RETROSPECTIVE REVIEW OF PROSTATE BIOPSIES AT A REGIONAL LEVEL HOSPITAL

By

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Submitted in partial fulfillment of the academic requirements

for the degree of MMed

in the Department of Urology

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

Durban

2018

Declaration

I Vishan M. Ramloutan (204501212) declare that

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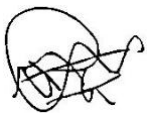
Signed:  Date: 24-04-2019

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Supervisor 1: As the candidate's co-supervisor I have approved this thesis for submission.

Dr RJ Urry 2019/05/19

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Supervisor 2: As the candidate's co-supervisor I have approved this thesis for submission.

Signed: Name: C Aldous Date: 15 May 2019

Dedication

This body of work is dedicated to my loving family for all their support in particular my caring mother.

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Overview

The context surrounding prostate cancer has changed drastically in the last three decades. This is largely due to discoveries allowing identification of patients earlier in the disease course and newer, novel therapies to treat patients at different stages in the disease. However prostate cancer management, and in particular screening, is not without controversy. Owing to a supposed indolent nature of a large percentage of diagnosed tumours the need for a screening program and early identification of patients has been questioned. To this end a selective screening program has been suggested to target sub population groups at increased risk for aggressive disease (of note is that Black African individuals are considered an at-risk group for aggressive prostate cancer). How and if this should be affected has still not been established. The South African based Prostate Cancer Foundation recommends general population PSA based screening after the age of forty-five years (with screening after the age of forty years in males deemed at increased risk), however there are no guidelines on screening from the National Department of Health. To date most studies undertaken locally have included a cohort that does not accurately reflect the population of South Africa (these studies were based in the Western Cape and had a selection bias towards White males). Of the two studies undertaken in KwaZulu-Natal, one was undertaken in a general hospital with a 'satellite' Urology department. The other study assessed prostate biopsy waiting times as its primary outcome. In this descriptive study, a review of the outcome of prostate biopsies at a regional hospital for a two-year period was undertaken to establish if there is evidence either for a general or sub population specific serum PSA based prostate cancer screening program and what guidelines should govern such a program. This was accomplished by comparing the incidence of prostate cancer amongst the different racial groups of patients undergoing a prostate biopsy at St. Aidan's Mission Regional Hospital and specifically looking at the number of patients with advanced disease as well as the initial serum PSA readings the patients presented with. Patients referred to St. Aidan's Mission Regional Hospital for a prostate biopsy represent a cohort of patients who largely were referred after an opportunistic serum PSA test was performed at the referring healthcare facility. It was found that nearly two thirds of patients had a positive cancerous histology after the first biopsy with more than 90% of patients diagnosed with prostate cancer being risk stratified to a category requiring some form of either curative or palliative treatment.

Table of Contents

Chapter 1: Introduction

Introduction

The face of prostate cancer has changed in the last 30 years. Initially a disease where late presentation and high mortality was the norm, the paradigm has shifted due to numerous discoveries in the preceding years. At one end of the spectrum the discovery of PSA and its approval for the use in prostate cancer treatment and screening in the late 1980s and early 1990s enabled clinicians to identify 'early', in some cases pre-symptomatic disease. The resultant effect was the reduction in prostate cancer mortality (with an increase in diagnosis and treatment) (1, 2).

Literature review

However, with the increase in histologically confirmed, organ confined disease, it also became readily apparent that the burden of new prostate cancer cases was skewed towards low grade, seemingly indolent disease with possibly little aggressive potential within a patient's lifetime (1-3). This trend in "over diagnosis" of prostate cancer lead to suggestions that screening of prostate cancer with serum PSA readings should be abandoned (3, 4). Studies done to establish consensus initially further confounded the issue by offering seemingly juxtaposed results and therefore conclusions. The *European Randomised Study of Screening for Prostate Cancer (ERSPC)*(5*)* revealed an 8.2% incidence of prostate cancer in the routine PSA screening group (versus 4.8% prostate cancer incidence in the control group). PSA based screening reduced prostate cancer mortality by 20%. To effect this however the estimation from this study was that 1410 men would need to have PSA screening for prostate cancer with 48 additional cases of Prostate cancer diagnosed to prevent one death from prostate cancer(1). These are the quoted figures from the nine year follow up of the ERSPC study. The figures from the 16 year follow up are that 570 men need to be screened with 18 additional cases of prostate cancer diagnosed to prevent one death from prostate cancer(6).

The 2010 Göteborg Prostate Cancer Screening Trial(7) findings were in congruence with the ERSPC, with 293 men needing to be screened and twelve new cases of prostate cancer diagnosed to prevent one death from prostate cancer. In comparison the figures quoted for breast cancer screening is that one additional death from breast cancer will be prevented with every 400 patients screened (between the ages of 50-70 years)(8). The data and initial conclusions from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial however, did not demonstrate any significant reduction in prostate cancer related mortality(1). A review of the data in the ERSPC and PLCO trials by Tsodikov et al however using mean lead time estimations, and accounting for differences in implementation and setting, revealed that both studies provided compatible evidence that screening reduces prostate cancer mortality(9).

The results of these findings should be considered with the conclusions gained from other prostate cancer studies. Prostate cancer screening and indeed PSA based prostate cancer screening may still not be indicated for the general male population despite the findings of the *ERSPC*, *Göteborg* or *PLCO*. "The risk of a fifty year old man with a 25 year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer 9,5% and of dying of prostate cancer 2,9%." (4). However a man in his forties with three close relatives diagnosed with prostate cancer (e.g. father, uncle and brother) has a 30-40% lifetime risk of developing clinically significant disease (4). It would therefore appear that prostate cancer screening should be directed to subsets of the population that are deemed at risk. The need for criteria in terms of which sub population groups qualify for a biopsy is important as a prostate biopsy is not an innocuous procedure (4, 10). Sepsis and heamaturia are two common complications with sepsis rates on average of 1-7% reported and heamaturia rates of between 2-34%.

Use of the Serum PSA level to decide on the need for a biopsy is in itself fraught with difficulties (11). Factors often cited against a PSA screening program are the poor specificity of PSA as a bio-marker of prostate cancer, the likelihood that a biopsy proven cancer may not be clinically significant and actually indolent in nature and that a prostate biopsy by its nature is a very invasive procedure fraught with many potential complications (12, 13).PSA can be considered prostate disease specific and not necessarily prostate cancer specific. Various factors can cause a raised PSA, among them infection of the prostate, urinary tract instrumentation and prostate malignancy. To further cloud the use of PSA a poorly differentiated prostate cancer may actually not secrete any PSA or may even secrete a reduced amount in comparison to a normal prostate cell. A PSA value between 0-4ng/ml is commonly accepted as a "normal PSA". Further to this there has also been suggestions that higher PSA cut offs should be deemed age appropriate (14). However in a study of 332 men who were fifty years or older with serum PSA value between 2.6-4ng/ml, prostate biopsies revealed cancer in 22% of them (4). A study by Oesterling suggested that PSA range of 0-4.5 should be appropriate for men 60-69 years of age while a PSA of 0-6.5 should also be normal for men 70-79 years of age. It therefore should be considered "safe" to omit biopsies in these men with these PSA readings (assuming the digital rectal examination is normal). However a retrospective review of prostate biopsies (14) contradicted this, revealing that if this protocol had been followed 60% of aggressive cancers would be missed.

Despite the controversies of whether general prostate cancer screening should be instituted or indeed how prostate cancer screening should be carried out, certain sub population groups are at greater risk for the development of the disease either purely by a predisposing genetic risk factor, lack of awareness of the disease or both of these factors. To this extent people of Black African ancestry represents one such sub group.

