

Investigating Racial Differences in Clinical and Pathological Features of Prostate Cancer in South African Men

by

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Declaration

I, Malcolm James Dewar, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Signed by candidate

Date: 8 May 2016

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List of abbreviations

- AA – African American
- AAM – African American Men
- AS – Active Surveillance
- ASR – age-standardised rate
- BRFS – Biochemical Recurrence Free Survival
- CaP – Prostate cancer
- EA – European American
- EAM – European American Men
- EBRT – External Beam Radiotherapy
- HG PIN – High Grade Prostatic Intraepithelial Neoplasia
- LUTS – Lower Urinary Tract Symptoms
- PCSS – Prostate Cancer Specific Survival
- PSA – Prostate Specific Antigen
- RP – Radical Prostatectomy
- SEER – Surveillance, Epidemiology and End Results (the US national population based cancer registry)
- TRUS – Transrectal Ultrasound
- TURP – transurethral resection of the prostate
- VA – Veterans Administration

Part A: Protocol

Purpose of the study

The aim of this project is to study the clinical and pathological features of prostate cancer in men from different racial groups in the Western Cape in an attempt to define the characteristics of the disease locally. Specifically we wanted to compare black with coloured and white patients.

Background

Prostate cancer is among the most common non-cutaneous cancer diagnosed in men worldwide, and the first or second commonest cause of male cancer deaths in many countries (1). This applies to South Africa as well, where it is second only to lung cancer in terms of mortality (2).

African American men have been shown to have a higher incidence of prostate cancer, higher stage at presentation, higher histological grade, a greater propensity to relapse after curative treatment, and a higher disease-specific mortality (3,4). Men with West-African ancestry from elsewhere, such as South America, the United Kingdom and the Caribbean, have a similarly high rate of prostate cancer (5). Delayed diagnosis accounts in part for the higher stage at presentation and possibly some of the increased mortality. This delay in diagnosis has been attributed to healthcare access problems, reduced health-seeking behaviour, and often health-provider prejudice. Many studies have attempted to correct for these factors, and have concluded that there is most likely a real difference in tumour biology between African American men and other American men, and this is most likely due to underlying genetic factors (4).

Epidemiological studies on South African populations have uniformly found prostate cancer to be more common in white than black South Africans (2,6). However, Heyns, et al found that the black patients being diagnosed with prostate cancer at Tygerberg Hospital between 1995 and 2005 had higher PSA values at presentation, that their tumours were significantly more locally advanced and that they had a higher histological grade (7). The impression of the authors of that study was that prostate cancer was more common in black South Africans than in other population groups, possibly in a similar way to African American populations. These

seemingly discordant findings suggest that prostate cancer in the South African black population might be underdiagnosed by a large extent. Prostate cancer incidence within a population is heavily influenced by screening practices. The average black male in South Africa might be less likely to be screened for prostate cancer, and thus be less likely to have a prostate biopsy than one of his white, coloured or Indian counterparts. This is illustrated by the finding that the biopsy-proven incidence in black men in South Africa is less than a quarter that of white South African men, but the mortality rate is more than double (2).

It has also been our overall impression that of the men being referred for prostate biopsy in our unit, the black patients seemed to have higher PSA values, larger prostates, be more symptomatic, and have a higher chance of having prostate cancer diagnosed. We have therefore set out to analyse our biopsy database to determine if that is the case.

Methodology

Literature review

Searches will be conducted using the following Medline MeSH (Medical Subject Headings) strings:

- Prostatic neoplasms / ethnology
- Prostatic neoplasms / epidemiology, ethnology AND South Africa
- Prostatic neoplasms / epidemiology, ethnology, aetiology AND Africa south of the Sahara

Similar searches will be done in Google Scholar.

Where studies cover similar material, the more recent articles will be favoured.

Study design

All prostate biopsies done in the Department of Urology at Groote Schuur since 2008 have been entered prospectively into a database containing demographic information, clinical findings, PSA values, and ultrasound findings, among other details.

This study will be a retrospective review of the prostate biopsy database, with the intention of comparing age, self-reported race, symptoms, serum PSA values, measured prostate volume, presence of cancer, and histological grade.

The database in question currently contains over 1000 patients.

Characteristics of study population

The prostate biopsy database contains 1027 patients from the beginning of 2008 to the end of June 2014.

These patients had all been referred to the Urology service via normal channels and had biopsies as part of their routine clinical care. No patient was at any time specifically recruited for this research project, nor did any have a biopsy solely for the purpose of research.

All patients on the database will be included in the study unless:

- Identifying data, age, PSA, prostate volume or histology are not available.
- Biopsies have been limited (ie. fewer than 12 cores) or inadequate (ie. not representing prostatic tissue) *and* those biopsies have been negative for malignancy.

It is recognised that limited biopsies that are positive might result in underestimation of the grade of cancer diagnosed because of the fewer cores taken. It is, however, felt that this is not enough of a concern to exclude those patients from the analysis.

Being a retrospective review of records, this population would not be considered vulnerable or at risk.

This research project will be conducted within the Division of Urology at Groote Schuur Hospital.

Recruitment and Enrolment

The patients on the database represent biopsies done during routine clinical practice within the Division of Urology. Indications for biopsy are an elevated serum PSA level or a palpably abnormal prostate on digital rectal examination. At our institution we do not routinely offer screening to asymptomatic men, but will do so on patient request after good counselling on the matter.

Research Procedures and Data Collection Methods

Transrectal ultrasound-guided (TRUS) biopsy of the prostate is the worldwide standard investigation for the definitive diagnosis of prostate cancer(8). The guidelines of the European Association of Urology recommend that 10 to 12 cores be taken at biopsy (9).

Note again that these biopsies have already been done as part of standard care. The description of the routine procedure is described for completeness.

Prostate biopsy is performed in the office setting after informed consent and the administration of a dose of prophylactic antibiotic. The patient is positioned on the examination bed in the left lateral decubitus position with knees pulled towards the chest. A full tube of local anaesthetic jelly is inserted transrectally and a digital rectal examination (DRE) performed. A trans-rectal ultrasound probe with a biopsy guide attached is introduced into the rectum. Submucosal local anaesthetic injection can be done, but it is not our practice, as the procedure is generally equally well-tolerated without it. Ultrasound examination of the prostate is then performed. This includes measurement of dimensions in three planes (with a calculated estimated volume) as well as the noting of any abnormalities such as capsular distortion, focal hypo- or hyper-echoic areas, calcification or increased vascularity. A spring-loaded needle biopsy gun is used to take two cores of prostate tissue from each of six different areas of the prostate – the left and right bases, mid zones and apices. Any hypoechoic areas visualised on ultrasound are sampled with additional biopsies. The cores from each sextant, and any additional biopsies, are sent for histology separately to give information about extent and location of the tumour.

The most common complications of the procedures are infection and bleeding, resulting in hospitalization in around 1.9% and death in less than 0.1% of patients (10).

The prostate biopsies are performed by one of the trainees in the department of urology.

Data from each patient are entered onto a pro-forma data sheet at the time of biopsy (see Appendix A), and the histology results then subsequently added to the database once they become available.

Information gathered at each biopsy includes the patient's name, hospital number, date of birth, age, presenting symptoms, PSA, findings on DRE, ultrasound findings and prostate size measurement.

A deficiency of the database is that the race of the patients has not been recorded. To obtain this information we plan to look up the subjects' self-declared ethnicity, as recorded by the hospital administration staff on the computerised hospital administration system.

Incomplete data could be retrieved from the patient folders as necessary.

Data Analysis

Data will be analysed with the assistance of a statistician.

The overall characteristics of the sample will be analysed and compared.

Differences between all of the collected variables with respect to the patient's race group will be determined and tested for statistical significance. Any potential confounding factors will be looked for and excluded as far as possible.

Ethics

The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

Approval for this study has been granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town, after prior approval from the Surgical Departmental Research Committee. The reference number is 099/2015.

The prostate biopsy database has ongoing approval for use in clinical research within our department, with the most recent updated approval valid until 30 August 2017. The reference number for that is R033/2014.

Benefits

As this is a retrospective review, there is no direct benefit to the patients. However, the data obtained may allow us to improve our clinical management of patients with suspected prostate cancer. If groups at higher risk can be identified within the

South African population, then these patients may benefit from targeted screening programmes in future.

Privacy and Confidentiality

Patient confidentiality will be protected by keeping the hard copies of the data sheets in the urology registrar room, to which access is controlled by a combination lock. The electronic data (ie. spreadsheet) will be kept on the computer in the same room, which is further protected by a login code. Identifying data is necessary in the database, as it is used to check the histology results and allow access to the patients' files should incomplete data or outcome need to be determined, but will be de-identified prior to statistical analysis.

Expected outcomes

Based on the well-established risks conferred by African ancestry on prostate cancer incidence and severity, as described above, we hypothesised that the black patients in our series might similarly have worse clinical characteristics. We expected that the pre-test PSA levels would be higher, that the prostate volumes would be larger, that prostate cancer would be diagnosed more frequently, and that it might be of a higher histological grade. We anticipate delayed presentation being a factor in the clinical picture of our black patients. This is because our black patients are socio-economically disadvantaged and very often seem to be residents of the Eastern Cape who come to Cape Town because of real or perceived inadequacies of their local healthcare infrastructure. Determining the response to treatment and the treatment outcome is beyond the scope of this study.

