PCa, (4%) reported that their biological fathers had PCa. Most participants (n=1534 (97%)) did not have a biological brother diagnosed with PCa. Family history (brother or father) was associated with having PCa, p-value<0.05. Table 1 below illustrate the summary of the baseline characteristics of participants.

Table 1: Baseline characteristics of men who attended Chris Hani Baragwanath's Hospital from 2017 to 2021

Characteristics	Total N=2007	Controls N=1002	Cases N=1005	p-value
Participant age in years				
Mean Age	65.54 (8.09)	64.19 (8.37)	66.88 (7.58)	**<0.001***
Marital status				
Single	422 (21.03%)	246 (24.55%)	176 (17.51%)	**<0.001***
Married	1,353 (67.41%)	663 (66.17%)	690 (68.66%)	
Widowed	232 (11.56%)	93 (9.28%)	139 (13.83%)	
Education status				
Less than high school	1,615 (80.47%)	753 (75.15%)	862 (85.77%)	**<0.001***
High school graduate	264 (13.15%)	175 (17.47%)	89 (8.86%)	
More than high school	128 (6.38%)	74 (7.39%)	54 (5.37%)	
Employment status				
Unemployed	217 (10.81%)	139 (13.87%)	78 (7.76%)	**<0.001***
Employed	313 (15.60%)	176 (17.56%)	137 (13.63%)	
Retired	1,477 (73.59%)	687 (68.56%)	790 (78.61%)	
Income level				
Less than R5,000 per month	1,701 (94.34%)	803 (93.37%)	898 (95.23%)	0.23
R5,001 - R10,000 per month	68 (3.77%)	38 (4.42%)	30 (3.18%)	

Above R10,000 per month	34 (1.89%)	19 (2.21%)	15 (1.59%)	
History of alcohol consumption				
Never drank alcohol	568 (28.30%)	327 (32.63%)	241 (23.98%)	**<0.001***
Yes currently	860 (42.85%)	436 (43.51%)	424 (42.19%)	
Yes, in the past	579 (28.85%)	239 (23.85%)	340 (33.83%)	
History of cigarette smoking				
Never smoked	741 (36.92%)	412 (41.12%)	329 (32.74%)	**<0.001***
Current smoker	609 (30.34%)	330 (32.93%)	279 (27.76%)	
Past smoker	657 (32.74%)	260 (25.95%)	397 (39.50%)	
Biological brother diagnosed with PCa				
No	1,534 (97.46%)	813 (99.15%)	721 (95.62%)	**<0.001***
Yes	40 (2.54%)	7 (0.85%)	33 (4.38%)	
Biological father diagnosed with PCa				
No	1,431 (96.04%)	862 (98.40%)	569 (92.67%)	**<0.001***
Yes	59 (3.96%)	14 (1.60%)	45 (7.33%)	
BMI groups				
Underweight	93 (4.63%)	50 (4.99%)	43 (4.28%)	0.45
Healthy weight	775 (38.61%)	397 (39.62%)	378 (37.61%)	
Over weight	661 (32.93%)	330 (32.93%)	331 (32.94%)	

Obese	478 (23.82%)	225 (22.46%)	253 (25.17%)	
Diabetes Mellitus				
No	1644 (82.04%)	806 (80.52%)	838 (85.55%)	0.07
Yes	360 (17.96%)	195 (19.48%)	165 (16.45%)	
High blood cholesterol				
No	1838 (91.58%)	953 (95.11%)	885 (88.06%)	< 0.001*
Yes	169 (8.42%)	49 (4.89%)	120 (11.94%)	
Sexually transmitted infection				
No	1219 (60.74%)	617 (61.58%)	602 (59.90%)	0.44
Yes	788 (39.26%)	385 (38.42%)	403 (40.10%)	
Are you circumcised?				
No	1029 (51.27%	504 (50.30%)	525 (52.24%)	0.38
Yes	978 (48.73%)	498 (49.70%)	480 (47.76%)	

4.2 Logistic regression analysis

In a case-control design, both unconditional (unmatched) logistic regression (ULR) and conditional (matched) logistic regression (CLR) can be used. Conditional logistic regression is used when data include matched pairs, and it accounts for dependency introduced by the matching process(86). In the presence of strong confounders, matching is done thus analysis for a matched group using CLR is ideal (92). Additionally, Unconditional logistic regression is the standard logistic regression model used when there is no matching of cases and controls(90). In this study, both unconditional and conditional analyses were performed.

Conditional logistic regression

4.2.1 Univariate and multiple analysis for unmatched group

To assess the association between potential risk factors and prostate cancer among men of African descent, both univariate and multiple logistic regression analyses were conducted. The univariate analysis examined the crude associations between individual risk factors such as age, family history of PCa, lifestyle factors, comorbidities, and the likelihood of developing PCa. The multiple logistic regression adjusted for potential confounders, including age, family history, BMI, smoking status and dietary factors. Results are reported as odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values in table 2 below.

Table 2: Unconditional Logistic regression analysis for factors associated with prostate cancer among men of African descent aged 45 years and older attended at Chris Hani Baragwanath's Hospital in Gauteng Province (January 2017 – December 2021.

Characteristics	**Univariate logistic regression**		**Multiple logistic regression**	
	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Participant age in years				
Age	1.04 (1.032 – 1.055)	**<0.001***	1.04 (1.02 – 1.07)	**<0.001***
Marital status				
Single	1 (base)		1 (base)	
Married	1.45 (1.17 – 1.81)	**<0.001***	1.41 (1.01 – 1.97)	**0.042***
Widowed	2.08 (1.51 – 2.89)	**<0.001***	1.53 (0.94 – 2.50)	0.086
Education status				
Less than high school	1 (base)		1 (base)	
High school graduate	0.44 (0.34 – 0.58)	**<0.001***	0.39 (0.26 – 0.60)	**<0.001***
More than high school	0.63 (0.44 – 0.92)	**0.015***	1.16 (0.72 – 1.89)	0.537
Employment status				
Unemployed	1 (base)		1 (base)	
Employed	1.38 (0.97 – 1.98)	0.072	1.75 (1.01 – 3.06)	**0.048***
Retired	2.05 (1.53 – 2.75)	**<0.001***	1.42 (0.84 – 2.43)	0.194
Income level				
Less than R5,000 per month	1 (base)			

R5,001 -R 10,000 per month	0.71 (0.43 – 1.15)	0.162		
Above R10,000 per month	0.71 (0.36 – 1.40)	0.318		
Have you ever drunk alcohol in your life?				
Never drank alcohol	1 (base)		1 (base)	
Yes currently	1.32 (1.07 – 1.63)	**0.011**	1.53 (1.10 – 2.15)	**0.013***
Yes, in the past	1.93 (1.53 – 2.44)	**<0.001***	2.06 (1.43 – 2.99)	**<0.001***
Have you ever smoked cigarettes for at least one year of your life?				
Never smoked	1 (base)		1 (base)	
Current smoker	1.06 (0.85 – 1.31)	0.604	1.07 (0.77 – 1.51)	0.679
Past smoker	1.91 (1.55 – 2.37)	**<0.001***	1.57 (1.13 – 2.19)	**0.008***
Were any of your biologically related brothers ever diagnosed with prostate cancer				
No	1 (base)		1 (base)	
Yes	5.32 (2.34 – 12.09)	**<0.001***	1.58 (0.59 – 4.25)	0.364
Was your biological father ever diagnosed with prostate cancer?				
No	1 (base)		1 (base)	
Yes	4.87 (2.65 – 8.95)	**<0.001***	8.04 (3.54 – 18.33)	**<0.001***
Circumcised				
No	1 (base)		-	
Yes	0.93 (0.78 – 1.10)	0.385		

Sexually transmitted infection				
No	1 (base)		-	
Yes	1.07 (0.90 – 1.28)	0.442		
BMI				
Underweight	1(base)		-	
Healthy weight	1.11 (0.72 – 1.70)	0.644		
Overweight	1.17 (0.76 – 1.80)	0.488		
Obesity	1.31 (0.84 – 2.04)	0.238		
Diabetes mellitus				
No	1 (base)		-	
Yes	0.78 (0.647 – 1.023)	0.078		
High cholesterol				
No	1 (base)		1 (base)	
Yes	2.64 (1.868 – 3.722)	**<0.001***	2.60 (1.58 – 4.29)	**<0.001***

The results show that age is positively associated with PCa with a 4% increased likelihood for every one-year increase in age (OR=1.04, 95%CI: 1.03 - 1.06). Those who were married (OR=1.45, 95%CI: 1.17 – 1.81) or widowed (OR=2.08, 95%CI: 1.51 – 2.89) had increased odds of having PCa than those who were single. Obtaining a high school education and having education more than a high school education reduced the likelihood effect of having PCa by 56% (OR=0.44, 95%CI: 0.34 - 0.58) and 37% (OR= 0.63, 95%CI: 0.44 -0.92) respectively compared to those who had less than high school education.