In the USA the lifetime risk of the general male population for prostate cancer is 15,9% and the risk of death is 2,8% (15). The incidence in African American men is almost 60% higher however then the general American population with the mortality being 2-3 times greater. Even in the pre PSA screening era the mortality rate amongst African American men was 55 per 100000 while in White American men it was 29 per 100000 (1) indicating that African American men have a more aggressive disease type independent of early detection. African American men have a strong West African ancestry. There is evidence to suggest that there is a disproportionate larger burden of disease in West African men (15). In men of African

ancestry prostate cancer may in fact transform into aggressive disease earlier than White men. Even studies such as the PCLO and ERSPC trial which initially revealed no or marginal benefit of screening for prostate cancer were underpowered for Black African population. There was an estimated 28006 deaths from prostate cancer in Africa in 2010 and this number is calculated to rise to 57048 deaths in 2030, an increase of 104% (16).

However based purely on figures from the World Health Organisation worldwide cancer data, West African men have a lower prostate cancer incidence and mortality compared to African American men (17). The quagmire is rendered further murkier by a reported higher prostate cancer mortality rate in the Afro-Caribbean population – a population sharing a genetic ancestry to West African men. Is this increase in West African descendants due purely to environmental and dietary factors or could it be still be due to a genetic link? Men with African ancestry who reside in the Americas and the Caribbean nations by and large can trace their ancestry to the Transatlantic Slave Trade. The present-day countries from which individuals were captured for slavery are Benin, Nigeria, Ghana, Gambia, Senegal, Mozambique and Angola. Therefore, it is likely that the population of the Americas and the Caribbean nations that claim Black African ancestry likely have a genetic mixture from the above African countries and are not just purely West African. The last two mentioned African countries are geographically neighboring countries to South Africa. Furthermore, Odedina et al(17) found that the World Health Organization cancer data for African countries (and indeed developing countries in general) may be under reported and not accurate. The true prevalence and incidence therefore may be higher, and the role of environmental factors limited (17, 18).

The PROCESS study (18), carried out at selective sites in and around London in the United Kingdom, compared the incidence and prevalence of prostate cancer in the different ethnic groups inhabiting the United Kingdom. In addition to merely comparing the Black race to the White race in terms of incidence and prevalence it went further by actually comparing Black males of Caribbean origin to Black males originating from the African continent. Census data indicated that Black UK males are largely first-generation migrants from either the Caribbean or Africa (by and large West Africa) therefore allowing a head to head analysis of these groups. The findings of the PROCESS study were congruent with other studies by revealing that Black men in general had a higher relative risk of developing prostate cancer than their White counterparts (this risk was more marked for younger men). The risk was still less than that seen for Black men in the United States. There was no statistically difference in prostate cancer incidence in Black Caribbean and Black African men.

Owing to British/European colonialism of the Caribbean and South Africa, the ethnic make-up of the populations of both these regions are similar with Black males of African origin and Asian males with roots from the Indian subcontinent(12). A study done in Tobago (17) revealed that the Black population (of West African descent) had a significantly higher prevalence when compared to the Asian-Indian group. The age group looked at was between 50-64 year age group. A study conducted in the UK including the Indian-Asian population as well as the Black and White population (17, 18) revealed similar data with the Indian-Asian population having the lowest incidence of Prostate Cancer, the White population a similarly low incidence of prostate cancer and the Black population a significantly higher incidence and risk.

Previous studies on PSA based general population screening for Prostate Cancer were underpowered to reflect a Black population of African origin. Given the increased incidence, younger age at presentation and more aggressive disease pattern a PSA screening program for the Black African population or a general population PSA screening program in a country with a majority Black African population may actually prove worthwhile and cost effective (12). Even a targeted screening program of these at-risk men with PSA and then further bio, gene or radiological markers to direct which patients would then qualify for a biopsy appears to be the next logical step (13). The other confounding factor with PSA that should be considered is race specific PSA with the purported higher baseline PSA levels in Black African men regardless of age and Prostate Cancer status. Despite this it has been cited by Jyoti et al. that the use of traditional PSA cutoff threshold values would result in 40% of cancers being missed (12) (This article cites an article by Morgan et al however the footnote in the reference section corresponds to an article by Speights et al).

An additional compounding factor adding to the aggressive disease seen in Black men is the lack of knowledge of prostate cancer or PSA screening. In a study done by Nathaniel Mofolo et al. (19) only 39,5% of Black African patients in that study had indicated that they had heard of prostate cancer. A study by Elizabeth A. Tindall et al. (20) revealed that patients in Limpopo presented later and with more aggressive prostate cancer due to lack of PSA awareness and testing. This can have the knock-on effect of Black patients not seeking PSA screening when latent disease may be at a curative stage or of even not going on to have a prostate biopsy, even when counselled that a biopsy is indicated. In a study by Heyns et al. (3) only 19% of Black patients requiring a biopsy underwent the procedure versus 47% of Coloured (mixed ethnicity) patients. The study by Le Roux et al. (21) in a peri-urban setting in KwaZulu-Natal 66% of Black African men had incurable disease in stark contrast to a study in California USA where 6% of African American patients had metastatic disease. This drastic increased incidence of metastatic prostate cancer in the KwaZulu-Natal study population may in part be due to the late presentation of patients (the mean age of patients in the study by Le Roux et al. was seventy-one years, in the American SEER data base mean age of presentation is sixty-four years). The other conclusion of Le Roux et al. made was that prostate cancer was under diagnosed in this region (there were only 81 diagnosed cases of prostate cancer over the 24-month period, out of an estimated 150000 men over forty years of age in the region). This again in part can be attributed to the lack of awareness of prostate cancer and PSA screening. The reliance on traditional medicine before allopathic remedies are sought, could be another contributory factor.

The impact of genetic predisposition to prostate cancer in general and aggressive forms of the disease is just beginning to be investigated. Vanessa Hayes in conjunction with other authors has published three papers (22-24) looking at the role unique genes present in the South African Black male may play in causing a phenotype of early and or aggressive prostate cancer. Early work on a small sample of patients has demonstrated the association between high risk prostate cancer (defined by the authors as gleason >=8 prostate cancer or Serum PSA >=20) and a subset of genes believed to code for this aggressive disease.

The economic effect of treating metastatic prostate cancer is another factor that should be considered. The modern treatment of metastatic prostate cancer has rendered it almost akin to a chronic disease

rather than a rapidly progressing fatal malignancy. However even the most basic first line treatment for metastatic prostate cancer - Androgen Deprivation Therapy - has a cost on average of R6000 per treatment (with the patient required to take the treatment every three months, lifelong thereafter). Patients are on this treatment until their death and during the course of treatment may require the addition of other medications as the cancer progresses. A national prostate cancer screening program, that utilises serum PSA, may likely allow the detection of prostate cancer at an earlier stage in the course of the disease. This would result in more patients being offered curative treatment and the knock-on effect of this would likely be a cost saving to both Government and private sector health care funders alike.

Research Question

What is the incidence of prostate cancer in the patient population presenting to St. Aidan's Hospital (general and by individual race)? What is the incidence of intermediate, high risk and metastatic prostate cancer (general patient population and by race)? What is the relationship between serum PSA and the diagnosis of prostate cancer?