Dissemination of results

The results of this study will be submitted as a mini-dissertation to the University of Cape Town and, if accepted, will then be part of the public domain and be available online from the university library. The second part of the dissertation will be submitted to various academic journals for peer review and publication. The study will also be presented at one or more academic urology meetings in the city of Cape Town, as well as at the South African Urological Association annual congress.

Lay summary

Prostate cancer is a common cancer among men worldwide, becoming more common as men get older. In most countries around the world prostate cancer is one of the five most common causes of death from cancer in men (11).

Many scientific studies have shown that men in Africa, particularly in West Africa, and men elsewhere who have West African ancestry, are at particularly high risk for prostate cancer. Not only do they have a higher chance of getting prostate cancer, but they also get it at a younger age. Some studies have also shown that men with African ancestry have a more aggressive type of prostate cancer, have a worse outcome after treatment, and are more likely to die of prostate cancer (12).

Unfortunately, most of this information comes from areas outside of Africa, such as the United States of America, Brazil, the Caribbean and the United Kingdom (13–16). Information coming from Africa is often sparse, and compounded by problems with recording and reporting of cases. Even when the proven cases of prostate cancer are well recorded, the numbers are often thought to be very much underestimated because of generally poor access to healthcare (17). This seems to be true of South Africa too, where the incidence reported for South African men is one fifth that of the rate in America, and the rate in black South Africans is one tenth that of the rates reported in African American men (2,18).

In this study, we aimed to investigate whether the black African men seen at a tertiary hospital in Cape Town did have a higher chance of being diagnosed with cancer, and whether the characteristics of their cancer were more severe. We did this by retrospectively analysing the details of approximately 1000 patients who had undergone a biopsy of the prostate between 2008 and 2014. More specifically, we looked at: age; whether they presented with symptoms of prostate problems or were picked up on PSA screening; the prostate-specific antigen (PSA) level; the size of the prostate; whether or not cancer was diagnosed, and if so, the histological grade and clinical stage. We hope that this information will help us to better understand who might be at increased risk for prostate cancer in our community.

Part B: Literature review

Introduction

Cancer of the prostate (CaP) is one of the most common cancers diagnosed in men. Worldwide it is the second most frequent non-cutaneous cancer occurring in men and it is the fifth commonest cause of death due to cancer (11). In 2012 there were an estimated 1.112 million new cases and 307 000 deaths due to prostate cancer worldwide(11). The population adjusted incidence of prostate cancer in the United States is 137.9 per 100,000 population. Thus it is the commonest cancer diagnosed in US men. There were an estimated 220,800 new cases in 2015 (19). The number of prostate cancer deaths reported in the United States in 2015 was 27,540, which made it the second commonest cause of death in males after lung cancer (19). In South Africa between 2006 and 2009, prostate cancer was the second leading cause of deaths due to cancer in men after lung cancer (2).

It has been well established that prostate cancer is more common in men of African descent (13–15), and there is some evidence that some African populations might share a similarly high incidence of prostate cancer (20). The exact mechanisms conferring this increased risk are unknown. Many single nucleotide polymorphisms have been shown to be associated with increased risk for CaP, although these are not necessarily causative. Some occur with higher frequency in populations of African descent. There is also some evidence that differences in androgen metabolism might account for the discrepant risk. Various oncogenic events, such as TMPRSS2:ERG gene fusions, also occur more commonly in men with African ancestry (21). Men with African ancestry have been shown to have higher baseline PSA values at presentation, tumours that are more locally advanced and with higher histological grade, shorter times to biochemical recurrence following treatment, and a higher overall mortality rate (12).

Data on cancer incidence and mortality in Africa are poor. There are very few population based cancer registries in Africa. The data that are available are thought to underestimate the true prevalence of cancers generally, but of prostate cancer in particular (17,22). Prostate cancer is common in South Africa, but information on the true incidence and mortality rate are also limited and conflicting. Some studies

based on histological diagnosis report a lower incidence of CaP in South Africa than in Western countries and a lower rate yet in black South Africans (2,23). Other South African studies suggest that black South Africans might share some of the increased risk noted in other African populations (7,24).

Objectives

- To form a broad overview of the worldwide epidemiology of prostate cancer.
- To perform a more extensive review of epidemiology, clinical features, and treatment outcomes with respect to race, with particular focus on African origins.
- To review the work done on potential underlying causes for racial disparities.
- To review the data on prostate cancer epidemiology in sub-Saharan Africa.
- To review the literature on prostate cancer in South Africa.

Methodology

A Medline search was conducted using the following MeSH terms:

- Prostatic neoplasms / ethnology
- Prostatic neoplasms / epidemiology, ethnology, aetiology AND Africa south of the Sahara
- Prostatic neoplasms AND South Africa

The relevance of articles was screened on title, then abstract, then body as necessary. Newer articles were favoured, with search limited to English language articles. A search on Google Scholar was also performed with search terms similar to those used above. Relevant references from other articles followed up as necessary. Other internet searches were performed as necessary for information such as census data and reported national cancer statistics.

Summary of the literature

Global epidemiology of prostate cancer

Prostate cancer (CaP) is the commonest cancer that occurs in men. Autopsy studies have shown that the prevalence of incidental CaP is high among middle-aged and elderly men, being proportionate to the age of the population studied. The exact prevalence rates vary widely between studies, based on the populations studied and histological techniques used. In a meta-analysis of the literature on this topic, Rebbeck and Haas (25) concluded that more than a third of men over 60 years of age had latent prostate cancer.

The most comprehensive report of worldwide cancer incidence and mortality is the GLOBOCAN series, which is an ongoing project run by the International Agency for Research on Cancer, a division of the World Health Organisation (11). This project uses available cancer statistics from around the world, as well as inferred data from countries where such information is not readily available. They estimate that in 2012 there were 1.1 million new cases of CaP and that there were over three hundred thousand deaths attributable to CaP. Worldwide, the average man has a cumulative lifelong risk of 3.8% of being diagnosed with prostate cancer, which is second only to lung cancer (at 3.9%). In developed countries, CaP is the most common cancer diagnosed in men. This is thought to be due to the more widespread use of PSA screening in those countries. Developed countries accounted for 70% of the CaP diagnoses worldwide in 2012.

The population of Africa comprises approximately 15.5% of the world population (26) but GLOBOCAN estimates the cancer incidence in Africa at 6.0% and mortality at 7.2%. Although Africa has the youngest population of any continent (26), the figures might still suggest that the cancer burden in Africa is somewhat underestimated. Crocker-Buque, et al (17) concluded that the cancer registration systems used to calculate incidences in sub-Saharan Africa for the GLOBOCAN 2008 report were of poor quality, with 20 African countries having no registration systems at all. There is a large variation in mortality and incidence rates of CaP between regions, with mortality rates varying 10-fold and incidence rates varying

24-fold (1). The regions with the highest incidence in the world are Australia/New Zealand, North America, and Scandinavia, among others. The highest mortality rates are noted in the Caribbean as well as isolated countries in South America and sub-Saharan Africa.

Secular trends in Prostate Cancer Incidence

Beginning in the late 1980's and into the 1990's, there was a dramatic increase in the incidence of prostate cancer in the United States. This was initially due to more transurethral resection of the prostate being performed, and later due to the rising use of PSA screening on the asymptomatic male population (27). This has led to a stage migration in prostate cancer, with a much greater proportion of men now being diagnosed with localised disease.

During the same period, prostate cancer survival has increased dramatically. This is due to both a lead time bias and also to the "Will Rogers effect" of including men with clinically insignificant disease who would previously not have been recognised as having prostate cancer (28).

People over the age of 60 years comprise the fastest growing segment of the worldwide population, growing at 3.26% year on year (26). Largely because of the ageing population, the worldwide incidence of prostate cancer is predicted to rise to 1.7 million cases and 499 000 deaths by the year 2030 (1).

Prostate cancer in people of African descent

The transatlantic slave trade transported approximately 15 million people from West Africa to Europe, the Americas and the Caribbean during the 15th to 19th centuries (29). That number does not include the many millions who died en route. The areas from which these people were taken are primarily in the present day countries of Benin, Nigeria, Ghana, Gambia, Senegal, Mozambique, and Angola. This accounts for the majority of African ancestry in those countries that were supplied with slaves during that time.

African ancestry, particularly West African ancestry, is a very well-established risk factor for CaP (30). Although the direct cause of prostate cancer remains elusive,

there is clearly a heritable component to the disease. This is demonstrated by the correlation between family history and personal risk of CaP diagnosis (3).

Incidence

Rates of prostate cancer in populations of African descent are the highest in the world (31). The age-standardised rate (ASR) of CaP incidence in African American men (AAM) between 1999 and 2008 was 239 cases per 100,000 compared to a rate of 151 in European American men (EAM), indicating a relative risk for diagnosis of 1.59 (18). The age adjusted incidence of prostate cancer in men from Kingston, Jamaica in the early 1990's was calculated as 304 per 100,000 (14). A more recent study from Barbados calculated the incidence at 160 per 100,000 (32). Although this rate was lower than the incidence noted in African American men, the mortality rate for CaP that the authors calculated was higher in the Barbados community than that reported for the African American population. Incidences rates have also been shown to be higher in Brazilian men of African descent compared to their white countrymen, with risk 1.59 fold higher (15). The Prostate Conditions in Ethnic Subgroups Study (PROCESS) was a UK-based retrospective cohort study that examined the incidence and clinical features in men that had been diagnosed with CaP within a set geographical area. The study was designed to compare black men with their white counterparts living in those specific areas. The main finding of the study was that the incidence of CaP in black men was three times that of the white men (166/100,000 vs 56.4/100,000). The increased risk was more pronounced in the younger age groups (13).