Those retired had increased odds of PCa (OR=2.05, 95%CI: 1.53 – 2.75) compared to those who were unemployed. Currently drinking alcohol (OR=1.32, 95%CI: 1.07 – 1.63), drank alcohol in the past (OR=1.93, 95%CI: 1.53 – 2.44) and past smokers (OR=1.91, 95%CI: 1.55 – 2.37) had an increased likelihood of having PCa compared to never drank alcohol and never smoked respectively. Having a brother diagnosed with PCa (OR=5.32, 95%CI: 2.34 – 12.09) and having a father with PCa (OR=4.87, 95%CI: 2.65 – 8.95) increased the likelihood of having PCa compared to having no brother or father with PCa respectively. Those with high cholesterol levels (OR=2.64, 95%CI: 1.87 – 3.72) had an increased odds of PCa compared to those with low cholesterol levels.

After adjusting for other variables, a one-year increase in age increased the possibility of having PCa by 4% (AOR=1.04, 95%CI: 1.02 – 1.07). Those who were married had 41% higher odds of having PCa (AOR=1.41, 95%CI: 1.01 – 1.97) compared to those who were not married. High school graduates had 61% reduced odds of having PCa (AOR=0.39, 95%CI: 0.26 – 0.60) compared to those with less than a high school education. Those employed had increased odds of having PCa (AOR=1.75, 95%CI: 1.01 – 3.06) compared to those unemployed. Those currently drinking alcohol had 53% increased odds of having PCa (AOR=1.53, 95%CI: 1.10 – 2.15) while those with past drinking behaviour had 2.06 times (95%CI: 1.43 – 2.99) increased odds of having PCa compared to those who never drank alcohol. Those who were past smokers

had increased odds of having PCa (AOR= 1.57, 95% CI: 1.13 – 2.19) compared to those who never smoked. Those with a father diagnosed with PCa (AOR=8.04, 95%CI: 3.54 – 18.33) had increased odds of having PCa. Those with high cholesterol levels (AOR=2.6, 95%CI: 1.58 – 4.29) had increased odds of having PCa compared to those with low cholesterol levels.

4.2.2 Univariate and multiple conditional analysis for the matched group.

Variables for the multiple conditional analysis were selected using a stepwise regression backward selection. The results are summarized in Table 3 below.

Those who were widowed (condOR=1.55, 95%CI: 1.07 – 2.34) had increased odds of having PCa than those who were single. Obtaining a high school education and having education more than a high school education reduced the likelihood effect of having PCa by 47% (condOR=0.53, 95%CI: 0.39-0.72) compared to those who had less than a high school education. Currently drinking alcohol (condOR=1.5, 95%CI: 1.18 – 1.9), drank alcohol in the past (condOR=1.85, 95%CI: 1.43 – 2.4) and past smokers (condOR=1.87, 95%CI: 1.48 – 2.37) had an increased likelihood of having PCa compared to never drank alcohol and never smoked respectively. Having a brother diagnosed with PCa (condOR=4.63, 95%CI: 2.02 – 10.64) and having a father with PCa (condOR=7.05, 95%CI: 3.39 – 14.66) increased the likelihood of having PCa compared to having no brother or father with PCa respectively. Those with diabetes had 30% reduced odds of having PCa (condOR=0.7, 95%CI: 0.55 –0.9). Those with high cholesterol levels (condOR=2.59, 95%CI: 1.79 – 3.74) had increased odds of PCa compared to those with low cholesterol levels.

Table 3: Conditional Logistic regression analysis for factors associated with prostate cancer among men of African descent aged 45 years and older attended at Chris Hani Baragwanath's Hospital in Gauteng Province (January 2017 – December 2021

Characteristics	**Univariate conditional logistic regression**		**Multiple conditional logistic regression**	
	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Marital status				
Single	1 (base)		1 (base)	
Married	1.13 (0.89 – 1.45)	0.320	1.45 (1.01 – 2.09)	**0.042***
Widowed	1.55 (1.07 – 2.34)	**0.021***	1.63 (0.96 – 2.77)	0.07
Education status				
Less than high school	1 (base)		1 (base)	
High school graduate	0.53 (0.39 – 0.72)	**<0.001***	0.38 (0.24 – 0.61)	**<0.001***
More than high school	0.94 (0.62 – 1.40)	0.746	1.39 (0.82 – 2.40)	0.22
Employment status				
Unemployed	1 (base)		1 (base)	
Employed	1.49 (0.99 – 2.24)	0.06	1.94 (1.05 – 3.61)	**0.036***
Retired	1.12 (0.72 – 1.73)	0.62	1.25 (0.66 – 2.41)	0.492
Income level				
Less than R5,000 per month	1 (base)		-	
R5,001 - R10,000 per month	1.07 (0.62 – 1.86)	0.79		
Above R10,000 per month	1.59 (0.66 – 3.85)	0.30		

Have you ever drunk alcohol in your life?				
Never drank alcohol	1 (base)		1 (base)	
Yes currently	1.50 (1.18 – 1.90)	**<0.001***	1.59 (1.09 – 2.33)	**0.016***
Yes, in the past	1.85 (1.43 – 2.40)	**<0.001***	2.01 (1.33 – 3.04)	**0.001***
Have you ever smoked cigarettes for at least one year of your life?				
Never smoked	1 (base)		1 (base)	
Current smoker	1.16 (0.92 – 1.48)	0.214	0.99 (0.69 – 1.45)	0.99
Past smoker	1.87 (1.48 – 2.37)	**<0.001***	1.79 (1.24 – 2.61)	**0.002***
Were any of your biologically related brothers ever diagnosed with prostate cancer				
No	1 (base)		1 (base)	
Yes	4.63 (2.02 – 10.64)	**<0.001***	1.24 (0.43 – 3.58)	0.685
Was your biological father ever diagnosed with prostate cancer?				
No	1 (base)		1 (base)	
Yes	7.05 (3.39 – 14.66)	**<0.001***	8.67 (3.35 – 22.45)	**<0.001***
Circumcised				
No	1 (base)		-	
Yes	0.94 (0.779 – 1.14)	0.558		
Sexually transmitted infection				

No	1 (base)		-	
Yes	1.06 (0.88 – 1.30)	0.66		
BMI				
Underweight	1 (base)		-	
Healthy weight	0.90 (0.57 – 1.44)	0.66		
Overweight	0.95 (0.59 – 1.51)	0.822		
Obesity	1.02 (0.64 – 1.66)	0.907		
Diabetes mellitus				
No	1 (base)		1 (base)	
Yes	0.70 (0.55 – 0.90)	**0.006***	0.52 (0.36 – 0.75)	**<0.001***
High cholesterol				
No	1 (base)		1 (base)	
Yes	2.59 (1.79 – 3.74)	**<0.001***	3.76 (2.16 – 6.53)	**<0.001***

After adjusting for other variables, those who were married had 45% higher odds of having PCa (condAOR=1.45, 95%CI: 1.01 – 2.09) compared to those who were not married. High school graduates were 62% reduced odds of having PCa (condAOR=0.38, 95%CI: 0.24 – 0.61) compared to those with less than high school education. Those employed had increased odds of having PCa (condAOR=1.94, 95%CI: 1.05 – 3.61) compared to those unemployed. Those currently drinking alcohol had 59% increased odds of having PCa (condAOR=1.59, 95%CI: 1.09 – 2.33) while those with past drinking behaviour had 2.01 times (95%CI: 1.33 – 3.04) increased odds of having PCa compared to those who never drank alcohol. Compared to those who never smoked, those who were past smokers had increased odds of having PCa (condAOR=1.79, 95% CI: 1.24 – 2.61) compared to those who never smoked. Those with a father diagnosed with PCa (condAOR=8.67, 95%CI: 3.35 – 22.45) had increased odds of having PCa. Those with diabetes had 48% reduced odds of having PCa (condAOR=0.52, 95%CI: 0.36 –0.75). Those with high cholesterol levels (condAOR=3.76, 95%CI: 2.16 – 6.53) had increased odds of having PCa compared to those with low cholesterol levels.