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Chapter 2: RETROSPECTIVE REVIEW OF PROSTATE BIOPSIES AT A REGIONAL LEVEL HOSPITAL

Abstract

Background

Prostate cancer is a leading cause of male mortality worldwide and its incidence is on the increase. Evidence currently points to there being an increased risk of developing the disease amongst Black African males. Prostate cancer studies done in South Africa to date have not however included cohorts that accurately reflect the demographics of South Africa i.e. a majority Black African population.

Objectives

To gauge if there is an increased risk in incidence of clinically significant prostate cancer amongst Black African males and if this does exist whether this supports the use of a Serum PSA based population screening program in South Africa.

Methods

A retrospective review was carried out of the outpatient charts of patients who underwent a prostate biopsy at St. Aidan's Mission Regional Hospital between the period 01 January 2016 to 31 December 2017. Pertinent data was recorded and analysed with SPSS.

Results

Of the 205 outpatient files analysed (mean age 68,6 years), 61% of these belonging to Black African patients, 136 patients (66,34%) were found to have prostate cancer – 133 patients were diagnosed with cancer after the first biopsy and the other 3 patients on subsequent biopsies. Almost 40% of the patients diagnosed with prostate cancer had evidence of metastases with 25% of the cancer patients not having their metastatic status confirmed (often due to them defaulting follow up). Patients referred to St. Aidan's Mission Regional hospital for prostate biopsy represent patients who underwent opportunistic PSA screening at their base healthcare facility.

Conclusion

The significantly higher incidence of prostate cancer (and intermediate to high risk and metastatic prostatic cancer) seen in our study consisting of a cohort with a majority of Black African patients (61,95%) compared to similar South African studies with cohorts more representative of a European country (i.e. a small percentage of Black African patients) infers that the Black African male is at increased risk of Prostate Cancer and that there would likely be a benefit from a Serum PSA based Prostate Cancer screening program. Further studies are recommended to provide definitive evidence to support this hypothesis.

INTRODUCTION

Prostate cancer is one of leading causes of mortality in males worldwide. The estimated global burden of disease will see almost two million new cases by the year 2030 with almost 500000 deaths(1-3). In addition, the economic burden of treating prostate cancer is likely to be immense as newer novel therapies allow even metastatic disease to be managed as a chronic condition. With this in mind emphasis should be placed on a screening program in at-risk populations to improve the diagnosis and treatment of disease in the early stages(4). Multiple observational studies have concluded that men with Black African ancestry represent an at-risk population for the onset of prostate cancer at an earlier age and with a more aggressive subtype(3, 5-7). Very few studies have been carried out in Africa that have looked at the incidence and prevalence of prostate cancer in either the general population or specific ethnic population groups(8). Some of the population-based studies carried out in South Africa examining the incidence and prevalence of prostate cancer consisted of cohorts underpowered for the Black African ethnic population group(9, 10). As the majority population group in South Africa the true extent of prostate cancer and its impact will not be known until more studies with a more accurate South African demographic are undertaken.

The chronicity of metastatic prostate cancer, gifted by advances in treatment, have seen healthcare costs escalate. This life extending treatment itself is not without significant side effects and adverse events. As a developing economy, South Africa needs to rationalize the use of its health care budget. Screening programs to pick up and treat premalignant precursor conditions or even to allow the diagnose and treatment of cancer at early curative stage may be the way in which this is accomplished. Previous studies that have examined the possibility of general population screening studies for prostate cancer have shown a benefit, albeit with a large number of patients having to be screened just to prevent one death(1, 11). These studies however also consisted of cohorts underpowered with patients of Black African ancestry.

It is likely that a general population-based screening program in a society with a large Black African population may require a smaller number of patients to be screened to reduce the death rate from prostate cancer. In order to assess the viability of such an intervention a study to first gauge the incidence of prostate cancer and advanced Prostate cancer should be undertaken. The aim of this study is to report the incidence of prostate cancer and advanced prostate cancer over a two-year period in the cohort of patients referred to St. Aidan's Mission hospital for prostate biopsies. The catchment area of St. Aidan's Mission Hospital Urology department is wide and far reaching and encompassing most of the province of KwaZulu-Natal (only the catchment areas of Pietermaritzburg, Ngwelezane, Newcastle and Ladysmith do not refer to St. Aidan's hospital but instead to the tertiary hospitals located in those towns.

METHODS:

This study was designed to be a quantitative, observational, descriptive study. As such a retrospective review of outpatient records was undertaken to obtain the data. All patients undergoing a prostate biopsy at the St. Aidan's Urology clinic had their details (name, out-patient folder number) recorded in a

procedure book kept by the clinic nursing staff. This book was perused, and a list was compiled of patients eligible for the study i.e. those who underwent a biopsy from the period 01 January 2016 to 31 December 2017. Thereafter the relevant patients' files were requested from the hospital registry department. A total of 215 patients were identified as eligible for accrual into the study, however only 206 of these patients' files could be located. The normal protocol for a prostate biopsy at St. Aidan's Hospital is for each patient to have a 12 core (6 cores per lobe) biopsy of the prostate on an outpatient basis under a peri-prostatic block, via a transrectal ultrasound to visualize the prostate. Once a patient was accrued into the study the outpatient chart for that patient was analysed and the data surrounding the index biopsy (i.e. the biopsy performed in 2016-2017), all preceding biopsies and/or all subsequent biopsies were recorded.

The primary aim of the study was to determine the racial profile of prostate cancer amongst the patients referred for prostate biopsy and to support or refute the hypothesis that the Black African male is at increased risk both in terms of incidence of prostate cancer and aggressive forms of the disease. To this end the race of the patients in the study was determined by the main investigator and the nursing sister assisting him with data collection by analysing both the patients name and a copy of his ID document. Patients have never being asked to self-assign their race at the hospital (as stated in a previous study performed at the same institution(12)). The study was also geared towards risk stratifying patients diagnosed with prostate cancer between Low, Intermediate and High-risk groups in order to assess the proportion of patients diagnosed with so called clinically significant prostate cancer.

Permission to conduct the study was obtained from the hospital management and National Health Research Department. Ethical approval to conduct the study was obtained from the Biomedical Ethics Committee of University of KwaZulu-Natal(BREC REF NO: BE464/18).

Measurements

The patients demographics (date of birth, race), the date the patient was first seen, initial PSA, digital rectal examination findings, date of prostate biopsy and results of the biopsy (benign hypertrophy versus prostate cancer versus Infection and Gleason score of tumour if malignancy present), any documented post biopsy complications (e.g. Sepsis, Heamaturia, Acute Urinary Retention) the patient may have experienced, bone scan results (if done) and the chosen treatment option were recorded. Patients with a clinically abnormal feeling prostate on rectal examination had a T stage assigned according to the AJCC TNM staging system for prostate cancer by the doctor who had seen them (13). Using a combination of the patients T stage, Gleason score and initial serum PSA value at diagnosis patients were risk stratified according to the D'Amico classification system (14). Race was determined based on a combination of patients' appearance in their ID photo together with their name/surname and the opinion of the lead investigator and his data collection assistant. The waiting period from first consultation to the first prostate biopsy was calculated based on the dates of the two events.

Data Collection and Statistical Analysis

Data was obtained by reviewing urology outpatient department charts of patients who underwent a prostate biopsy during the period under consideration. Data initially was recorded onto a "data sheet" (See Appendices) and thereafter was entered from the data sheet onto an Excel spreadsheet to allow for

easier analysis of the data. The Excel spread-sheet had been stored on a password-protected computer that only the primary investigator had access to. Once obtained the data was analysed with the aid of SPSS with the assistance of one of the co-supervisors.