Prevalence

Autopsy studies have shown that undiagnosed or latent CaP is much more prevalent in men of African descent. Rebbeck and Haas (25) performed a comprehensive review of autopsy studies on the subject. They identified 58 studies that looked for latent prostate cancer in men who had died of unrelated causes. They found that prevalence across all race groups increased progressively with age. Men of African descent reached 50% prevalence by the age of 60 years, whereas men of European and Asian descent reached 50% prevalence at age 80 and 90

years, respectively. Latent prostate cancer under the age of 40 was found in 37% of African men, 9% of European men, and 4% of Asian men.

Grade, Stage and Positive Surgical Margins

Other clinical characteristics have also been shown to be worse in black men. It is postulated that men with African ancestry are prone to prostate cancer that is more aggressive and that progresses more rapidly than in their contemporaries (33).

A large autopsy series from Detroit (4) that included men who had died of causes other than prostate cancer showed that AA and EA men had similar prevalence rates of HG PIN and latent CaP when younger than 60 years. It seemed that transformation to significant disease occurred at an earlier age in AA men.

When on active surveillance (AS), black patients have been shown to be more likely to be histologically upgraded on repeat biopsy. In one study of men fulfilling the NCCN very low risk criteria who were on active surveillance, 36% of AA patients were upgraded on serial biopsy compared to 16% of EA patients (34).

An analysis of all of the radical prostatectomies done at Johns Hopkins between 1992 and 2013 was performed by Faisal, et al (35). It was found that low-risk African American men were significantly more likely to have had upgrading, upstaging and positive margins.

Another study from Johns Hopkins analysed RP specimens of patients who had had NCCN very low risk disease preoperatively, selecting 89 EAM and 87 AAM that had been treated between 2004 and 2012 (36). Compared to EAM, AAM were significantly more likely to have extraprostatic disease (14.9% vs 3.4%), positive surgical margins (19.8% vs 5.6%) and upgrading to Gleason 7 or above (36.8% vs 11.2%). Total tumour volume was found to be higher in AA men (0.423 vs 0.185 cm³) and AA men were more likely to have multifocal disease (83.9% vs 60.7%). When considering the size and location of dominant nodules, it was found that AA men were more likely to have an anteriorly situated dominant nodule (50.6% vs 28.7%), which were more likely to be greater than 0.5 cm³ (31.0% vs 13.5%). These anteriorly situated tumours, especially the large ones, seemed to account for much of the histological upgrading in the AA men.

Ha, et al analysed their series of men who had had radical prostatectomies who would have been candidates for active surveillance. They found that non-organ-confined disease was present in 9.4-10.1% of white patients, whereas 15.8-19.4% of the AA patients were similarly upstaged (the risks varying depending on the AS criteria used). In this study, there was no statistically significant difference in upgrading of cancer (ie. higher Gleason) between African American and white patients (37). In a very similarly designed study, Jalloh, et al did not find significant differences in upstaging or upgrading, although they did find that the positive surgical margin rate was higher (31% vs 21%) (38). They did concede that their study was limited by the low proportion of AAM in the cohort (6.5%).

A retrospective analysis of a radical prostatectomy series by Rabbani, et al in 2009 found that African American patients were more likely than white patients to have positive surgical margins (17.1% vs 11.6%). Interestingly, ethnicity was only a significant predictor of positive margins at the apex, with an odds ratio of 1.76 (39).

One potential explanation for the increased positive apical margins in black patients might be pelvic anatomy. Patients who have deep and narrow pelvis and with deeply situated prostatic apices have been shown to have higher rates of positive margins at the apex (40). Von Bodman, et al analysed the preoperative MRI's of 482 Caucasian and 103 African American patients and found that the AA men had steeper symphysis-pubic angles, smaller pelvic inlets and more inferiorly situated prostatic apices (41). They found that the depth of the prostatic apex in their series was independently predictive of positive apical margins, which was more pronounced in AA men.

Equal Access vs Fee Paying Systems

Studies performed in so-called "equal access" healthcare systems often find fewer differences in the clinical and pathological features of prostate cancer. These systems include free national healthcare systems and the Veterans Administration hospitals in the US.

In the UK, healthcare is free at the point of delivery to all residents. An analysis of the PROCESS cohort determined that although the black patients were diagnosed at a younger age and with higher age-adjusted PSA levels, there were no differences

detected in prostate cancer disease characteristics such as D'Amico risk group, Gleason grade and pathological stage (42).

There have been some attempts at identifying and quantifying contributing factors to racial disparities in prostate cancer. Jones, et al (43) performed a multivariate logistic regression analysis of a pre-PSA cohort of patients to quantify the effects of various potential explanatory factors on stage at diagnosis and on survival. They calculated that modifiable factors such as sociodemographic ones and screening practices accounted for more than 60% of the racial difference in stage at presentation. AA patients were 53% more likely to die of prostate cancer during follow up. Histological grade of cancer accounted for just over half of the increased risk of death. The remainder of the increased risk was explained fully by socioeconomic status and medical insurance coverage.

The impact of insurance coverage was investigated by Fedewa, et al (44). They examined all of the CaP cases listed in the US National Cancer Database during 2004-2006. They found that patients who were uninsured or on Medicaid were more than four times more likely to be diagnosed with CaP, compared to those with private health insurance. Comparing AAM with EAM in the cohort, AAM were 2.7x more likely to be diagnosed with CaP. Thus, insurance status seemed to account for a substantial portion of risk of CaP. It was also found that lack of insurance or Medicaid insurance and African American race were both independent predictors of higher PSA at diagnosis, higher clinical stage, and higher Gleason sum.

African ancestry has been shown to be a risk factor for a worse response to treatment, with lower biochemical progression-free survival and cancer-specific survival.

Response to Treatment

The study by Faisal, et al analysing the radical prostatectomy outcomes from Johns Hopkins from 1992 to 2013 found that biochemical recurrence, stratified by NCCN risk category, was significantly worse for African American men (35).

Gooden, et al (45) studied the influence of surgeon and hospital volume on racial differences in BRFS between black and white patients. This was done by reviewing the SEER data for patients who had had radical prostatectomies from 1991 to 1999.

High volume centres and high volume surgeons produced better biochemical recurrence free survival rates for their patients. AAM were more likely to be operated on by a low volume surgeon, even when at a high volume centre. AAM were more likely to experience BCR overall, which was significant in medium and high volume hospitals (HR 1.30 and 1.36, respectively) even when controlling for multiple covariates, such as NCCN risk and surgeon volume.

Even in equal access healthcare systems, black patients might still have lower long term biochemical recurrence free survival (BRFS) rates. Schreiber, et al studied the outcomes following RP at New York Harbor VA, an institution serving a predominantly AA population (46). They found that 5 year biochemical control was 90.2% in the EA patients but only 75.4% in the AA patients. The difference was more pronounced in the low risk group where 5 year BRFS was 97.6% vs 81.7%.

Mortality

Population based mortality rates from prostate cancer have also been found to be higher among men of African descent. Often the racial disparity in mortality is less than that found in incidence rates due to the detection bias being less.

Mortality rates in African Americans have been found to be 2.4 times higher than in white Americans (47). This finding was based on analysis of the SEER database. It is not entirely clear whether the increased mortality in these populations is entirely due to increased prevalence of prostate cancer, or if the prostate cancer that these men get is also more likely to result in death.

The PROCESS study, mentioned above, did not find differences in mortality within their cohort.

Powell, et al (48) analysed the SEER database, looking at prostate cancer survivorship in the US. They compared mortality rates between AA and EA men during 1973-1994 to represent the pre-PSA era, and during 1998-2005 to represent the current PSA era. In the pre-PSA era, the overall survival was significantly lower ($P < 0.0001$) for AA men, with relative survival approximately 10% lower throughout the period. In the PSA era more data was available on cancer stage and treatment. The investigators found that AA men have a higher incidence of prostate cancer, are more likely to present with metastatic disease, and they die on average 5 years

younger than their EA counterparts. However, when matched for stage at presentation, there was no statistically significant difference between the two groups.

Graham-Steed, et al attempted to investigate the relationship between race and prostate cancer specific mortality rates, controlling for healthcare access disparities (49). They performed a literature search for studies on race and prostate cancer mortality from the UK, Canada, or VA hospitals in the US. In addition, they analysed their own cohort of VA patients from the New England area. The five studies that they identified in their literature review all concluded that in those settings, overall and disease specific mortality rates were similar between black and white patients. The analysis of their cohort revealed that the black patients presented at a younger age, with higher PSA values, higher histological grade tumours and higher clinical stage compared to the white patients. Despite this, the prostate cancer specific mortality was not significantly different between the two groups.

The impact of access to healthcare on CaP mortality was also demonstrated by a study by Freeman, et al (50). In a sample of 833 CaP patients from the Chicago area during 1986-1990, socioeconomic status (SES) was estimated from the area that the patients lived in, and was compared to overall mortality. Patients in the lower SES quartile were 2.37x more likely to die of CaP than those in the highest quartile. Hazard ratios for death from CaP among AAM compared to EAM were 1.31 and 0.96 in privately insured and VA patients, respectively. Also, on adjusting for SES, there were no statistically significant differences in mortality rates between black and white patients. These findings suggest that access to healthcare, socio-economic status, but not race, accounted for the disparities in mortality seen within the population.