4.3 Survival analysis for matched data

4.3.1 Time to diagnosis of prostate cancer using Kaplan Meier survival curves.

The results of Kaplan Meier survival for patients with prostate cancer with age are shown in Figure 4. It is observed that most cases of prostate cancer are between the age of 50 years and 80 years. It is also noted that the median age of having PCa is 70 years in this study. A few cases of PCa are diagnosed beyond the age of 80 years.

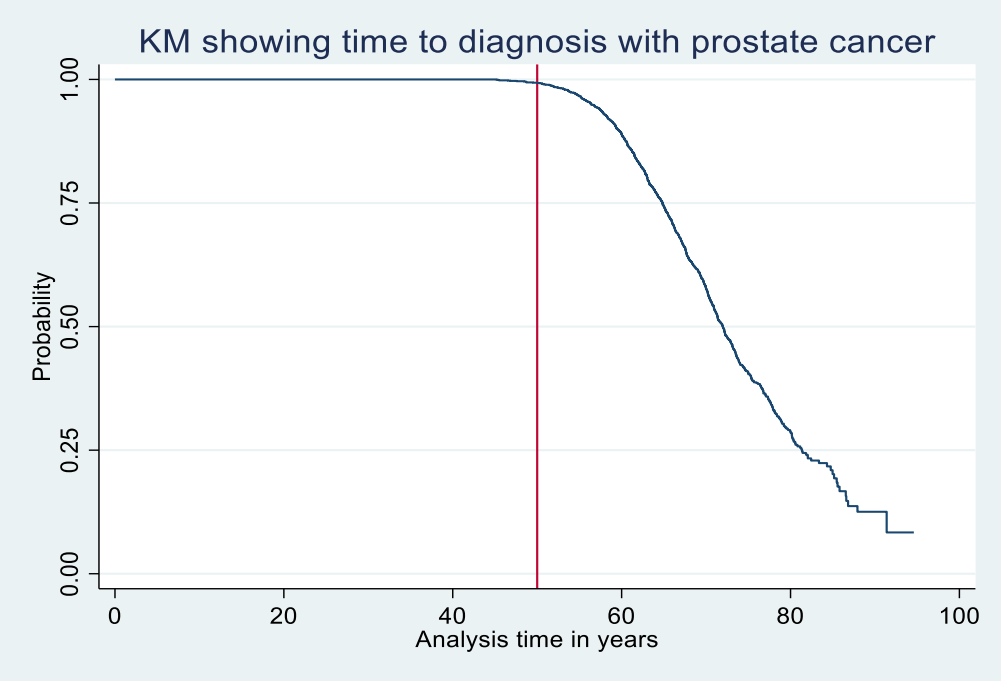


Figure 4 This is the Kaplain-Meier curve showing the time to diagnosis and when most cases are diagnosed.

4.3.2 Kaplain-Meier curves for time to diagnosis stratified by baseline categories.

Table 4 shows the diagnosis rates of the participants. Retired men's PCa rate of 7.61 per 1000 person-years (95%CI: 7.1 – 8.16) was significantly higher than for unemployed men, p-value<0.001. Men who earned R10,000 per month had a significantly higher PCa rate of 7.55 per 1000 person-years (95%CI: 4.55 – 12.52) than those who earned less than R5000 per month, p-value<0.001. Men who drank alcohol in the past had a significantly higher PCa rate of 8.65 per 1000 person-years (95%CI: 7.78 – 9.63) than those who never smoked, pvalue<0.001. Men who once smoked in the past had a significantly higher PCa rate of 8.86 per 1000 person-years (95%CI: 8.04 – 9.78) compared to those who never smoked.

Table 4: Rates per 1000 person-years and Log-rank tests of prostate cancer for men of African descent baseline characteristics at Chris Hani Baragwanath's Hospital, 2017 – 2021.

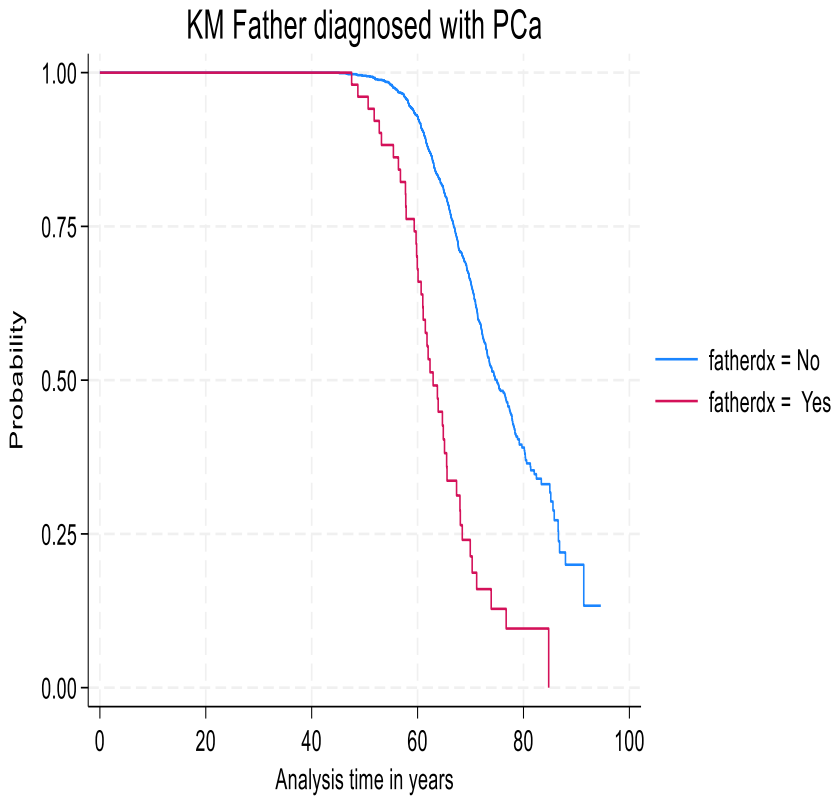
Characteristics	PCa cases	Rate per 1000 person-years	95% CI of rates	Log-rank p-value
Marital status				
Single	176	6.59	5.685 – 7.639	**<0.001***
Married	690	7.53	6.987 – 8.112	
Widowed	139	8.39	7.105 – 9.908	
Education Status	707	7.67	7.12 – 8.26	**0.190**
Less than high school	79	5.64	4.52 – 7.04	
High school graduate	50	7.67	5.81 – 10.11	
More than high school				
Employment status				
Unemployed	78	6.21	4.97 – 7.75	**<0.001***
Employed	137	7.38	6.24 – 8.72	
Retired	790	7.61	7.09 – 8.16	
Income level				
Less than R5,000 per month	898	7.71	7.22 – 8.23	**<0.001***
R5,001 – R10,000 per month	30	6.88	4.82 – 9.85	
Above R10,000 per month	15	7.55	4.549 – 12.519	
Have you ever drunk alcohol in your life?				
Never drank alcohol	241	6.183	5.449 – 7.015	**<0.001***
Yes currently	424	7.48	6.80 – 8.23	
Yes in the past	340	8.65	7.78 – 9.63	
Have you ever smoked cigarettes for at least one year of your life?				
Never smoked	329	6.52	5.86 – 7.27	**0.001***
Current smoker	279	7.02	6.25 – 7.89	
Past smoker	397	8.86	8.04 – 9.78	
Were any of your biologically related brothers ever diagnosed with prostate cancer?				
No	721	7.00	6.51 – 7.53	**0.002***
Yes	33	12.24	8.70 – 17.22	
Was your biological father ever diagnosed with prostate cancer?				