RESULTS:

A total of 205 patients were accrued into the study of which 127 were Black African men (40 were Indian, 23 were White and nine were Coloured). The race of 6 patients could not be determined. The ages of the patients varied from 40 years to over 80 years old with the majority of the patients (93) lying in the 60-69-year age group. The mean PSA at presentation was 460,2 ng/ml (the median PSA was 32,2). The majority of the patients were clinically staged to having T1 prostate on digital rectal examination (Table 1).

Table 1: Clinical T-Stage of Patients

		Number	Percent
	T1c	62	30.1
	T2a	33	16.0
	T2b	12	5.8
	T2c	12	5.8
	T3a	19	9.2
	T3b	3	1.5
	T4	43	20.9
	T Stage Unknown	21	10.7
	TOTAL	205	100

The outcomes from the first biopsy are indicated in Table 2. Prostate cancer was found in 64,9 % of patients.

Table 2: Outcomes of First Biopsy

		Frequency	Percent
	Cancer	133	64.9
	BPH	15	7.3
	Chronic prostatitis	50	24.4
	ASAP	3	1.5
	No prostate tissue	4	2.0
	Total	205	100.0

A second biopsy was indicated in 15 patients for reasons of a persistent elevated PSA (n=9), suspicious DRE with a negative biopsy (n=2), no prostate tissue in the first biopsy (n=3) and due to inability to locate the results from the first biopsy (n=1). However only 14 patients underwent the repeat biopsy (one patient defaulted). Of these 14 patients 3 were diagnosed with cancer (5 patients had BPH, 5 patients had chronic prostatitis and 1 patient had ASAP). Only 2 patients underwent a third biopsy with one patient having prostate cancer on his histology results and the other patient 's histology revealing BPH. Therefore, after considering all the biopsy findings out of 205 patients 66,3% (n=136) had prostate cancer with 33,7% (n=69) having a non-cancerous histological diagnosis.

Of the 136 patients diagnosed with prostate cancer 39,7% had radiologically or bone scan confirmed metastases, 35,3% of the prostate cancer patients had no metastases with 25% of the patients not having their metastatic status determined for a variety of reasons (often because the patients defaulted follow-up). After risk stratification using the D'Amico classification 35,3% of prostate cancer patients fell into the Organ Confined High Risk grouping and 39,7% of prostate cancer patients had metastatic disease (Figure 1).

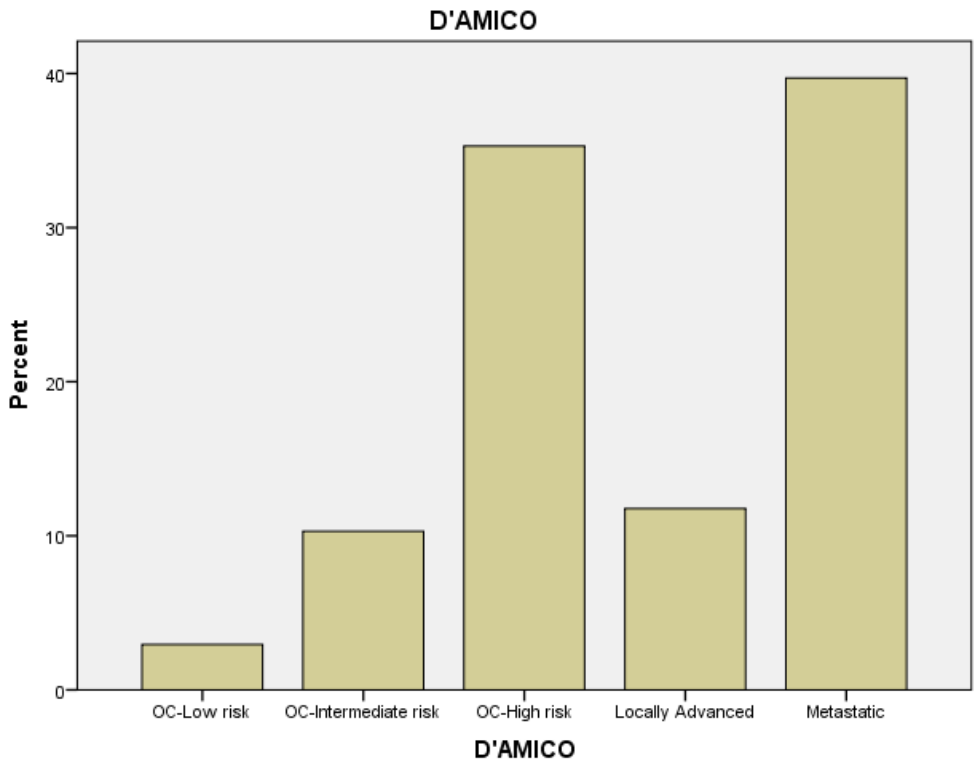


Figure 1: D'Amico Risk Stratification

A crosstabulation of D'Amico risk stratification versus chosen treatment options revealed the following:

Table 3: Crosstabulation between D'Amico and Chosen Treatment

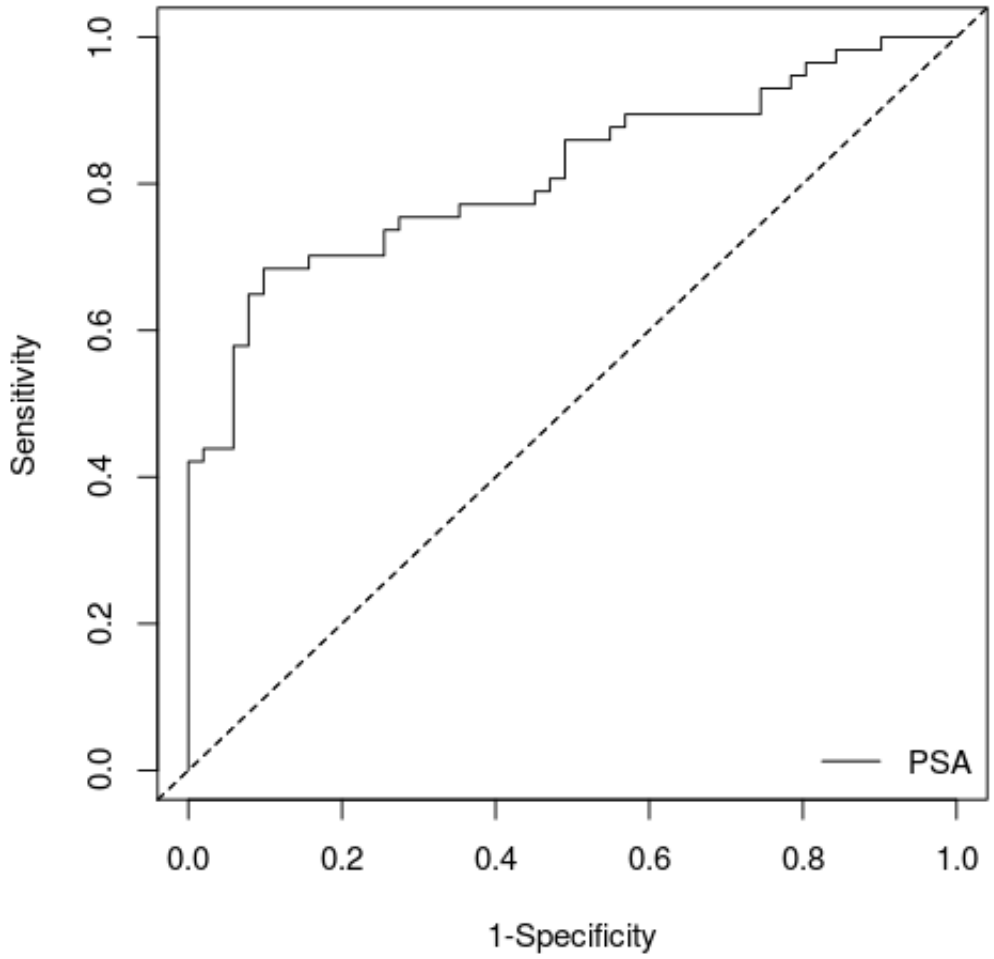
MANAGEMENT CODED * D'AMICO Crosstabulation