Biological explanations for disparities

Although health-seeking behaviour, access to adequate healthcare and other socio-economic factors account for a good deal of the racial differences in prostate cancer incidence, there is clearly also a biological component that contributes to these differences.

Genome-wide association studies have revealed a number of single nucleotide polymorphisms (SNPs) that are associated with prostate cancer risk. This includes CYP3A4, 8q24, and EphB2, among many others (21). Frequencies of these alleles vary between AAM and EAM.

Differences in androgen-mediated mechanisms could also be responsible for CaP disparities. The CYP3A4*1B allele, which is more prevalent in AA people, results in less efficient oxidative deactivation of testosterone. Prostatic androgen concentrations have also been shown to be higher in AAM. Polymorphisms in the number of CAG repeats in the AR gene have been shown to affect the function of the androgen receptor. Long CAG repeats inhibit the receptor leading to reduced androgen activity. AAM have been shown to have a higher prevalence of short CAG repeats. Short CAG repeat length has been shown to be a risk factor for higher stage at diagnosis, metastasis and death from CaP (21).

TMPRSS2:ETS fusions are oncogenic events that were shown to be more common in CaP tissue from AAM, although more recent studies have actually reported a lower incidence (21).

Diabetes mellitus (DM), specifically type II DM, has been shown to be associated with an increased risk high grade CaP (51). The risk is higher in obese diabetics. The mechanisms accounting for this increased risk are unknown. The Centers for Disease Control and Prevention (CDC) estimate that the prevalence of DM in African Americans over the age of 20 is 18.7%, compared to a rate of 10.2% in whites (52). This could partly account for the increased incidence of CaP among AA men.

Differences in vitamin D levels and the vitamin D receptor have also been thought to play a role in CaP incidence, but data on this are inconclusive (21).

Other environmental influences, such as level of exercise, trans fatty acid intake and cooking practices, have also been implicated (53–55).

Summary

To summarise, it is clear that men with African ancestry have a greater risk of being diagnosed with prostate cancer and that that risk is higher in the younger age groups. This is probably due to a higher prevalence in those populations, but the

differences in incidence might be more pronounced because of more aggressive screening practices in those populations.

Differences in stage of presentation, pathological features, positive margins, biochemical recurrence and cancer specific survival for prostate vary widely between populations, but are probably less marked in populations served by equal access healthcare systems.

Prostate Cancer in Africa

Studies on the epidemiology of CaP on the African continent are few. Analysis of the GLOBOCAN 2012 data reveals that CaP is the commonest cancer diagnosed in men in Africa (56). Interestingly, the mortality to incidence ratio for CaP in Africa was estimated to be 71%. By contrast, the number of deaths due to prostate cancer in North America in 2012 was only 13.1% of the total number of new cases (11). The high incidence to mortality ratio in Africa is indicative of a high level of underdiagnosis of CaP.

Zimbabwe is one of the few sub-Saharan African countries with a population based national cancer registry (56). Data from the city of Harare are considered the most reliable. The incidence of CaP in the black population of Harare has been noted to be increasing at a rate of 6.4% annually over the last twenty years. The ASR for CaP was calculated as 30.1 in 1991-1995, rising progressively to 73.3 in 2006-2010 (57). This is the highest ASR reported for CaP in any African population, although notably still around half the incidence of CaP in white Americans. In the time period 1991-1997 the age standardised incidence of prostate cancer in Harare was 15% higher in whites, but by 2004-2010 it was 33% higher in the black population. This was due entirely to the rising incidence in black men (58). Screening for CaP is said to be uncommon in Zimbabwe. The authors of these studies postulate that the rising incidence might be due to increased awareness of CaP, more transurethral or open surgery being performed for LUTS, and to more histological analysis being performed on such operative specimens (57).

The incidence of CaP has also been shown to be rising rapidly in Maputo, Mozambique. It is now the most commonly diagnosed cancer in men, with an ASR

of 61.7 per 100,000. This figure was calculated from a pathology based registry held at the central referral hospital in the city. The authors of this study also indicate that the rising incidence is most likely not due to screening for prostate cancer, and might be due to similar reasons as those mentioned in the Harare study above (59).

The age standardised rate of prostate cancer in Kampala, Uganda was calculated as 39.6 per 100,000 in the years 2002-2006. The rate in Kampala has been rising by approximately 4.5% annually over the last 25 years (60).

West Africa is the region that would be of particular interest in prostate cancer epidemiology. It was the centre of the transatlantic slave trade from the 15th to the 19th centuries, and thus is the ancestral population of most of the “African diaspora” throughout Europe, the Caribbean and the Americas (29). Secondly, the Niger-Congo (or Niger-Kordofanian) group of languages originated in West Africa within the last 10,000 years. The Bantu language group of central, Eastern and Southern Africa is part of the Niger-Congo family. The Bantu expansion of people began from West Africa approximately 5,000 years ago, largely displacing existing populations as it progressed into central Africa, then eastwards and southwards. Genetic admixture seems to have been relatively minimal during much of this process, resulting in a good correlation between genetic and linguistic lineage (61,62). So despite the fact that within population genetic diversity is greatest in African populations (63), it is plausible that a genetic risk factor for prostate cancer might be shared by populations as widely separated as African Americans and Southern African Bantu speakers. Comparing the distribution of prostate cancer risk within Africa to the distribution of the Niger-Congo language group (see figure 1) and bearing in mind the abovementioned inadequacies in CaP epidemiology in Africa, it is also plausible that increased risk for prostate cancer might correlate more specifically with Niger-Congolese ancestry.

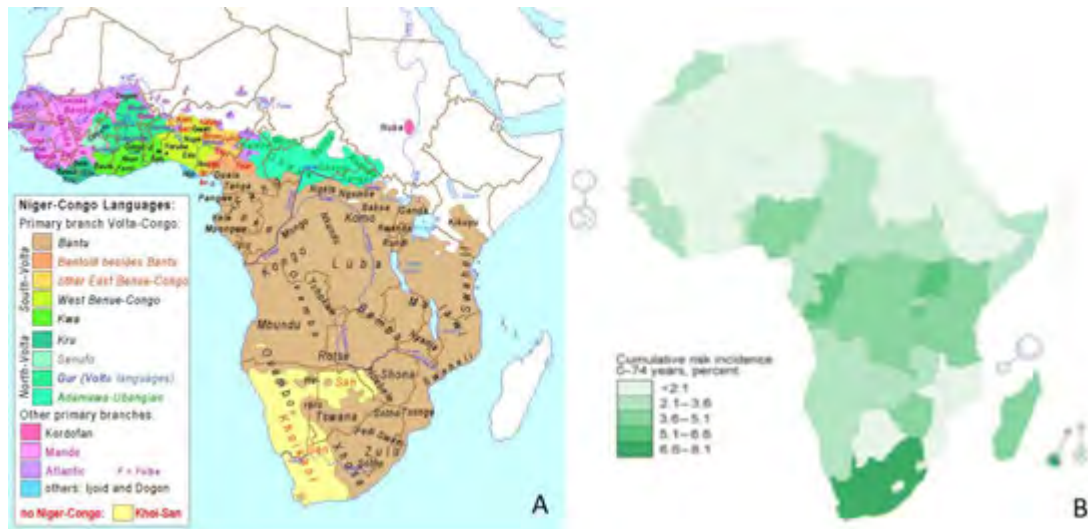


Figure 1A: Distribution of Niger-Congo languages – Image in the public domain, from <https://commons.wikimedia.org/w/index.php?curid=2987335>.(64).

Figure 1B: Incidence rates of prostate cancer in Africa – Image from Parkin *et al*, Cancer Epidemiol Biomarkers Prev, 2014 (56).

The ASR in Conakry, Guinea in 1992-1995 was found to be 8.1 per 100,000 (65). The authors mention that screening for CaP and histological examination of prostatectomy specimens did not occur in the area at the time.

Between 1995 and 1997, the ASR for CaP in Abidjan, Ivory Coast was 31.4 per 100,000, where it was the most commonly diagnosed cancer in men (66).

A study from Nigeria summarising the cancer registries of Ibadan and Abuja showed that prostate cancer was the most common cancer diagnosed in men in both areas during the period of 2009-2010 (67). The calculated ASR for CaP of both areas combined was 19.1 per 100,000.

Laryea, et al reported the results of a population based cancer registry in Kumasi, Ghana for 2012 (68). Although CaP was the second most commonly diagnosed cancer in males after liver cancer, the estimated ASR was only 1.7 per 100,000.

The reported low incidence of CaP in Ghana might be misleading. Hsing, et al performed a population based screening project in Accra, Ghana in 2004-2006 that involved 1037 healthy men who were randomly selected for recruitment (20). As an indication of the prevalence of screening within that population, only 2.4% of the study participants (aged 50-74) had ever had a PSA test. To contrast, it was found in 2001 that 75% of American men over 50 years of age had had at least one prior PSA

test (69). What was found in Ghana was that 352 (33.9%) of the men screened had either an elevated PSA or an abnormal DRE. 307 patients underwent TRUS-guided biopsy and 73 were confirmed to have CaP. Using a cut off PSA value of 4.0 ng/ml, the screening detected prevalence was 5.8%. In white Americans this value is 1.6%, while in African Americans rates vary from 2.2% to 5.4%. This important study suggests that the incidence of CaP in West Africa might be similar to that of African Americans if screening practices were the same. It also illustrates that even with good population based cancer registries, comparisons between incidence rates might be misleading if screening practices are not taken into account.