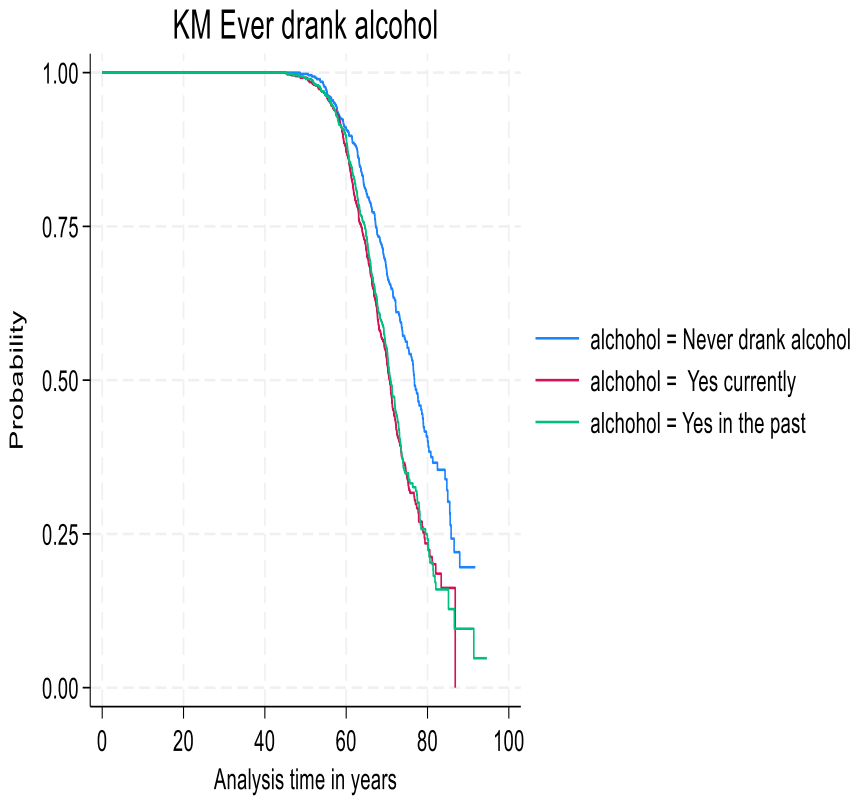
No	569	5.89	5.43 – 6.34	**<0.001***
Yes	45	12.16	9.08 – 16.28	
Diabetic mellitus				
No	838	7.61	7.11 – 8.14	**0.016***
Yes	165	6.70	5.753 – 7.806	
High cholesterol				
No	885	7.17	6.72 – 7.66	**0.009**
Yes	120	10.39	8.695– 12.436	

*Significant p-value calculated using log-rank test, PCa- prostate cancer

Those who had a brother who was diagnosed with PCa and a significantly higher rate of PCa of 12.24 person-years (95%CI: 8.70 – 17.22) than those who did not have a brother diagnosed with PCa, p-value=0.0002. Men who had a father who was diagnosed with PCa and a significantly higher rate of PCa of 12.16 person-years (95%CI: 9.08 – 16.28) than those who did not have a father diagnosed with PCa, p-value<0.001. Diabetic men had a significantly lower rate of PCa of 6.7 person-years (95%CI: 5.75 – 7.81) than those who did not have diabetes, p-value=0.017. Men with significantly higher cholesterol levels had a higher rate of PCa of 10.39 per 1000 person-years (95%CI: 8.69-12.4) compared to those with low cholesterol levels, p-value=0.0009.

Figure 5 presents Kaplan-Meier curves illustrating the time to diagnosis, stratified by baseline characteristics including family history of prostate cancer in the father, alcohol consumption history, smoking history, and employment status. These survival curves depict the proportion of individuals remaining undiagnosed over time, providing insights into potential differences in diagnostic timing across these key risk factors and lifestyle variables.


KM Father diagnosed with PCa
1.00
0.75
0.50
0.25
0.00
Probability
0
20
40
60
80
100
Analysis time in years
fatherdx = No
fatherdx = Yes


KM Ever drank alcohol
1.00
0.75
0.50
0.25
0.00
Probability
0
20
40
60
80
100
Analysis time in years
alchohol = Never drank alcohol
alchohol = Yes currently
alchohol = Yes in the past

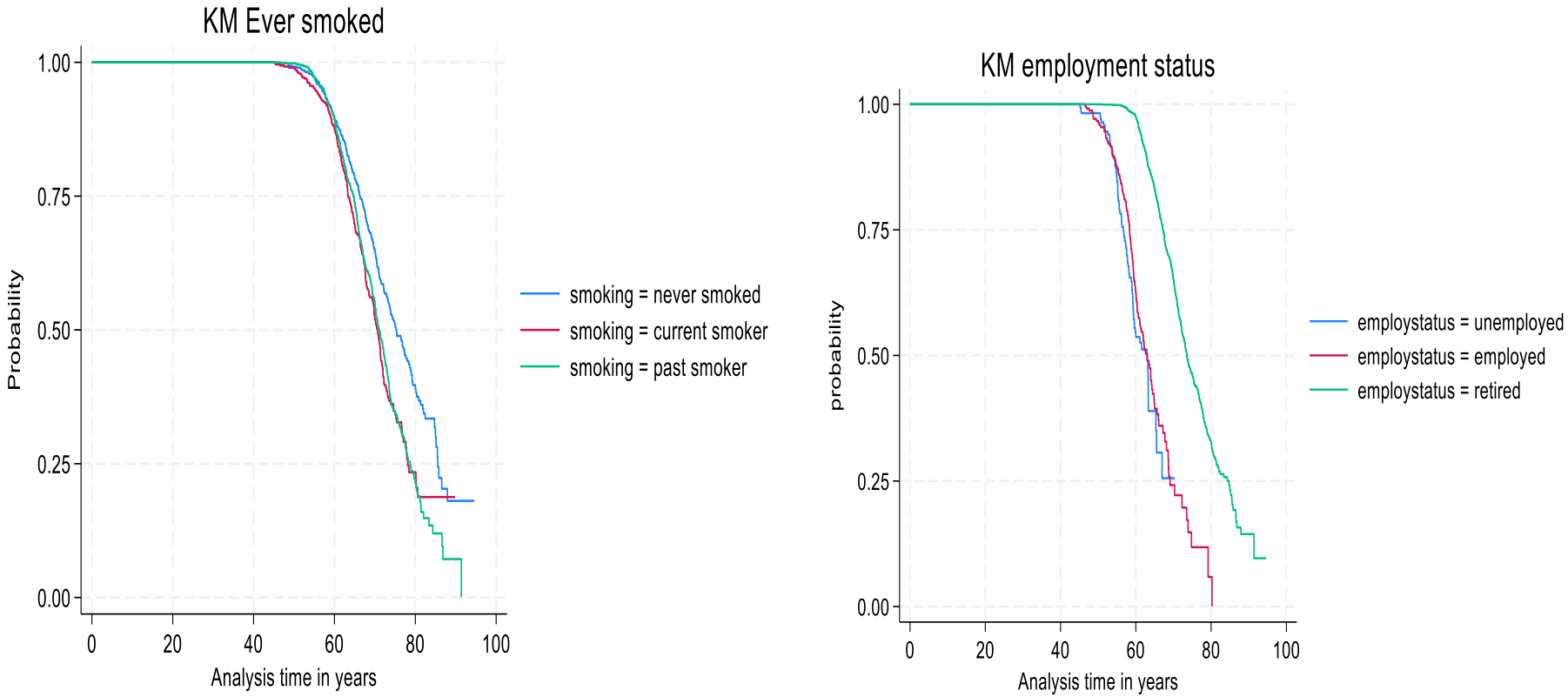


Figure 5: Kaplain-Meier curves for time to diagnosis stratified by baseline categories for the family history of the father diagnosed with PCa, ever drunk alcohol, ever smoked, and employment status.

4.3.3 Univariate and multiple Cox regression model for factors associated with time to diagnosis with prostate cancer.

A Cox proportional analysis was conducted to observe the time till diagnosis, with prostate cancer as a failure variable. To determine the risk factors from birth to the time of being diagnosed with PCa, Cox proportional hazard regressions were fitted for the matched group and the findings are summarised in Table 5.

Those who were married and widowed were 22% (HR=0.68, 95%CI: 0.57– 0.81) and 41% (HR=0.59, 95%CI: 0.46 - 0.76) less likely to develop PCa, respectively, than those who were single. Those who were employed and retired were 33% (HR=0.67, 95%CI: 0.5-0.89) and 85% (HR=0.15, 95%CI: 0.12-0.2) less likely to have PCa, respectively, compared to those who were unemployed. Those who were earning R5001-R10,000 (HR=1.45, 95%CI: 1.00-2.10) and those earning above R10,000 (HR=3.75, 95%CI: 2.21-2.39) were more likely to have PCa compared to those who were unemployed. Currently drinking alcohol (HR=1.69, 95%CI: 1.42 – 2.01), drank alcohol in the past (HR=1.62, 95%CI: 1.35 – 1.95), currently smoking (HR=1.54, 95%CI: 1.29-1.84) and past smokers (HR=1.49, 95%CI: 1.27 – 1.75) were more likely to have PCa compared to those never drank alcohol and never smoked respectively. Having a brother diagnosed with PCa (HR=1.94, 95%CI: 1.33 – 2.81) and having a father with PCa (HR=3.82, 95%CI: 2.55 – 5.71) increased the risk of having PCa compared to having no brother or father with PCa respectively. Those who had an STI were 31% (HR=1.31, 95%CI: 1.14-1.51) more likely to have PCa compared to those without an STI. Those with diabetes had a 24% reduced risk of having PCa (HR=0.76, 95%CI: 0.63 –0.92). Those with high cholesterol levels (HR=1.42, 95%CI: 1.16 – 1.75) had an increased risk of PCa compared to those with low cholesterol levels.