			D'AMICO					
			OC-Low risk	OC-Intermediate risk	OC-High risk	Locally Advanced	Metastatic	Total
MANAGEMENT CODED	WW	Count	0	1	0	0	0	1
		% of Total	0.0%	0.7%	0.0%	0.0%	0.0%	0.7%
	RP	Count	1	0	0	0	0	1
		% of Total	0.7%	0.0%	0.0%	0.0%	0.0%	0.7%
	BT	Count	0	2	1	0	0	3

		% of Total	0.0%	1.5%	0.7%	0.0%	0.0%	2.2%
	EBRT	Count	2	7	14	0	0	23
		% of Total	1.5%	5.1%	10.3%	0.0%	0.0%	16.9%
	ADT	Count	1	3	22	13	52	91
		% of Total	0.7%	2.2%	16.2%	9.6%	38.2%	66.9%
	BSO	Count	0	0	1	0	1	2
		% of Total	0.0%	0.0%	0.7%	0.0%	0.7%	1.5%
	CHEMO	Count	0	0	0	0	1	1
		% of Total	0.0%	0.0%	0.0%	0.0%	0.7%	0.7%
	UNKNOWN	Count	0	1	10	3	0	14
		% of Total	0.0%	0.7%	7.4%	2.2%	0.0%	10.3%

Sixty-two patients underwent a biopsy purely for a raised PSA (i.e. the DRE findings of the patients revealed benign feeling glands). Of this result twenty-two patients had positive biopsies for prostate cancer (32,25%). In patients with an abnormal DRE finding (One hundred and forty-three patients in total), positive biopsies for prostate cancer were found in one hundred and fourteen patients (79,7% of abnormal DRE patients). This revealed a significant association between abnormal DRE and positive biopsy result - $P < 0.001$ (chi squared).

The use of PSA to detect metastatic disease revealed that PSA is a good test for detecting metastatic disease ($P<0.001$) -see receiver operator curve below. The optimum PSA cut off point for metastatic disease was 100.4ng/ml (Youden Index).



Area under curve: 0.81

Figure 2: Receiver Operator Curve For Performance of PSA to Detect Metastatic Disease

Table 4: Association between PSA >= 100ng/ml and Metastatic Disease

METASTASES * PSA 100 CODED Crosstabulation

			PSA 100 CODED		
			No	Yes	Total
METASTASES	No	Count	46	5	51
		% within METASTASES	90.2%	9.8%	100.0%

		% within PSA 100 CODED	71.9%	11.4%	47.2%
		% of Total	42.6%	4.6%	47.2%
	Yes	Count	18	39	57
		% within METASTASES	31.6%	68.4%	100.0%
		% within PSA 100 CODED	28.1%	88.6%	52.8%
		% of Total	16.7%	36.1%	52.8%
Total		Count	64	44	108
		% within METASTASES	59.3%	40.7%	100.0%
		% within PSA 100 CODED	100.0%	100.0%	100.0%
		% of Total	59.3%	40.7%	100.0%

Table 5: Predictive Value of PSA >= 100ng/ml and Metastatic Disease

	$P < 0.001$
Sensitivity	68.4%
Specificity	90.2%
PPV	88.6%
NPV	71.9%

It was found that there was no significance in the age of presentation of the Black African patients compared to the Non-Black patients (Black 68.4 years vs Non-black 68.7 years). There was however a significant difference in the mean PSA that Black African patients presented with compared to their non-Black counterparts (Black 491ng/ml vs. Non-Black 210.4 ng/ml). Furthermore, there was no association between the Black African race group and any specific Gleason grade groupings (3+3,3+4,4+3,4+4,9-10), neither was it found that the Black African race group was an independent risk factor that increased the risk of metastatic disease in prostate cancer.

DISCUSSION:

The St. Aidan's Mission Regional Hospital Urology department (located in Durban) is the referral center for Urological patients for most of the province of KwaZulu-Natal (seven out of eleven health districts in the province refer Urology patients to St. Aidan's hospital urology department). Based on population data obtained from the KZN Health Website(15) this equates to 5 875 683 people residing in these districts serviced by St. Aidan's hospital. Male patients referred to St. Aidan's Hospital Urology for any illness related to their prostate gland fall into three groups that are not mutually exclusive. These individuals either have a raised PSA that is normally performed by way of opportunistic screening (i.e. the patient will

present to their base hospital with some other complaint and not specifically seeking a medical opinion for prostate cancer and will then have a serum PSA level test performed), they may be referred specifically for lower urinary tract symptoms refractory to medical therapy (including them being catheter dependent) or lastly them may be referred with heamaturia for further assessment. Opponents to PSA screening often quote literature that a PSA based screening program will result in unnecessary prostate biopsies revealing either no cancer or low risk cancer that would not be clinically significant within a patient's lifetime (1, 2, 4, 10).

All patients (bar six) referred to St. Aidan's Hospital Urology and who eventually underwent a biopsy had an opportunistic PSA screening performed at their base health care facility and were therefore referred due to a raised serum PSA level as at least one of the reasons for referral. From the 6 patients who were referred to St. Aidan's Hospital Urology department for other reasons only 1 of these patients had a prostate biopsy revealing prostate cancer. Data adjusted for this excluding the above patients reveals positive prostate cancer biopsies in 135 patients out of 199 patients biopsied (increasing the percentage of patients with cancer to 67,83%). Of the 136 patients with histological proven prostate cancer 97,1% of patients were risk stratified according to the D' Amico classification into a risk grouping that required some form of intervention for their cancer either in the form of curative therapy or palliative hormonal manipulation (age of the patient not considered), i.e. these patients did not have so called indolent low risk cancers (16, 17). Of note is that four patients had the T stage recorded as T4 clinically which would have indicated an advanced cancer, but their biopsies did not reveal any cancer. All four patients underwent only one biopsy that was not repeated after their initial histology was reviewed. Three of the patients were Black African and of these three, one patient did not have any prostate tissue represented in his biopsy (the other two had histology results revealing BPH and BPH chronic prostatitis respectively). One possible explanation for this is the hypothesis that Black African men have a higher concentration of prostate cancer in the anterior part of the prostate (18)– a region that may not be sampled conventionally on trans rectal ultrasound guided prostate biopsy. This has however not been proved conclusively. The other patient, an Indian male, had a histological diagnosis of BPH/Chronic Prostatitis. Furthermore, it has been found that in patients with an initial negative prostate biopsy for cancer, a repeat biopsy may reveal cancer in up to 23% of cases(9).

A PSA screening study done by Heyns et al (9) were by patients were invited specifically to have PSA screening performed and thereby undergo a biopsy if indicated (either due to raised PSA, abnormal DRE or both) revealed prostate cancer in 32% (37 patients) out of 114 patients biopsied. The patient demographics in that study did not reflect those of the South African population at large i.e. 69% Black African, 18% White, 11% coloured/mixed race and 4% Indian)(19). This was acknowledged by the paper's authors. The demographics of patient seen in our cohort are more reflective of the national population.