A study conducted in rural Nigeria by Ukoli, et al randomly invited men for PSA testing (70). 15.7% of men over the age of 50 years had PSA values of ≥ 4.0 ng/ml. None of the men, however, underwent prostate biopsy. In the previously mentioned Ghanaian study by Hsing, et al, 16.0% of men had similarly elevated PSA values. This could indicate that the prevalence of latent cancer in Nigeria might be similar to that found in Ghana.

In North Africa, the rates of prostate cancer tend to be lower than in sub-Saharan Africa. The age standardised rates have been reported as 11.4 in Libya, 5.4 in Algeria, 7.9 in Tunisia, and 7.5 in Egypt (71).

Prostate cancer in South Africa

The information on prostate cancer epidemiology is scanty in comparison to that of more developed countries.

The South African National Cancer Registry was set up in 1986. Prior to this, all epidemiological data on prostate cancer was derived either from death certification or from institutional case series (2,6,72–75).

South African studies tend to report race as one of four categories, mirroring the categorisation used in the South African Census. Those are black, white, coloured and Asian/Indian. The coloured race group refers to South Africans of mixed ancestry, and is sometimes referred to in the literature as “Cape Mixed Ancestry”. The major ancestral components of this population are Khoesan, Bantu-speaking African, European and Asian (76).

Several of the reports on prostate cancer mortality from the 1960's and 1970's excluded black South Africans because it was felt that death notification in that segment of the population was too sporadic and thus insufficient (72,73). Bradshaw and Harington reported in 1982 on the deaths in South Africa due to various types of cancer (6). They found that between 1970 and 1974, the mortality rate from CaP amongst whites was 17-19 per 100,000, and for coloureds it was 13-17 per 100,000. These figures were both higher than those of the USA or the UK, which had been reported at 14 and 12, respectively. The report also found that the mortality rate for prostate cancer was far lower in black and Asian men – the highest recorded rate for both groups was 8 per 100,000.

There is only one population based cancer registry in South Africa. It covers several rural areas in the former Transkei region of the Eastern Cape. The registry was set up by the Medical Research Council in 1981, mainly to monitor oesophageal cancer, which is particularly common in that area. The vast majority of the population covered are Xhosa-speaking black Africans. The most recent summary of that registry was published in 2015 (77), comparing various time periods from 1998 to 2012. The age standardised incidence rate for prostate cancer was found to be 4.4 per 100,000 in 1998-2002, rising to 9.9 in 2008-2012. In comparison, the national ASR for CaP as reported by the NCR for the year 2000 was 33.47 (78). The national rate is based on a pathology based registry, which would be expected to have a lower pickup rate for cancers than a population based one. In their discussion, the authors do not offer a hypothesis to explain the unexpectedly low incidence, although they think that the progressively increasing incidence might be related to more awareness, improved healthcare delivery, and better access to TURP.

The South African Prostate Cancer Study (SAPCS) is an international project being run by the Garvan Institute of Medical Research in conjunction with the J. Craig Venter Institute and the universities of Limpopo, Pretoria and New South Wales. It is a population based study that is recruiting black South African men with and without prostate cancer from various urology services in the Gauteng and the Limpopo Provinces. They aim to analyse their genetic profiles and to follow them up

in a longitudinal manner. Their stated goal is to investigate genetic and environmental risk factors in an “as yet un-investigated, potentially high risk population” to better understand global disparities in CaP, particularly those pertaining to African ancestry (79).

A report on the clinical presentation of approximately the first 1000 participants was recently published (24). The majority of their patients had presented with LUTS and presentation for screening was uncommon. The investigators also found that the men with CaP presented with more aggressive and more advanced disease. 83% presented with a PSA level of ≥ 20 ng/ml, with a median PSA of 98.8ng/ml. 36% had Gleason score of ≥ 8 . By contrast, the majority of men in the US are diagnosed with CaP after being screened, and only 16-17% are diagnosed with Gleason 8 or higher.

The group initially began by performing genome-wide association studies (GWAS) incorporating multiple single nucleotide polymorphisms (SNP) that were developed mostly in European populations. The findings were that these studies were not predictive of disease in the SAPCS population, indicating that these are probably not appropriate for clinical use in a Southern African Bantu population (79). The investigators speculate that some of the reasons for the discrepancies might be socioeconomic factors, late presentation and the lack of PSA screening.

Heyns, et al conducted a study in 2000-2001 screening attendees of the Urology clinic at Tygerberg Hospital in the Western Cape for prostate cancer using a DRE and PSA level. They found, in a cohort averaging 59.4 years of age, that 9.6% of the screened men had PSA values above 4ng/ml. Black patients were less likely to have high PSA levels than coloured patients, although there was no indication of whether this was statistically significant or not. There were 400 black patients screened, of whom 31 had abnormal PSA values. Only 6 of them had biopsies, two of which were positive for cancer.

In another study by Heyns and colleagues (7), an analysis was performed of all the patients diagnosed with prostate cancer at Tygerberg Hospital from 1995 to 2005. They considered the patients’ self-assigned race, their PSA value, the findings on DRE, the histological grade and whether the disease was localised or metastatic. The study included 901 patients, 32% of whom were white, 59.8% coloured and

7.9% black. PSA values were high. The median PSA of the group as a whole was 33.5, with a mean of 526.3 ng/ml. Median PSA values were highest in the black group, being 105 ng/ml, compared to 19.6 ng/ml in the white group and 42.5 ng/ml in the coloured group. The white patients presented more commonly with T1-T2 disease (53%), compared to the black and coloured patients, who presented more often with T3-T4 disease (62% and 61%, respectively). Black patients also had higher histological grade tumours on biopsy. The pathology laboratory reported according to the MD Anderson grading system (80) which grades CaP from 1 to 3 – low, intermediate and high grade. Grade 1 was the most common grade in white (37%) and coloured groups (39%), while black patients were most commonly diagnosed with grade 2 tumours (39%). Of the patients whose M-stage was known, 53% of black men had metastatic disease at presentation, compared to 28% of white patients. Although the mean age at presentation was significantly higher for the white patients, they were the most likely to be given potentially curative treatment. 31% of whites, 23% of coloureds and 12% of black patients were given radical treatment. The vast majority of black patients (88%) were treated with initial androgen deprivation therapy or with watchful waiting. Outcome data was not available for this cohort, but mortality was tentatively inferred from the duration of follow-up, which was significantly shorter for the black patients (24 months) than it was for the white (35 months) or coloured patients (31.5 months).

This study is particularly pertinent to our current study, since it also covers a Cape Town population, with similar socio-economic status and in an overlapping time period. The most salient finding of this paper was that men who access the public health services in Cape Town are diagnosed with CaP when the disease is more advanced than their counterparts in the US. Furthermore, black patients in the Western Cape present even later than the white and coloured patients do. No inferences can be made as to incidence rates for the population or whether one group might have a higher incidence than any other. A recent study from KwaZulu-Natal also found that there was high proportion of men presenting with locally advanced and metastatic CaP (81).

South Africa is one of the few African countries to have a national cancer registry. Ours is a pathology based registry rather than a population based one, so it does not include cancers diagnosed on clinical, radiological or post-mortem investigation. A pathology based registry also does not include clinical information such as presentation, tumour stage, treatment given, or outcome. The South African National Cancer Registry (NCR) is a program run jointly by the National Health Laboratory Service (NHLS) and the Medical Research Council (MRC).

A recent paper by Babb, et al (2) summarises the data on CaP in South Africa from the NCR (1986-2006), as well as mortality data obtained from death certificates by Statistics SA (1997-2009). Race categories used for the NCR are the same as those used in the national census, being: black, white, coloured (mixed ancestry), and Asian/Indian. Racial categories for cause of death were only available for 2009.

The authors report a steady increase in the incidence of CaP over the 20 years from 1986 to 2006, with the most rapid increase being between the years 1996 and 1999. Since 1996, CaP has been the most commonly diagnosed cancer in men in South Africa. The mean age of diagnosis in 2006 was 68 years, which was not significantly different between race groups. Diagnosis of CaP was shown to be very rare below 45 years, with a steady increase with age to a peak at 75 to 80 yrs. The ASR for CaP in 1986 was 17 per 100,000, increasing to 27 per 100,000 on 2006. In 2006 the ASR amongst black men was 12 per 100,000 compared to their white contemporaries at 52 per 100,000. In fact, every year since 1986 without exception, there were more individual cases of CaP diagnosed in white patients than in black patients – despite the fact that whites are a minority group in the population.

The mortality from CaP in South Africa is also increasing steadily. CaP is now the second leading cause of death due to cancer among men, accounting for 13% of cancer deaths. Lung cancer is the commonest at 19%. The age standardised mortality rate for CaP rose from 12.29 per 100,000 in 1997 to 16.67 per 100,000 in 2009. Only 11% of the men who died from CaP in 2009 were white, while 42% were black, 22% coloured, 2% Asian/Indian, and 23% from an unknown population group.

The authors of this study concede that the incidence and mortality rates are almost certainly underestimated across the board, but especially in the black population. They suggest a number of reasons for this. Firstly, since the NCR is a

pathology based registry, the cases that have been diagnosed on clinical grounds (ie. PSA, DRE, radiology) would not be included in the registry. Secondly, black men might be underdiagnosed more because of reduced access to medical care, or reduced use of these facilities. In the public sector, PSA screening is generally not available, while in the private sector it might be more commonly practiced. The authors point out that almost 70% of white people in South Africa have private medical insurance, while only 8.9% of the black population do. This suggests that in South Africa, white men are much more likely than black men to be screened for CaP. Because of competing mortality and a lower life-expectancy in the black population, black men in this country are less likely to live long enough to be diagnosed with CaP. The lower incidence might thus be partly due to the younger mean age of the black population.