Table 5: Cox proportional hazards models for factors associated with time to diagnosis of prostate cancer among men of African descent aged 45 years and older attended at Chris Hani Baragwanath's Hospital in Gauteng Province (January 2017 – December 2021.

	Category	**Univariate Cox proportional hazard**		**Multiple Cox proportional hazard**	
		UnHR (95%CI)	**Pvalue**	**HR (95%CI)**	**Pvalue**
Marital status	Single	1 (base)			
	Married	0.68 (0.567 – 0.804)	**<0.001***		
	Widowed	0.59 (0.463 – 0.758)	**<0.001***		
Education status	Less than high school	1 (base)		1 (base)	
	High school graduate	0.901 (0.714 - 1.137)	0.379	0.72 (0.5234 – 0.999)	**0.05***
	More than high school	1.25 (0.936 – 1.664)	0.130	1.53 (1.088 – 2.145)	**0.014***
Employment status	Unemployed	1 (base)		1 (base)	
	Employed	0.67 (0.503 – 0.887)	**0.005***	0.93 (0.612 – 1.414)	0.737
	Retired	0.15 (0.119 – 0.199)	**<0.001***	0.23 (0.154 – 0.333)	**<0.001***
Income level	Less than 5,000 per month	1 (base)			
	5,001 - 10,000 per month	1.45 (1.001 – 2.104)	0.049*		
	Above 10,000 per month	3.75 (2.206 – 6.395)	**<0.001***		
Have you ever drunk alcohol in your life?	Never drank alcohol	1 (base)		1 (base)	
	Yes currently	1.69 (1.417 – 2.013)	**<0.001***	1.66 (1.287 – 2.159)	**<0.001***
	Yes, in the past	1.62 (1.351 – 1.951)	**<0.001***	1.75 (1.326 – 2.305)	**<0.001***
Have you ever smoked cigarettes for at least one year of your life?	Never smoked	1 (base)		1 (base)	
	Current smoker	1.54 (1.294 – 1.842)	**<0.001***	1.33 (1.037 – 1.708)	**0.024***
	Past smoker	1.49 (1.267 – 1.752)	**<0.001***	1.39 (1.094 – 1.766)	**0.007***

Were any of your biologically related brothers ever diagnosed with prostate cancer	No	1 (base)			
	Yes	1.94 (1.332 – 2.811)	0.001*		
Was your biological father ever diagnosed with prostate cancer?	No	1 (base)		1 (base)	
	Yes	3.57 (2.60 – 4.90)	<0.001*	3.62 (2.616 – 5.015)	**<0.001***
Circumcised	No	1 (base)			
	Yes	1.05 (0.916 1.202)	0.483		
Sexually transmitted infection	No	1 (base)			
	Yes	1.31 (1.140 – 1.506)	<0.001*		
BMI	Underweight	1 (base)			
	Healthy weight	0.84 (0.607 – 1.165)	0.298		
	Overweight	0.98 (0.713 – 1.374)	0.952		
	Obesity	0.97 (0.701 – 1.369)	0.905		
Diabetes mellitus	No	1 (base)		1 (base)	
	Yes	0.76 (0.629 – 0.915)	0.004*	0.781 (0.613 – 0.995)	**0.045***
High cholesterol	No	1 (base)		1 (base)	
	Yes	1.42 (1.159 – 1.749)	0.001*	1.41 (1.065 – 1.866)	**0.016***

In the adjusted analysis, those who were high school graduates and had more than a high school education were 28% (AHR=0.72, 95%CI: 0.52-0.99) less likely to have PCa and 53% (AHR=1.53, 95%CI: 1.09-2.15) more likely to have PCa, respectively, compared to those who less than high school. Those who were retired were 77% (AHR=0.23, 95%CI: 0.15-0.33) and 85% (AHR=0.15, 95%CI: 0.12-0.2) less likely to have PCa, respectively, compared to those who were unemployed. Currently drinking alcohol (AHR=1.66, 95%CI: 1.29 – 2.16), drank alcohol in the past (AHR=1.75, 95%CI: 1.33 – 1.71), currently smoking (AHR=1.33, 95%CI: 1.04-1.71) and past smokers (AHR=1.39, 95%CI: 1.09– 1.77) were more likely to have PCa compared to those never drank alcohol and never smoked respectively. Having a father diagnosed with PCa (AHR=3.62, 95%CI: 2.62 – 5.02) increased the risk of having PCa compared to having no father with PCa.

4.4 Model Diagnosis

4.4.1 Unmatched logistic regression

The Hosmer-Lemeshow goodness of fit test was done to assess if the model was correctly specified. The model had a p-value greater than 0.05 which indicates that it was a good fit. We also assessed the area under the curve (AUC) for this model and the model showed that it had a predictive power of 71.53% as shown in Figure 6. The Akaike Information Criterion (AIC) was also estimated for the model and the model had an AIC value of 1506.415.

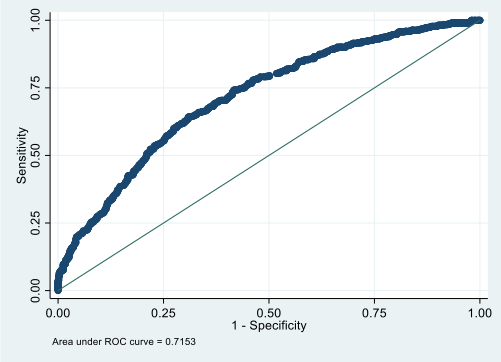


Figure 6:Area under the curve for the unconditional logistic regression model

4.4.2 Matched Logistic Regression

For model two which was the conditional logistic regression, the model had an AIC value of 1131.73.

4.4.3 Matched Cox Regression

A proportionality of hazards test was done using the Schoenfeld residual test after fitting the final multiple Cox regression model. Since the p-values are greater than 0.05, we conclude that the proportional hazards assumptions are satisfied as presented in Table 6.

Table 6: Test of proportional-hazards assumption table

Characteristics	**Global test**	
	Chi2	Prob>chi2
Having a brother diagnosed with prostate cancer	0.95	0.330
Having a father diagnosed with prostate cancer	2.96	0.086
Alcohol intake	0.47	0.492
Education status	0.01	0.9303
Diabetes mellitus	0.11	0.7353

We also assessed the proportionality of the hazard test using plots (see Figure 7) of expected survival from the model compared to the KM plots of survival and the log-log plots which assess if the curves show the same trend without crossover.



Figure 7: Proportional hazard assumption testing plots

Looking at Figure 6, the two curves for the log of fathers diagnosed with PCa show the same trend without crossing over each other which is an indication that PH assumptions are not violated. The KM predictive plot in Figure 7 above shows that the observed and predictive are

almost on top of each other which signifies that the proportional hazards assumptions seem to be met. The results from these graphs also concur with the Schoenfeld residuals results which were not significant (P-0.086) and therefore confirm the non-violation of the PH assumption.

4.4.4 Comparing the three models fitted.

Table 7: Results of Akaike Information Criterion for the 3 models fitted.

Model	**DF**	**AIC**
Logistic regression	16	1492.913
Conditional logistic regression	14	1131.727
Cox proportional regression	17	4557.981

Different methods to assess the assumptions of the logistic regression model and the proportional hazards assumption for the Cox regression were utilised. Using the AIC to compare the best model, the model with the lowest AIC was the conditional logistic regression; hence, this was the best model with the smallest AIC value of 1131.73. Our discussion in the next chapter will be based on the results from the Conditional logistic regression which is the best fit for this study after comparing all the possible models done (see figure 3B above).

CHAPTER 5 DISCUSSION AND CONCLUSION

5.0 Introduction

In this chapter, we discuss the main findings from this study and compare them to the available literature. Also, the strengths and limitations of the study are discussed. This chapter also states the recommendations that can guide policymakers in implementing strategies to increase prostate cancer awareness and screening among African men. Lastly, a concluding statement is also stated.