The study by Heyns et al also found that 41,3% of patients who underwent prostate biopsy for a raised PSA only had prostate cancer (compared to our figure of 32,25%). In comparison in the ERSPC study 30,2% of men biopsied purely for a raised PSA had prostate cancer. However, of 2365 patients, in the ERSPC study, who underwent biopsy for a either a raised PSA or abnormal DRE finding only 21,4% of patients were diagnosed with prostate cancer compared to the 64,9% seen in our study after the first biopsy (and 66,3% when considering the repeat biopsies). The prostate cancer percentage in the Heyns study after

the first biopsy was 32,5%. This may be partly explained by the use of a sextant prostate biopsy template (20) that was employed in that study (three cores taken from each lobe of the prostate), compared to the six cores taken in each lobe of the prostate in our study. The other explanation is the racial disparities seen in the Heyns study and our study in terms of patients biopsied (with our study having a majority Black African population that underwent prostate biopsy).

The management options by percentage chosen for patients with potentially curative (localized) disease in the Heyns screening study (9) were Watchful Waiting in 62,5% of patients, Radiotherapy in 20,8% of patients and Radical Prostatectomy in the remaining 16,7% of patients i.e. curative treatment was chosen by only 37,5% of patients. This differs greatly for the ERSPC study in which 89% of patients with organ confined/localized disease chose a curative modality of treatment (radiotherapy 51%, radical prostatectomy 38%) and is also in stark contrast to our study were only 19,8% of patients with organ confined disease chose a curative treatment modality. It should be noted that this percentage is made up of three patients that underwent Prostate Brachytherapy a treatment modality that does not form part of the standard treatment options on offer at St. Aidan's Hospital. These patients benefitted from a teaching workshop hosted by a private company BARD that also donated the brachytherapy seeds.

Another study by Heyns et al looked at PSA as a surrogate for a prostate biopsy in the diagnosis of cancer (21). The study concluded that a PSA of >=60ng/ml had a positive predictive value of 98%, specificity 98% and a sensitivity of 65% for the presence of Prostate Cancer. A PSA of 100ng/ml had a positive predictive value of 99%, specificity of 99% and a sensitivity of 53%. The association between PSA values and positive metastases was not investigated however. Taking into account the findings from our current study this would suggest that a PSA of 100ng/ml can be taken as surrogate of both prostate cancer diagnosis and of diagnosing metastatic disease. The mean waiting period for a biopsy in our cohort was 102 days. The study done by Singh et al (12) looking at a cohort in the same institution during 2013 revealed a prostate biopsy waiting time of 55 days. This would indicate that the biopsy waiting time has almost doubled and therefore would negatively affect patients by delaying their time to diagnosis. However, our biopsy time does include one outlier who waited 2605 days for his biopsy (the reason for this waiting time is unknown). With this outlier removed the waiting period for a prostate biopsy decreases to 89 days. Furthermore our study was conducted over a two year period while the study by Singh et al (12) was conducted over a six month period. Our longer period of review probably indicates a more accurate reflection of the actual waiting time for a prostate biopsy at this facility rather than indicating a worsening of the quality of the prostate biopsy service at St. Aidan's Hospital.

Our findings of Black African patients presenting with a significantly higher PSA than other races is congruent with other studies done in KZN (12), elsewhere in South Africa (9, 10, 22) and the world (3, 5-7, 20). However despite this the reason (or reasons) for this correlation has still not been conclusively proven; whether the reason is that Black African men present with larger prostate volumes compared to other race groups or if there a defect in the prostate acinar cell basement membrane of Black African men that causes these higher serum PSA levels is still unknown.

CONCLUSION:

Although the data accrued by us did not initially seem to suggest that the Black African race group was more at risk for Prostate Cancer in general or even at an increased risk for metastatic prostate cancer the higher incidence of histologically diagnosed prostate cancer and high grade cancer diagnosed in our cohort (that was made up of 61,95% of patients from the Black African race group) compared to other similar studies infers that the Black African male is likely at an increased risk for prostate cancer both in terms of incidence of prostate cancer and higher grade of cancer seen. The study by Heyns et al (9) while based in South Africa (the Western Cape province) demonstrated a cohort more akin to the population of a European/Western country. Similarly, the findings of that study were more reproducible of the findings of other European/Western based PSA screening studies.

A study done by Cooner et al. (23) revealed a prostate cancer detection rate of 14,6% in a clinic population of symptomatic urological patients i.e. patients referred for a urological opinion and treatment – our finding of cancer detection rate of 66,3% is more than triple of that rate. The study of Cooner et al. (23) collated data from private urologists serving the general American population and was therefore likely made up of a population of majority White males. Therefore, even if the argument that our study population represents a symptomatic population of urology patients rather than a population of patients referred specifically for a prostate biopsy after an opportunistic PSA screening was done, is considered, our incidence is still substantially higher. Globally there is enough evidence to suggest that there should be some type of PSA based prostate screening program in a population made up of individuals whose ethnicity contains that of the Black African race group.

Of note is that almost 40% of the 136 patients diagnosed with Prostate cancer had confirmed metastases at diagnosis (25% of the prostate cancer patients did not have their metastatic status confirmed therefore the actual number could be much higher than 40%). It is unlikely that these patients developed de novo metastatic disease and with 58% of the patients biopsied being below 70 years of age an active effort should be made to diagnose patients with prostate cancer before the development of metastases. By and large the patients who underwent biopsy in this study did so due to a raised PSA being found as a result of opportunistic PSA testing. A formal PSA screening program should be developed given that PSA has a higher specificity than mammography does for breast cancer detection(20), there is enough data to support that the Black African male is at increased risk for prostate cancer in general and aggressive forms of prostate cancer in particular, and that the Black African race group is the predominate race in South Africa. The Göteborg Trial(24), consisting of two cohorts of patients made up almost exclusively from the White ethnic group, estimated that 293 men would have to be screened with 12 newly diagnosed cases of prostate cancer to prevent one death from it (reported in that trial as been comparable in numbers to breast and colon cancer screening data). This is from cumulative prostate cancer incidence rates of 12,7% in the screening group and 8,2% in the control (non-screened) group. With our prostate cancer incidence of 66,3% the number needed to be screened and the number of patients diagnosed to prevent death in our context would likely be significantly lower thus making a Serum PSA based screening program more cost effective.

This study is constrained however as the biopsy data we have presented is only a reflection of the population seeking public healthcare as a source of diagnosis and treatment. We do not have the biopsy data of patients in our referral areas who would have underwent a prostate biopsy by a private urologist (with the tissue being processed by a private laboratory). Furthermore, even though 215 patients underwent a prostate biopsy over the period in question this does not mean that only 215 patients required a prostate biopsy during that period. The limiting factor to the number of patients that undergo a prostate biopsy is the staff complement and the availability of equipment. Over the period in question prostate biopsies were performed once a week with generally only up to 10 patients being biopsied every week. Therefore, we suggest that further comprehensive studies be undertaken to examine the above hypothesis that a serum PSA screening study will be of benefit in a population were the majority population group is Black African. Amongst these studies we suggest:

- Collating the prostate biopsy data from the other Urology referral centers, draining the rest of the province of KwaZulu-Natal, to demonstrate or refute the findings in our study.

- Reviewing the prostate biopsy data from the private laboratories in KwaZulu-Natal over a defined period and correlating it with the PSA readings for the patients that underwent a prostate biopsy.

-A PSA screening study with patients invited to screen and undergo a biopsy if indicated.