One notable finding from this study that was not dealt with in the discussion was the very high age adjusted mortality rate for the coloured population. The rate per 100,000 for black men was 11.4, for white men was 6.8, for Asian/Indian men was 6.3, but for coloured men it was 51.9. The highest reported national rate in the world is 53.6 per 100,000 in Trinidad and Tobago, which is more than double the second highest mortality rate of 22.6 in Cuba (1). The reason for the very high mortality rate in the coloured population was not speculated upon.

Further research

This literature review has identified several deficiencies in the knowledge base of the epidemiology of prostate cancer.

The causes of the increased risk for CaP faced by men with African ancestry are poorly understood. Also, it is not certain whether established genetic risk factors are applicable to South African populations. Genetic based studies such as the South African Prostate Cancer Study and the Johannesburg Cancer Case Control Study will hopefully shed light on these genetic associations and perhaps on the underlying aetiology of prostate cancer.

Although it has been clearly established that CaP is more common and occurs at a younger age in men of African descent, the statistics that are available for populations in Africa are generally of very poor quality or non-existent. The

establishment of population based cancer registries in Africa would greatly improve knowledge in this area.

In South Africa in particular, a national population based cancer registry would give much better estimates of our cancer incidences and outcomes. Because of our better infrastructure and healthcare system, this is a lot more feasible than establishing and maintaining such registries elsewhere in Africa.

The finding by Babb, et al (2) that the prostate cancer mortality among coloured men in South Africa in 2009 was calculated as 51.9 needs to be verified and, if it is that high, then the underlying reasons should be sought out.

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Part C: Manuscript

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Investigating Racial Differences in Clinical and Pathological Features of Prostate Cancer in South African Men

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Abstract

Background: Men with African ancestry living in Europe and the Americas are at higher risk of being diagnosed with prostate cancer, are diagnosed at a younger age, and might have more severe disease characteristics. Published reports present a conflicting picture of the disease South Africa, and it is unclear whether black South African men share this increased risk.

Objectives: We aimed to study the clinical and pathological features of men undergoing prostate biopsy from different racial backgrounds in South Africa, in an attempt to characterise the disease locally. Our hypothesis was that black African men presenting to our service had more severe disease characteristics than other patients.

Materials and methods: All patients who underwent a prostate biopsy at Groote Schuur Hospital, Cape Town from July 2008 to July 2014 were studied. For each patient, data were collected on age, self-assigned race, presenting symptoms, prostate-specific antigen (PSA) level, prostate volume, and histological diagnosis.

Results: A total of 1016 patients were studied. 162 (15.9%) were black and 854 (84.1%) were coloured (mixed ancestry), white, or Asian. Black patients were compared as a group to the coloured, white and Asian patients. The black patients in the series had higher PSA values (mean 167.8 vs 47.7, median 16.4 vs 10.9, $p < 0.001$). They were more likely to be diagnosed with cancer (57.4% vs 44.5%, $p = 0.003$), to present with locally advanced cancer (T3/4 16.1% vs 8.9%, $p = 0.028$), and

to have high grade disease (Gleason ≥ 8 45.2% vs 30.5%, $p = 0.011$). There was no difference in age, presenting symptoms, or prostate volume.

Conclusion: The black men diagnosed with prostate cancer at Groote Schuur Hospital had significantly worse clinical and pathological characteristics than the non-black men. Interpreting these differences as representative of a more common or aggressive disease among black men is not possible due to study limitations.

Introduction

Cancer of the prostate (CaP) is one of the most common cancers diagnosed in men. Worldwide, it is the second most common non-cutaneous cancer in men and it is the fifth commonest cause of death due to cancer (11). In South Africa, prostate cancer is the most frequently diagnosed cancer in men, and second only to lung cancer in terms of mortality (2).

African American men have been shown to have a higher incidence of prostate cancer, higher stage at presentation, higher histological grade, a greater propensity to relapse after curative treatment, and a higher disease-specific mortality (3,4). Men with West-African ancestry living elsewhere, such as South America, the United Kingdom and the Caribbean, have similarly high rates of prostate cancer (5,14,15). Delayed diagnosis accounts in part for the higher stage at presentation and possibly some of the increased mortality. This delay in diagnosis has been attributed to healthcare access problems, reduced health-seeking behaviour, and often health-provider prejudice (82). Once diagnosed with prostate cancer, lower socio-economic status can, in many instances, lead to inferior management and worse outcomes following treatment. Studies attempting to correct for these factors conclude that they do not account all of the discrepancies seen and that some of the differences in disease characteristics must be due to differences in tumour biology between African American men and other American men (83). These are most likely the result of underlying genetic factors (4). The exact mechanisms conferring this increased risk are unknown. Many single nucleotide polymorphisms have been shown to be associated with increased risk for CaP, although these are not necessarily causative. Some occur with higher frequency in populations of African descent. There is also some evidence that differences in

androgen metabolism might account for the discrepant risk. Various oncogenic events contributing to the pathogenesis of CaP, such as TMPRSS2:ERG gene fusions, also occur more commonly in men with African ancestry (21).

Epidemiological studies on populations within Africa report far lower incidences of prostate cancer than those reported in populations of African descent in Europe and the Americas (56). There is some evidence, however, that these rates are misleadingly low due to underdiagnosis and underreporting of cases (20,70).

Heyns, et al analysed the series of patients that were diagnosed with CaP at Tygerberg Hospital in Cape Town between 1995 and 2005. Compared to their white and coloured (or mixed ancestry) contemporaries, the black patients had higher PSA values at presentation, more locally advanced and higher grade tumours (7). The impression of those authors was that prostate cancer was more common in black South Africans than in other population groups, possibly in a similar way to African American populations. However, epidemiological studies on South African populations have uniformly found prostate cancer to be more common in white than black South Africans (2,6). These seemingly discordant findings suggest that prostate cancer in the South African black population might be underdiagnosed to a large extent. Prostate cancer incidence within a population is heavily influenced by screening practices. Due to lower socio-economic status, the average black male in South Africa might be less likely to be screened for prostate cancer, and thus be less likely to have a prostate biopsy than one of his white, coloured or Asian counterparts. This is illustrated by the finding that the biopsy-proven incidence in black men in South Africa is less than a quarter that of white South African men, but their mortality rate is more than double (2).

It has also been our overall impression that of the men being referred for prostate biopsy in our unit, the black patients seemed to have higher PSA values, larger prostates, be more symptomatic, and have a higher chance of having prostate cancer diagnosed. We therefore set out to analyse our biopsy database to determine if that is the case.

Materials and Methods

Approval for the study was obtained by the human research ethics committee of the University of Cape Town. A comprehensive literature review on the topic of prostate cancer and race was carried out using Medline and Google Scholar.

The study was performed within the Division of Urology at Groote Schuur Hospital in Cape Town, South Africa. Since 2008, the division has prospectively kept a database of all the patients undergoing prostate biopsy. Data collected include demographic information, PSA value, presenting symptoms, findings on digital rectal examination (DRE), and histopathology results. All patients had been referred to the urology service via normal channels and had biopsies as part of routine clinical care. Indications for prostate biopsy included an elevated serum PSA level or an abnormal DRE. We routinely perform a 12 core transrectal ultrasound-guided biopsy under local anaesthetic. Any abnormal areas noted on TRUS are biopsied with additional cores.

A retrospective analysis of the database was performed, covering the patients biopsied between July 2008 and June 2014. Patients' self-assigned race, as recorded by hospital administration staff, was obtained from the electronic patient record database. Patients were excluded if PSA value, histology result or self-assigned race was not available. The data was analysed with the assistance of a statistician, with special emphasis on clinical and pathological characteristics correlated with race group.

The 2011 South African Census reported that the demographic profile of the city of Cape Town was 38.6% black African, 42.4% coloured (mixed race), 15.7% white, 1.4% Asian, and 1.9% other (84). The population breakdown of people over the age of 65 was 14.4% black, 39.0% coloured, 43.3% white, 1.5% Asian, and 1.9% other – the differences possibly due to different patterns of migration and discrepant life expectancy. The hospital record-keeping system uses the same race categories as those used in the census. The coloured population of South Africa is largely based in the Western Cape Province, which makes the proportion of coloured people living in Cape Town much higher than the national average, while the black population comprises a corresponding lower proportion of the total population. The

percentage of people of Indian descent living in the Western Cape is lower than in KwaZulu-Natal or Gauteng.

Our working hypothesis was that the black patients within our population might present with higher serum PSA levels, larger prostates, more locally advanced tumours, and tumours of a higher histological grade. We also thought that black patients might be more likely to present with lower urinary tract symptoms, and less likely to have been biopsied as a result of PSA screening. In keeping with our hypothesis that black patients might have worse clinical and pathological features, we compared the coloured, white and Asian patients as a group (“non-black” patients) with the black patients. Categorical data was compared using Pearson’s Chi-squared test. Parametric (patient age) and non-parametric (prostate volume measurements and PSA values) numerical data were compared using the Welch two sample t-test and the Wilcoxon rank sum tests, respectively. Statistical significance was defined as a p-value ≤ 0.05 .