5.1 Main findings

Looking at the multiple conditional logistic regression, which was the best-fit model for the data, the risk factors that were associated with PCa were an increase in age, marital status(if someone was married or widowed compared to single), the level of education (when someone has education up to high school compared to someone with less than high school education), employment status (when someone is employed compared to someone unemployed), alcohol intake (when someone currently takes alcohol or was taking alcohol in the past compared to one who never drank alcohol), cigarette smoking (when someone is a current smoker or past smoker compared to those whoever smoked), family history of a father who was diagnosed with PCa compared to negative family history, diabetes mellitus (when one is diabetic compared to someone not diabetic), and lastly high cholesterol level (when one has high cholesterol compared to someone with no high cholesterol).

5.1.1 Alcohol use

The result from this study shows that current alcohol users and past alcohol users had increased odds of having PCa compared to non-alcohol use. This result supports a study done by Hong et al (52) on alcohol consumption and the risk of PCa which reported that heavy use of alcohol causes cancer. The study mentioned that alcohol consumption results in about a 10% increase

in the incidence of PCa with each alcoholic drink consumed daily (52). Several studies done in S.A mentioned that alcohol use is one of the emerging concerns for public health globally and in S.A (2,12). These findings support the results from a systematic review and meta-analysis which showed an increased risk estimate for drinkers compared to non-drinkers(52,93). The use of alcohol among South African men has been identified as a contributing factor to poor health habits (2,94). The reason why we have PCa affecting alcohol users could be a result of acetaldehyde which is a toxic by product of alcohol which causes cell damage by binding with DNA thus resulting to incorrect replication of cells (93). Alcohol results in increased cell membrane permeability thus altering carcinogen metabolising enzyme activity and inhibiting DNA repair (93). We suggest that PCa screening should be emphasized among those who drink alcohol or once drank alcohol. Also, as a control measure, men should avoid taking alcohol or else adults who choose to drink do so in moderation- 2 drinks or less on a day for men. The age restriction to buying alcohol should be adhered to so that it delays early alcohol intake.

5.1.2 Smoking

Consistent with the results of several previous studies (55–57), this study identified an association between smokers and PCa. In addition, this study identified that even after smoke cessation the risk of having PCa is still high compared to non-smokers. This result is similar to a study done on the profile of black South African men diagnosed with PCa in Free State which states that smoking cigarettes >6 per day was associated with advanced PCa (57). Research on the relationship between smoking and PCa risk has produced mixed findings. Some studies suggest that former smokers have a moderately increased risk of developing PCa compared to non-smokers, possibly due to the long-term effects of tobacco exposure on prostate cells and hormonal pathways(95,96). However, other studies have found no significant association or even a reduced risk in former smokers, potentially due to differences in study design, population characteristics, or the time since smoking cessation(58,59,95). Additionally, while

some research indicates that heavy smoking and long-term exposure increase the likelihood of aggressive PCa, other findings suggest that smoking may primarily influence disease progression rather than initial development(59,97). These inconsistencies highlight the need for further investigation to clarify the role of smoking in PCa risk.

Smoking has been shown to be associated with an increased serum testosterone level in healthy populations and patients with PCa (32,55). Despite the proven link between smoking and several cancers, the correlation between cigarette smoking and PCa remains a matter of debate. Although PCa is not considered a tobacco-related disease, cigarette smoke is known to contain multiple carcinogens including N-nitroso compounds which are known as animal carcinogens(95). An association with smoking could have a hormonal source with male smokers having higher androsterone and testosterone levels which may compound PCa risk or influence cancer progression(35,56,58,95). Further studies done in other provinces in S.A. are necessary which will look at the quantity smoked and the length of the cessation of smoking among men of African descent to refine the association between smoking and PCa.

5.1.3 Family history of a father diagnosed with prostate cancer.

It is worth mentioning that having a father diagnosed with PCa was positively associated with PCa. A family history of PCa is a recognised strong risk factor for PCa. Our study showed that having a father who had PCa increased the chances of developing PCa regardless of adjustment for other factors such as smoking, alcohol intake, and level of education thus indicating a high-risk category. This observation is in line with previous studies addressing the contribution of genetics on the risk factors of PCa which showed a threefold to fourfold increased risk among those with a first-line family history of PCa (40,79). A study found a very comparable association between the family history of a father diagnosed and PCa between black South Africans diagnosed with PCa in Free State province (57). Studies associating first-degree

relative of PCa among the African ancestry performed in African American men and men of African descent have shown to have an 80% contribution to the disease (34,40,79). The observed association with the disease status is particularly attributed to abnormalities in chromosome 7, 8p, 10q and 16q(98). Acknowledging that 80% of African men with fathers who had PCa will develop the disease in their lifetime. Men with a positive history ought to be counselled with regard to their significantly increased PCa risk and should undertake proper screening measures for the disease.

5.1.4 High cholesterol levels

Our study further goes to show that there was a statistically significant association between high cholesterol and PCa with increased risk among those with high cholesterol (>5.5 mmol/L) compared to those with no high cholesterol levels (<5.5 mmol/L). These findings are in line with the findings from a study on the prevalence of multimorbidity in men of African descent with and without PCa in Soweto which stated that the observed rise in PCa incidence in S.A could be due to the increased prevalence of chronic diseases such as hyperlipidaemia, diabetes, obesity, unhealthy lifestyle, and metabolic diseases (9). It was noted in a study undertaken in Finland that middle-aged men diagnosed with metabolic syndrome including high cholesterol, are more likely to develop PCa when compared to men without metabolic syndrome and that this risk was even greater in men who were overweight and obese(66). In a population-based case-control study on dietary factors and risks for PCa among Blacks and Whites in the United States, increased consumption of foods high in animal fat was linked to PCa among Black Americans but not among American Whites (46). This agrees with the European prostate cancer guidelines (99) and literature which states that consuming saturated fats increases the chances of having PCa (48,77,100). A diet high in red meat has also been found to increase cholesterol levels as stated by some authors (99), The observed positive association, coherent with results from other ethnic groups (46,101) on PCa screening emphasises the significance

of a reduced fat diet among African men. A diet high in vegetables, fruits, and legumes such as beans and peas may lower cholesterol thus reducing the risk (60). Lycopene a nutrient found in tomatoes and other vegetables is associated with a lower risk of PCa thus diet high in fruits and vegetables should be encouraged among those with high cholesterol levels (32,46,60).

5.1.4 Level of education

In this study, the level of education was associated with PCa. This study identified that attaining high school education among African men reduces the risk of having PCa. This result is similar to a study which also revealed that attaining education higher than high school decreases the risk of PCa (102). In another study done in S.A., an increase in the utilisation of PCa screening services might be associated with actual or perceived knowledge of PCa based on the level of education one has attained was found not significant (103). Education has a profound influence on a person's course of life. Low education level has been associated with less screening, and higher cancer stage at diagnosis, resulting in worse overall survival (10,102). Attaining education above high school is an indirect indicator of high social status, better awareness, and better health-seeking behaviour (20,102). There is their fore a need for improved methods to reach out to both educated and uneducated men regarding their health and PCa health. Bridging the gap between educated and uneducated men in S.A. can improve men's health-seeking behaviour.

5.1.5 Marital status

We found that those who were married and those widowed have an increased odds of having PCa compared to the single. This result is similar to a review which stated that widowed men were 1.19 times more likely to be diagnosed with PCa compared to married or men without partners (104,105). Another study showed that widowers were at risk of being diagnosed later

than married or single men as a result present with metastasised disease (105). This could be a result that men who live alone have fewer healthy habits. Another study revealed that men may consume more alcohol or unhealthy food after their spouse dies, as well as experience physical and emotional impacts from bereavement which makes them prone to PCa (106). Since living with a partner promotes a healthier lifestyle which has been proven in previous studies (107,108), widowed men may not follow up with their doctor and screening appointments thus poor health conditions. However, more studies done (104,106,109) looked at the overall survival among widowed men with PCa and have shown that mortality rates were significantly greater compared with the other groups. Social support interventions and medical follow-up in this sub-populace should be supported. More studies among African men in the S.A. are needed to expand understanding of the association between marital status and PCa risk.