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APPENDIX 1: Study Protocol

University of KwaZulu-Natal

College of Health Sciences

School of Clinical Medicine

Title: Retrospective Review of Prostate Biopsies at a Regional Level Hospital

Degree: MMED Urology

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EXECUTIVE SUMMARY

Statement of purpose

The context surrounding Prostate Cancer has changed drastically in the last three decades. This is largely due to discoveries allowing identification of patients earlier in the disease course and newer, novel therapies to treat patients at different stages in the disease. However prostate cancer management, and in particular screening, is not without controversy. Owing to a supposed indolent nature of a large percentage of diagnosed tumours the need for a screening program and early identification of patients has been questioned. To this end a selective screening program has been suggested to target sub population groups at increased risk for aggressive disease (of note is that Black African individuals are considered an at-risk group for aggressive prostate cancer). How and if this should be affected has still not been established. The South African based Prostate Cancer Foundation recommends general population PSA based screening after the age of forty-five years (with screening after the age of forty years in males deemed at increased risk), however there are no guidelines on screening from the National Department of Health. The purpose of this descriptive study is to review the outcome of prostate biopsies at a regional hospital for a two-year period to establish if there is evidence either for a general or sub population specific PSA based prostate cancer screening program and what guidelines should govern such a program. To date most studies undertaken locally have included a cohort that does not accurately reflect the population of South Africa (these studies were based in the Western Cape and had a selection bias towards White males). Of the two studies undertaken in KwaZulu-Natal, one was undertaken in a general hospital with a 'satellite' Urology department. The other study assessed prostate biopsy waiting times as its primary outcome.

THE PROTOCOL

TABLE OF CONTENTS

1. BACKGROUND AND LITERATURE REVIEW

1.1 Defining the Clinical Problem

Prostate cancer is one of leading causes of mortality in males worldwide. The estimated global burden of disease will see almost two million new cases by the year 2030 with almost 500000 deaths. In addition, the economic burden of treating prostate cancer is likely to be immense as newer novel therapies allow even metastatic disease to be managed as a chronic condition. With this in mind emphasis should be placed on a screening program in at risk populations to improve the diagnosis and treatment of disease in the early stages.

1.2 The literature review

The face of prostate cancer has changed in the last 30 years. Initially a disease were late presentation and high mortality was the norm, the paradigm has shifted due to numerous discoveries in the preceding years. At one end of the spectrum the discovery of PSA and its approval for the use in prostate cancer treatment and screening in the late 1980s and early 1990s gifted clinicians with the means to identify 'early', in some cases pre symptomatic disease. The resultant effect was the reduction in prostate cancer mortality (with an increase in diagnosis and treatment) [1, 2].

However, with the increase in histologically confirmed, organ confined disease, it also became readily apparent that the burden of new prostate cancer cases was skewed towards low grade, seemingly indolent disease with possibly little aggressive potential within a patient's lifetime [1-3]. This trend in "over diagnosis" of prostate cancer lead to suggestions that screening of prostate cancer with serum PSA readings should be abandoned [3, 4]. Studies done to establish consensus initially further confounded the issue by offering seemingly juxtaposed results and therefore conclusions. The *European Randomised Study of Screening for Prostate Cancer (ERSPC)* revealed an 8.2% incidence of prostate cancer in the routine PSA screening group (versus 4.8% prostate cancer incidence in the control group). PSA based screening reduced prostate cancer mortality by 20%. To affect this however the estimation from this study was that 1410 men would need to have PSA screening for prostate cancer with 48 additional cases of Prostate cancer diagnosed to prevent 1 death from prostate cancer [1].

The *2010 Göteborg Prostate Cancer Screening Trial* findings were in congruence with the *ERSPC*, with 293 men needing to be screened and 12 new cases of prostate cancer diagnosed to prevent one death from prostate cancer. In comparison the figures quoted for breast cancer screening is that one additional death from breast cancer will be prevented with every 400 patients screened (between the ages of 50-70 years) [5]. The data and initial conclusions from the *Prostate, Lung, Colorectal and Ovarian (PLCO)* trial however, did not demonstrate any significant reduction in prostate cancer related mortality [1]. A review of the data in the *ERSPC* and *PLCO* trials by Tsodikov *et al* however using mean lead time estimations, and accounting for differences in implementation and setting, revealed that both studies provided compatible evidence that

screening reduces prostate cancer mortality [6].

The results of these findings should be considered with the conclusions gained from other prostate cancer studies. Prostate cancer screening and indeed PSA based prostate cancer screening may still not be indicated for the general male population despite the findings of the *ERSPC*, *Göteborg* or *PLCO*. "The risk of a fifty-year-old man with a 25-year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer 9,5% and of dying of prostate cancer 2,9%." [4]. However, a man in his forties with three close relatives diagnosed with prostate cancer (e.g. father, uncle and brother) has a 30-40% lifetime risk of developing clinically significant disease [4]. It would therefore appear that prostate cancer screening should be directed to subsets of the population that are deemed at risk. The need for criteria in terms of which sub population groups qualify for a biopsy is important as a prostate biopsy is not an innoxious procedure [4, 7]. Sepsis and heamaturia are two common complications with sepsis rates on average of 1-7% reported and heamaturia rates of between 2-34%.

Use of the Serum PSA level to decide on the need for a biopsy is in itself fraught with difficulties. PSA can be considered prostate disease specific and not necessarily prostate cancer specific. Various factors can cause a raised PSA among them infection of the prostate, urinary tract instrumentation and prostate malignancy. To further cloud the use of PSA a poorly differentiated prostate cancer may actually not secrete any PSA or may even secrete a reduced amount in comparison to a normal prostate cell. A PSA value between 0-4ng/ml is commonly accepted as a "normal PSA". Further to this there has also been suggestions that higher PSA cut offs should be deemed age appropriate [8]. However, in a study of 332 men who were fifty years or older with serum PSA value between 2.6-4ng/ml, prostate biopsies revealed cancer in 22% of them [4]. A study by Oesterling suggested that PSA range of 0-4.5 should be appropriate for men 60-69 years of age while a PSA of 0-6.5 should also be normal for men 70-79 years of age. It therefore should be considered "safe" to omit biopsies in these men (assuming the digital rectal examination is normal). However, a retrospective review of prostate biopsies [8] contradicted this revealing that if this protocol had been followed 60% of aggressive cancers would be missed.

Despite the controversies of whether general prostate cancer screening should be instituted or indeed or how prostate cancer screening should be carried out, certain sub population groups are at greater risk for the development of the disease either purely by a predisposing genetic risk factor, lack of awareness of the disease or both of these factors. To this extent people of Black African ancestry represents one such sub group.

In the USA the lifetime risk of the general male population for prostate cancer is 15,9% and the risk of death is 2,8% [9]. The incidence in African American men is almost 60% higher however then the general American population with the mortality being 2-3 times greater. Even in the pre-PSA screening era the mortality rate amongst African American men was 55 per 100000 while in White American men it was 29 per 100000 [1]. African American men have a strong West African ancestry. There is evidence to suggest that there is a disproportionate larger burden of disease in West African men [9]. In men of African ancestry prostate cancer may in fact transform into aggressive disease earlier than White men. Even studies such as the PCLO and ERSPC trial

which initially revealed no or marginal benefit of screening for prostate cancer were underpowered for Black African population. There was an estimated 28006 deaths from prostate cancer in Africa in 2010 and this number is calculated to rise to 57048 deaths in 2030, an increase of 104% [10].