Results

The database contained details on 1027 men. 11 patients were excluded from the analysis due to missing data on PSA value, race group, or histology results. Thus, a total of 1016 patients were included in the analysis. 162 (25.9%) were black, 757 (74.5%) were coloured, 89 (8.8%) were white, and 8 (0.8%) were Asian. The mean age of the cohort was 65.8 years, and was matched across race groups ($p = 0.378$).

We examined the mode of presentation of the patients and classified them into four groups. *Asymptomatic* patients were those who presented requesting PSA screening without symptoms of prostate pathology, or those who were referred to us having had a screening PSA. Men presenting with symptoms were classified as having *LUTS* (obstructive or irritative lower urinary tract symptoms), symptoms of *metastases* (bone pain, loss of weight, paraplegia), or *other* (haematuria, haematospermia, etc). The rate of screening in this cohort was low, with only 21.5% of the patients being asymptomatic. The likelihood of a positive biopsy among the asymptomatic men was similar between the black and non-black patients (41.4% vs 42.8%, respectively). 77.2% presented with LUTS, 0.8% with symptoms of metastases, and 0.7% with other symptoms. There were no statistically significant

differences between the race groups in terms of presenting symptoms ($p = 0.731$). More black patients presented with obstructive urinary symptoms (70.6% vs 64.3%), but this difference did not achieve statistical significance ($p=0.127$).

Black patients presented with significantly higher PSA values than the coloured, white and Asian patients ($p < 0.001$). The mean PSA value among black patients was 167.8 ng/ml, compared to 47.7 ng/ml in the non-black patients. The mean values in both groups were somewhat skewed by a few very high outliers. Median PSA values were 16.4 and 10.9 ng/ml, respectively (See figure 1).

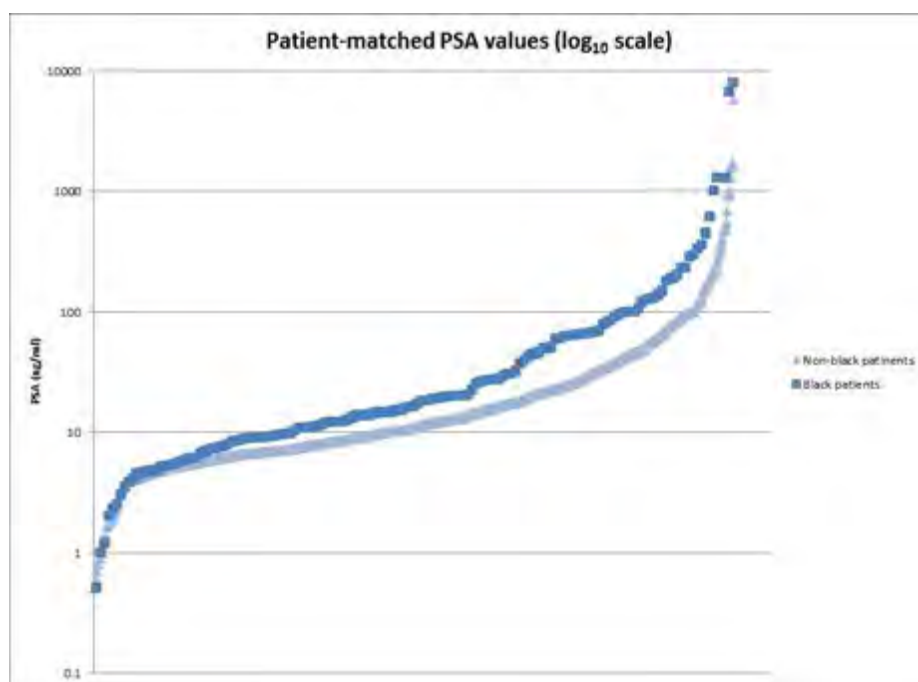


Figure 1: Scatter plot of all PSA values – black vs non-black ($p < 0.001$)

Mean estimated prostate volume was higher in the black patients (57.8g vs 50.6g), but this was not statistically significant ($p = 0.165$). There was also no statistically significant difference, with respect to race, in the PSA densities of the patients who had negative biopsies (mean PSA-d 0.433 ng/ml/ml in black patients vs 0.376 ng/ml/ml in non-black patients, $p=0.3603$).

The overall positive biopsy rate was 46.6% (473/1016). Coloured, white and Asian patients had cancer diagnosed 44.5% (380/854) of the time, while black patients had positive biopsies in 57.4% (93/162). This translated into black patients having a 29% higher chance of being diagnosed with cancer, which was highly statistically

significant ($p = 0.003$). The mean ages of men with positive biopsies were similar between black and non-black patients (68.3 vs 67.2 years).

Higher grade tumours were noted in the black patients. They were significantly more likely to have tumours that were Gleason ≥ 7 (74.4% vs 62.5%, $p=0.033$) and Gleason ≥ 8 (51.1% vs 36.5%, $p=0.011$) (see figure 2).

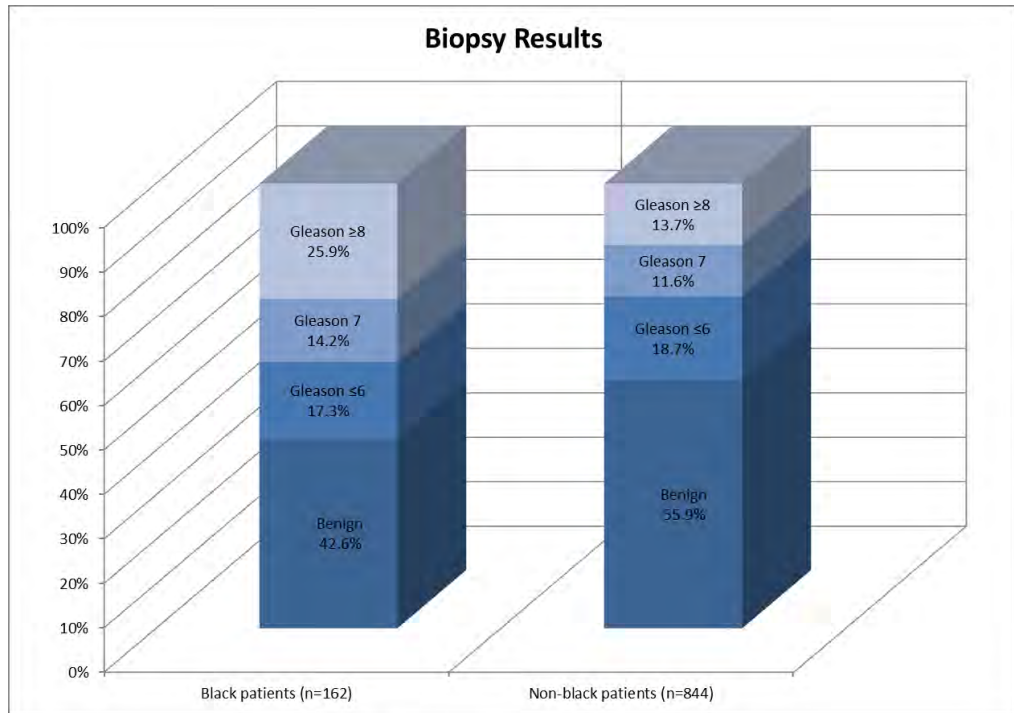


Figure 2: Histological diagnosis – black vs non-black

Black patients were more likely to have extraprostatic disease clinically. Of the black patients diagnosed with cancer, 15/93 (16.1%) had T3 or T4 disease on DRE, compared to 34/380 (8.9%) of non-black patients ($p = 0.028$) (see figure 3).

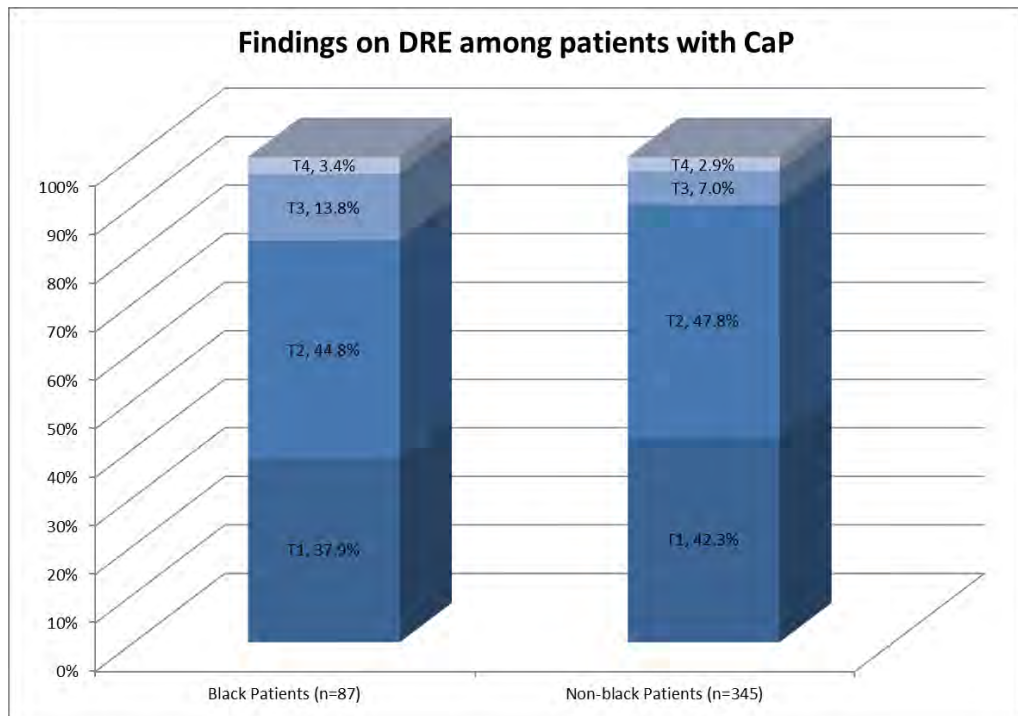


Figure 3: DRE findings

	Black Patients n = 162 (15.9%)	“Non-Black” Patients n = 854 (84.1%)	Total N = 1016	p-value
Asymptomatic	29/162 (18.5%)	177/854 (21.8%)	206/1016 (21.2%)	0.731
Obstructive symptoms	115/162 (71.0%)	555/854 (65.0%)	670/1016 (66.0%)	0.125
PSA value in ng/ml (mean / median)	166.8 / 16.4	47.5 / 10.9	66.6 / 12.0	<0.001
Prostate volume (mean / median)	57.8g / 40.5g	50.6g / 40.9g	51.7g / 41.0g	0.165
Positive biopsy	93 (57.4%)	380 (44.5%)	473 (46.6%)	0.003
Gleason ≥ 7	65/93 (69.9%)	214/380 (56.3%)	307/473 (64.9%)	0.033
Gleason ≥ 8	42/93 (45.2%)	116/380 (30.5%)	158/473 (33.4%)	0.012
DRE - T3/T4	15/93 (16.1%)	34/380 (8.9%)	49/473 (10.4%)	0.028

Table 1 – Summary of results.