5.1.6 Diabetes mellitus

This case-control study showed that men with diabetes mellitus had a significantly, approximately 30% lower risk of developing PCa than those without. These findings conflict with the results of a previous meta-analysis on the effect of metabolic syndrome and its components on PCa risk which stated that metabolic syndrome is not associated with PCa (110). On the contrary, a study done in Soweto among African men also found a protective effect of diabetes mellitus against metastatic PCa (9). However, conflicting findings have been reported for diabetes mellitus as a risk factor for prostate cancer (35,63,79). This protective effect against PCa might be due to aggressive disease management among men with diabetes mellitus. Furthermore, this might reflect a more socioeconomically affluent group, more aware of PCa and its symptoms (9). In our setting, where the metabolic disease burden is high, integrated PCa screening services in diabetic clinics, might be of benefit to early detect the disease before it advances.

5.2 Strengths and Limitations

This study is limited because it is a retrospective study which used data that was collected in one hospital (CHBAH) in Johannesburg with patients only residing in Soweto. Only cases which were diagnosed six months prior to the commencement of the study were considered for analysis. Despite being based on single-site dataset, the study is generalizable since the hospital (CHBAH) serves a diverse patient population, encompassing various ethnicities, age groups, and socioeconomic backgrounds, which enhances the applicability of the findings to broader population. Additionally, the large sample size ensures robust statistical power, making the results more likely to reflect broader trends. Furthermore, consistency of results with studies from other African countries strengthens the overall applicability. These factors ensure that the study's conclusions can be generalized to other populations with similar characteristics. . it will also provide valuable information for academics and policymakers on the risk factors of PCa among men of African descent and thus emphasize the need for improvement in screening and diagnosis among high-risk groups.

5.3 Recommendations

This study identified several factors associated with prostate cancer among men of African descent.

One recommendation is that prostate cancer screening should be discussed with African men by healthcare providers who will clear any misconceptions. Men of African descent who are diagnosed with prostate cancer should have their potential genetic risks emphasized and their male family members should be appropriately counselled for screening at the appropriate age. Additionally, a recommendation on smoke reduction among current smokers and discourage smoking among those who have not started. This can be done by enforcement of the increased taxation of tobacco products and regulating tobacco purchase. While S.A has implemented

various tobacco control measures, illicit trade remains a major challenge, with an estimated 30-40% of cigarettes sold(111). This undermines the effectiveness of taxation policies. Further regulatory measures such as restricting point of sale advertising and tightening youth access could also contribute to reducing smoking prevalence(112). Alcohol use also placed men of African descent at greater risk of prostate cancer even when they had stopped, therefore we recommend that men should avoid taking alcohol or else adults who choose to drink do so in moderation- 2 drinks or less on a day for men. Findings from this study further stated that High cholesterol level is associated with prostate cancer thus interventions to help lower or maintain health levels like increasing intake of fruits, vegetables, and replacing refined grains with whole grains should be encouraged. More studies are needed to identify the risk factors of PCa among men of African descent in the different provinces of South Africa. Further research is essential to assess the benefits of applying preventive interventions in at-risk populations.

5.4 Conclusion

The purpose of this study was to identify risk factors for prostate cancer among men of African descent who are above 45 years attended Chris Hani Baragwanath's hospital. Men of African descent have an increased risk of PCa compared to other ethnic groups. The study has also highlighted modifiable risk factors that must be considered for policymaking to improve life expectancy among men of African descent. PCa interventions should reach men in hard-to-reach areas who might be less educated on the importance of early PCa screening. Bridging the gap between educated and uneducated men in S.A. can improve men's health-seeking behaviour.

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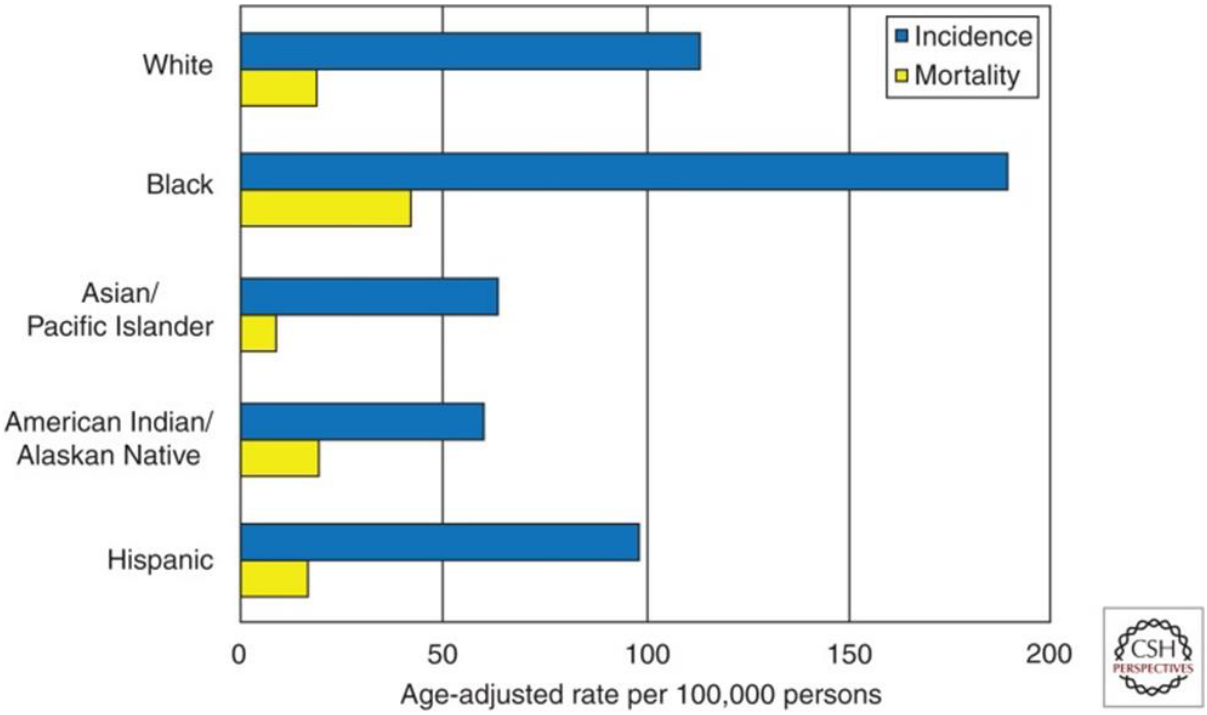
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APPENDICES

Appendix A: prostate cancer incidence and mortality rate in different ethnic groups (113)



Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms TS Simelane
School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

E-mail: 2187697@students.wits.ac.za

CC: Supervisor: Professor E Musenge and Dr W Padayachee
<Eustasius.Musenge@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/06/05

REF: R14/49

PROTOCOL NO: **M230312** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Risk factors for prostate cancer in men of African descent aged 45 years and older in Gauteng Province, South Africa 2017-2021: a case control study*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms TS Simelane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230312

NAME: (Principal Investigator)	Ms TS Simelane
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Risk factors for prostate cancer in men of African descent aged 45 years and older in Gauteng Province, South Africa 2017-2021: a case control study*
DATE CONSIDERED:	2023/03/31
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor E Musenge and Dr W Padayachee
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/06/05 **EXPIRY DATE:** 2028/06/04

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix B: Data gatekeepers letter of support

WITS HEALTH CONSORTIUM

Wits Health Consortium (Pty) Ltd
Reg No.: 97/15443/07

Tel: +27 11 274 9200
31 Princess of Wales Terrace, Parktown, 2193, South Africa

Postnet Suite 189, Private Bag X2600, Houghton, 2041

20 February 2023

Attention: Mr Iain Burns
Human Research Ethics Committee (Medical)
Philip Tobias Building, 3rd Floor

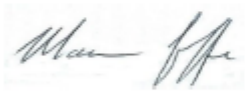
Reference: **Letter of Support: MSc(EPI) Thobile Sakhile Simelane**

Dear Iain,

This document serves to grant permission to the study investigators from the University of the Witwatersrand, to access the research data collected within the MADCaP study for use for the study entitled: **"Risk factors for prostate cancer in men of African descent aged 45 years and older in Gauteng province, South Africa 2017 - 2021: Case-control study."**

This investigators involved will be allowed access to the MADCaP database from the date of the Wits Human Research Ethics Committee (Medical) approval to the end of December 2023. This study involves secondary data analysis of the MADCaP study data. No new data will be collected.