The other compounding factor adding to the aggressive disease seen in Black men is the lack of knowledge of Prostate Cancer or PSA screening. A study done by Nathaniel Mofolo et al. [11] only 39,5% of Black African patients in that study had indicated that they had heard of prostate cancer. A study by Elizabeth A. Tindall et al. [12] revealed that patients in Limpopo presented later and with more aggressive prostate cancer due to lack of PSA awareness and testing. This can have the knock-on effect of Black patients not seeking PSA screening when latent disease may be at a curative stage or even of not going on to have a prostate biopsy even when counselled that a biopsy is indicated. In study by Heyns et al. [3] only 19% of Black patients requiring a biopsy underwent the procedure versus 47% of coloured (mixed ethnicity) patients. The study by Hugo Le Roux et al. [13] in a peri-urban setting in KwaZulu-Natal 66% of Black African men had incurable disease in stark contrast to a study in California USA where 6% of African American patients had metastatic disease. This drastic increased incidence of metastatic prostate cancer in the KwaZulu-Natal study population may in part be due to the late presentation of patients (the mean age of patients in the study by Le Roux et al. was seventy-one years, in the American SEER data base mean age of presentation is sixty four years). The other conclusion of Le Roux et al. was that prostate cancer was been under diagnosed in this region (there were only 81 diagnosed cases of prostate cancer over the 24-month period, out of a estimated 150000 men over forty years of age in the region). This again in part can be attributed to the lack of awareness of prostate cancer and PSA screening. The reliance on traditional medicine before allopathic remedies are sort, could be another contributory factor.

The economic effect of treating metastatic prostate cancer is another factor that should be considered. The modern treatment of metastatic prostate cancer has rendered it almost akin to a chronic disease rather than a rapidly progressing fatal malignancy. However even the most basic first line treatment for metastatic prostate cancer - Androgen Deprivation Therapy - has a cost on average of R6000 per treatment. Patients are on this treatment until their death and during the course of treatment may require the addition of other medications as the cancer progresses. A national screening program with the emphasis been on early stage pick up and curative treatment may in the long-term result on health expenditure saving to both Government and the private sector funders.

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2. AIMS AND OBJECTIVES

Aim: To describe the burden of disease of prostate cancer and establish the outcomes of prostate biopsies at St. Aidan's Hospital Urology department during the period of 01 January 2016 to 31 December 2017.

Objectives:
1. To determine the demographics of patients undergoing prostate biopsy at St. Aidan's Mission Hospital.
2. To determine the patient characteristics and cancer parameters of patients diagnosed with prostate cancer.
3. To assess the sensitivity and specificity of a PSA >4ng/mL for detecting prostate cancer in the patient groups having prostate cancer.
4. To determine the relationship between PSA level and the likelihood of detecting prostate cancer in the patient groups presenting to St. Aidan's hospital.
5. To calculate the total cost of Androgen Deprivation Therapy, for two years, for all prostate cancer patients initiated onto it from the study group.

3. METHODS

3.1. Study Design

The study will be a designed to be a quantitative, observational, descriptive study using a retrospective review of records.

3.2. Setting

The study will be conducted using the files of patients' attending the St. Aidan's Mission Regional Hospital Urology out patients department. Permission has been obtained from hospital management.

3.3. Participant Selection and Sampling Strategy

All patients who underwent a prostate biopsy in the period 2016-2017 will be accrued as a participant for the study irrespective if the biopsy was an initial or repeat biopsy. Once a patient is accrued into the study the patients outpatient chart will be analysed and the data surrounding the index biopsy (i.e. the biopsy performed in 2016-2017), all preceding biopsies and/or all subsequent biopsies will be recorded.

3.4. Measurements

Data recorded will be of the patients demographics (date of birth, race), the date the patient was first seen, initial PSA, digital rectal examination findings, prostate biopsy results (benign hypertrophy versus prostate cancer versus Infection and Gleason score of tumour if malignancy present), any documented post biopsy complications (e.g. Sepsis, Heamaturia, Acute Urinary Retention) the patient may have experienced, bone scan results (if done) and the chosen treatment option. Race will be determined based on a combination of patients' appearance in their ID photo together with their name/surname and the opinion of the lead investigator and the nursing sister assisting him with data collection.

3.5. Data Collection and Statistical Analysis

Data will be obtained from review of urology outpatient department charts of patients who underwent a prostate biopsy during the period under consideration. Data will initially be recorded onto a "data sheet" (See Appendices) and will be entered from the data sheet onto an Excel spreadsheet at a later date to allow for easier analysis of the data. The Excel spreadsheet will be stored on a password-protected computer that only the primary investigator has access to. Once the data is obtained the assistance of a statistician will be sort to further interpret the data with the use of descriptive statistics and graphs.

4. ETHICAL CONSIDERATIONS

Patient Confidentiality and Protection:

All patient data is to be obtained retrospectively from outpatient charts with no direct patient interaction. Data obtained from the charts will not direct further management of patients. No further testing will be performed on patients. Patient's data will be kept confidential and recorded on a password-protected computer.

Patient Benefits:

The findings of this study may help to shape future prostate cancer screening guidelines thereby assisting the population at large by allowing the disease to be diagnosed and treated earlier, resulting in an improved life expectancy and quality of life. The patients, however, from whose charts data will be obtained, will unlikely benefit further from the findings of this study.

Conflict of interest:

No funding has been obtained from any private organisations (drug company or otherwise) with a vested interest in any potential outcomes. This study will be used to complete the research obligations of an MMED degree but there is no bias to any particular findings.

5. METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS

- Outpatient charts for patients shown in records to be biopsied may not be able to be found.
- Not all information needed for study may have been recorded.
-The race of all patients may not be determined therefore impacting on the findings of the study.

6. FEASIBILITY

There is no foreseeable monetary cost to the study. Files will be analyzed and the required data recorded by a nursing sister from St. Aidan's Hospital (Sister K. Chetty) and myself. Statistical assistance will be sort from the biomedical research department of UKZN.

7. STUDY SIGNIFICANCE

It is hoped that the findings of this study will add weight to the increasing evidence that there should be a nationally sanctioned prostate screening program in South Africa due to a large sub population group of Black African males. Furthermore, as a result of the high cost of treatment for metastatic prostate cancer, addressing it at an earlier, curable stage may reduce both the direct and indirect economic burden of the disease.

Appendix 2: Data Collection Sheet

Prostate Biopsy Details

Name: _____ DOB: _____ Race: _____

Hospital Number: _____

Reason Referred: _____ Date 1st Presentation: _____

TUC Dependent: ___ Date of Biopsy: _____ Initial PSA: _____

T Stage: _____ Initial Urea: _____ Initial Creatinine: _____

Diabetic: _____ Hypertensive: ___ Biopsy Sepsis: _____

Biopsy Left: _____

Biopsy Right: _____

Repeat Biopsy: _____

Reason for Repeat Biopsy: _____ Date repeat Biopsy: _____

Biopsy Left: _____ Biopsy Right: _____ Biopsy Sepsis: _____

Bone Scan: _____

Initial Management: _____

Date of Progression: _____ Castrate Resistant: _____

Testosterone Level: ____ Antiandrogen: _____

Date of Progression on AA: _____ Date Oncology Referral: _____

Reason Referred: _____ Date Surgery: _____

Surgery Gleason Score: _____ LAST PSA: _____

Last Date Patient seen: _____ Last Urea: _____ Last Creatinine: ____

Catheter Dependent Last Visit: ____ Post Prostatectomy Incontinence: ____

Known Demised: _____ Likely Demised From Prostate Cancer: _____