Discussion

Racial categorisation in medical research is a controversial area. Some authors contend that racial categories are arbitrary and subjective, that there is no genetic

basis for such classification and that they should not be used in medical research (85). Others have expressed concern that ongoing emphasis on race could serve to perpetuate racial categorisation in the literature (86). Many scientific journals encourage potential authors to identify the underlying causative factors, be they genetic or environmental, rather than report on race alone. Some feel that focus on race can highlight social, economic and healthcare inequalities, and act as a mechanism for ensuring redress (87). It has been recommended that the potential benefits in terms of diagnosis and research should be weighed against the potential social cost of doing so (88).

The black patients presenting to our service had more severe clinical and pathological features than the coloured, white and Asian patients. They presented with higher PSA values, had a higher risk of being diagnosed with cancer, were more likely to have locally advanced disease, and were more likely to have high grade tumours. There are several potential explanations for these observed differences. The equal proportions of asymptomatic black and non-black patients in the series suggest that the worse disease characteristics seen in our black patients was not due to reduced screening in that population group. Because the risk of having a positive biopsy was similar amongst the black and non-black men who had been screened, the different rate of positive biopsies was accounted for by the symptomatic men. It could be that black men in Cape Town only access the healthcare system when their symptoms are particularly severe. In a screening study at Tygerberg Hospital in Cape Town, Heyns et, al (89) had found it difficult to get prostate biopsies for the black patients with abnormal PSA values. It is therefore also possible that our black patients were less likely to accept the recommendation of prostate biopsy if they were minimally symptomatic.

Despite these possible explanations for the racial discrepancies seen, it seems likely that there is an underlying biological factor at play. The mean ages between race groups were matched, both overall and amongst the men diagnosed with CaP. This would suggest that black men were either developing prostate cancer at a younger age or that they were prone to more rapidly progressive disease. The finding that the black patients in the series were at significantly greater risk of being diagnosed with high grade tumours is also an indication that the cancers diagnosed

were more progressive and/or more longstanding. Prostate sampling bias is a phenomenon that arises from the random nature of the prostate biopsy – the same volume of cancer in a larger prostate will be more easily missed at biopsy, and smaller foci of higher grade tumour will similarly be missed. Because the prostate volumes were not significantly different between black and non-black patients, the differences noted were not due to such a bias.

When comparing our data to that of developed countries, the worse clinical and pathological features seen in our black patients is seemingly on a background of generally more severe disease among all of our patients. Overall, the patients in our series presented to us largely with symptomatic disease. A study published in 2001 found that 75% of US men over the age of 50 had previously been screened for prostate cancer (69). The finding that only 21% of our patients were asymptomatic shows indirectly that the rate of PSA screening in our population is probably very low.

The overall positive biopsy rate of 46.6% is somewhat higher than those of other published series' of first time TRUS-guided prostate biopsies, which one review reported to be 38-42% (8). Our high rate is probably another reflection of the low level of screening in our population. Our patients also presented with a higher rate of high grade disease than that seen in other settings. Only 35.1% of our patients had Gleason scores of 6 or less. A review of the CaPSURE database in the US reported that 64.9% of men on the database had Gleason scores of 6 or less (90). An analysis of the Rotterdam section of the ERSPC (European Randomized Study of Screening for Prostate Cancer) showed that 92.5% of patients diagnosed with CaP via screening had a Gleason score of ≤ 6 (91).

In the same CaPSURE review mentioned above, 79.3% of the patients had PSA values less than 10 ng/ml, whereas only 42.8% of our patients had a PSA values less than 10 ng/ml.

Presentation with locally advanced disease (T3 or T4) was 10.4%. This rate is similar to that found by Hoffman, et al (11.3%) in a large retrospective series in the US during 1994-1995 (92). This series was accrued during the early PSA era. A US study analysing temporal trends in prostate cancer reported a drop in the rate of T3/4 tumours at diagnosis from 19.2% in 1988 to 4.4% in 1998 (93). The higher PSA

values, higher Gleason scores and higher rate of locally advanced tumours that we see in our series are indicative of delayed diagnosis. Men served by the public health system in South Africa are probably less likely than their European or American counterparts to be screened for prostate cancer when asymptomatic. It is also possible that when South African men do become symptomatic, they are less likely to be tested for prostate cancer – due to healthcare access problems, reduced health-seeking behaviour, or health provider practices. Black South African men could be more affected by these problems than coloured, white, or Asian Patients.

We identified several limitations to our study. It was not possible to estimate prostate cancer incidences, since the population we serve is poorly defined and there are a number of other facilities in these areas at which patients might undergo prostate biopsy. TRUS and biopsy were performed by multiple and relatively junior clinicians, possibly affecting the accuracy of the prostate volume measurement and the targeting of the biopsy. While this factor may have reduced the accuracy of our results, it was spread evenly throughout the series. We also have no data on the incidence of biopsy-related complications, the subsequent management of these patients or their outcome following treatment. We only studied patients living in one city and accessing one hospital, so we cannot extrapolate those results across the entire population of South Africa. Also, our case series is most likely not a representative sample of the men living in Cape Town, since it excluded those accessing care at other public urology services and in the private sector. Although we found significant differences between the black and the non-black patients in our series, our study was not able to determine the underlying reasons for these discrepancies.

Groote Schuur is a tertiary referral hospital, with relatively few biopsies performed at referring hospitals. The resultant large numbers may increase the validity of the study.

Conclusion

Our study has demonstrated that the men who had prostate biopsies at Groote Schuur Hospital during 2008-2014 had more severe clinical and pathological characteristics, compared to American and European data.

The black patients we saw presented with significantly worse disease characteristics than their coloured, white, or Asian contemporaries. They had higher PSA values, were at higher risk of having cancer diagnosed, had higher grade tumours, and had more locally advanced disease.

The underlying reasons for these differences are speculative, and are likely to be multifactorial. Delayed presentation due to healthcare access disparities and different health-seeking behaviours could account for some of those differences. The different CaP characteristics seen could also be due to underlying biological factors. Whether different biological risk is due to genetic or environmental factors is also uncertain. Large genetic and epidemiological studies are required to answer these questions.

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Part D: Appendices

Appendix 1: Authors' guidelines for selected journal – Urology Gold Journal

This article falls into the category of Medical Oncology, for which the criteria are as follows:

- Structured article
- 250 word abstract
- Max 3000 word text
- Max 4 figures/tables
- Max 30 references

The full guidelines for authors are extensive. They can be found at:

<http://www.goldjournal.net/content/authorinfo#idp1297904>

Appendix 2: Data capturing form

Patient Name _____ Hospital no. _____	Date: ___ / ___ / ___ Surgeon: _____
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<input type="checkbox"/> Informed consent	<input type="checkbox"/> Ciprofloxacin 500mg stat	OPD appt date _____
<input type="checkbox"/> Information leaflet		

Symptoms:		<input type="checkbox"/> Obstructive <input type="checkbox"/> Irritative <input type="checkbox"/> Screening
PSA	Age	DRE

Discrete hypoechoic PZ	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Diffuse hypoechoic PZ	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Capsule distorted PZ	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Capsule intact	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Calcifications PZ	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Calcifications central	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Central hypoechoic areas	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Increased vascularity	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Left	<input type="checkbox"/> Right
Prostate size	_____ grams			

(Photo of ultrasound)

Biopsies: <input type="checkbox"/> First <input type="checkbox"/> Re-biopsy	<input type="checkbox"/> Standard 12 core <input type="checkbox"/> Added biopsies of abnormal areas
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Histology:	<input type="checkbox"/> Adeno-Ca <input type="checkbox"/> Gleason grade ___ + ___ =
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Appendix 3: Human research ethics committee approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 March 2015

HREC REF: 099/2015

Dr L Kaestner
Urology
E26, NGSH

Dear Dr Kaestner

PROJECT TITLE: INVESTIGATING RACIAL DIFFERENCES IN PROSTATE CANCER INCIDENCE IN SOUTH AFRICAN MEN (MMed candidate-Dr M Dewar)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th March 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the MMed student Dr Malcolm Dewar will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 099/2015