Sincerely,



Dr Maureen Joffe

Director: Strengthening Oncology Services Research Unit,
Faculty of Health Sciences,
University of the Witwatersrand

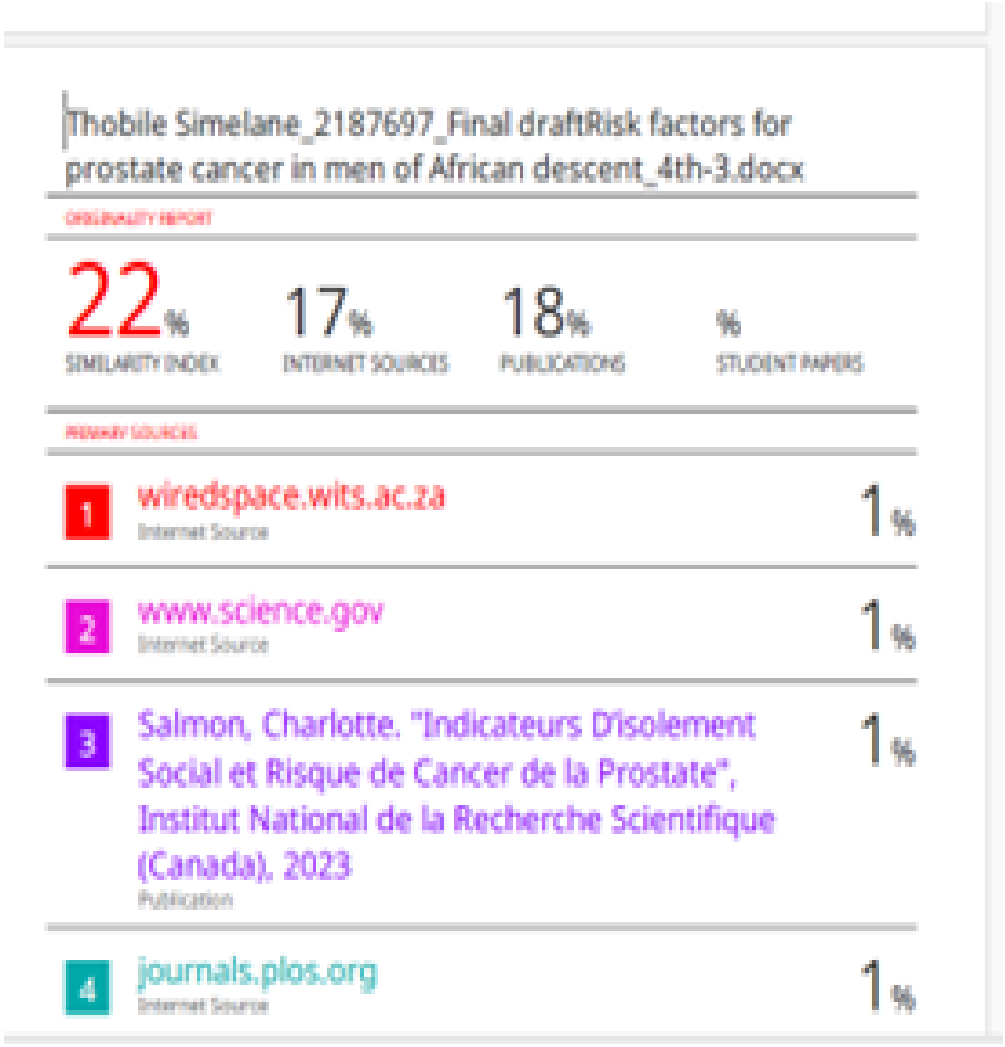
Principal Investigator: Men of African Descent, Carcinoma of the Prostate (MADCaP)

A wholly owned company of the University of the Witwatersrand

Directors: Prof. M. Veller (Chairman); Mr. D. Arnold; Prof. D. Ballot; Dr. R. Chikwamba; Mr. P. Desai; Mr. A. Farrell; Mr. M. Gani; Prof. J. Mahlangu; Dr. L. Motsepe; Prof. M. Papathanasopoulos; Prof. H. Rees; Prof. Z. Vilakazi.

www.witshealth.co.za

Appendix C: Turnitin report



Thobile Simelane_2187697_Final draftRisk factors for prostate cancer in men of African descent_4th-3.docx

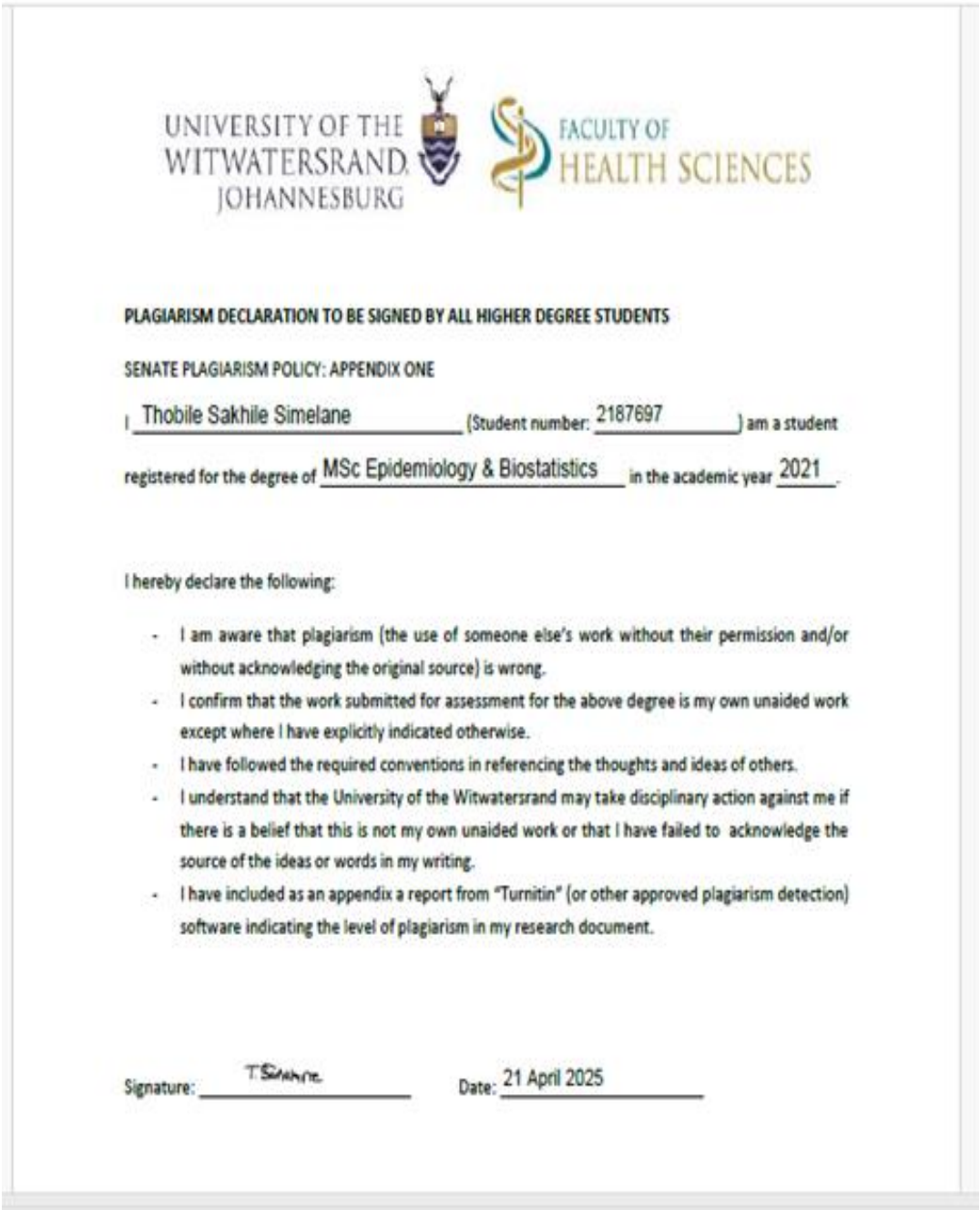
ORIGINALITY REPORT

22%	17%	18%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	1%
2	www.science.gov Internet Source	1%
3	Salmon, Charlotte. "Indicateurs D'isolement Social et Risque de Cancer de la Prostate", Institut National de la Recherche Scientifique (Canada), 2023 Publication	1%
4	journals.plos.org Internet Source	1%

Appendix D: plagiarism declaration



UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Thobile Sakhile Simelane (Student number: 2187697) am a student registered for the degree of MSc Epidemiology & Biostatistics in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: TSimelane Date: 21 April 2025