MODALITIES OF PROSTATE SPECIFIC ANTIGEN TESTING IN GAUTENG CLINICS AND HOSPITALS, SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree in Master of Medicine (Chemical Pathology).

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DECLARATION

I, Mpho Reginah Maphayi declare that this research report is my own work. It has been submitted for degree in Master of Medicine in the branch of Chemical Pathology at the University of Witwatersrand, Johannesburg. It has not been submitted before for examination or at this or any other university.

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06 day of JUNE 2018

DEDICATION

To my husband Kitemano Mbilinyi, thank you for your love, support and encouragement.

To my parents Esther and Lawrence Maphayi, thank you for your steadfast love and encouragement.

To my God and King, the bedrock under my feet, the reason I live, thank you.

ABSTRACT

Background: The use of prostate specific antigen (PSA) in screening for prostate cancer remains controversial. However, in developing countries mortality from prostate cancer remains high due to lack of screening facilities such as PSA testing. Prostate specific antigen testing could be beneficial in reducing advanced prostate cancer and mortality in developing countries like South Africa. The Prostate Cancer Foundation of South Africa has issued guidelines on the use of PSA in prostate cancer screening, diagnosis and management, but we do not know how this test is used in our healthcare facilities.

Aims and objectives: To describe modalities of PSA testing in screening and diagnosis of prostate cancer in terms of number of PSA test requests, patient demographic characteristics, type of health care facility (clinic versus hospital), prostate biopsy uptake and PSA level.

Methods: This was a descriptive retrospective study of PSA tests done at the National Health Laboratory Services laboratory at Charlotte Maxeke Johannesburg Academic Hospital from January 2013 to December 2013.

Results: 17 498 subjects had PSA tests. Of these 13 795 (79%) were done in Black African men (BA) while 3703 (21%)) in other racial groups (Others). More requests (62%) were from clinics versus than from hospitals (38%). The mean age for Black Africans (55.5 years SD (±13.3 years) was significantly lower than that of Others (62.9 years (±12.6 years, $p<0.005$), and median PSA level was significantly higher in Black African men from age 60 and above compared to Others (1.79 versus 1.53 µg/L, $p<0.001$).

More Black Africans aged 60 and above had PSA level above age specific reference interval than others of the same age category (33% versus 26%, $p<0.001$). Only 17% of all men had a PSA above 4.00 µg/L which is the cut-off used by the National Health Laboratory Services.

Of the four hundred and twenty-three men who underwent prostate biopsy, 213 (50%) had cancer. Fewer prostate biopsies were done in Black Africans than Others (2% vs. 4 % $p=0.01$), although Black African men were more likely to be diagnosed with prostate cancer on biopsy than Others (54% vs. 43%, $p=0.03$).

Conclusion: PSA testing is a common practice in our healthcare facilities. The numbers of PSA tests done differ by age and race of patients. Black African men had lower biopsy uptake even though they were likely to be diagnosed with prostate cancer on biopsy.

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PREFACE

Prostate specific antigen remains the most useful test in prostate cancer diagnosis and management. Despite controversies regarding its use in screening, countries with high utilization of the test have experienced a reduction in advanced disease and prostate cancer mortality. It has enabled clinicians to detect organ confined prostate cancers and institute curative treatment. In developing countries where the incidence of prostate cancer is lower, mortality related to prostate cancer is higher, probably due to late presentation and lack of access to screening facilities. Increased prostate specific antigen utilization may potentially cause a change in prostate cancer stage at first presentation in developing countries. However, it is not known how prostate specific antigen is used in our setting and whether its use may be beneficial. Knowledge on the modalities of prostate specific antigen testing in our population may lead to changes to local prostate cancer screening guidelines and improving access to screening facilities for at risk population.

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LIST OF ABBREVIATIONS

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

NHLS – National Health Laboratory Services

CDW – Corporate Data Warehouse

PSA – Prostate Specific Antigen

BA – Black Africans

IQR – Interquartile Range

SD – Standard Deviation

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

Prostate cancer is the second most common type of cancer affecting men in the world and the fifth leading cause of cancer death.[1] Whilst the incidence is highest in developed countries such as Australia, New Zealand and Northern America; countries with predominantly black populations such as the Caribbean and Sub-Saharan Africa have the highest mortality rates.[1]

1.2 Prostate cancer incidences in Africa

Generally, prostate cancer incidences among African men are low compared to incidences among African American men, however this is expected to increase with improvement of access to healthcare and screening facilities in African countries.[2] A meta-analysis by Adeloye et al reported an estimated pooled incidence of 22.0 (95% Confidence interval, 19.3 to 23.97) per 100 000 across the African continent, with the highest incidences in Sub-Saharan and Western Africa.[3] However the authors cautioned that this may be an underestimation because a lot of African countries do not have functional up-to-date national cancer registries.

In South Africa prostate cancer is the most common cancer in Black African, Coloured and Asian men and is second to basal cell carcinoma in White men.[4] Majority of cases are diagnosed in men from age 45 and above. A study by Babb et al found that prostate cancer mortality rates were higher in Black African men than White men.[5] Other studies have shown that Black African men tend to present late with advanced disease and those that present at age 40 to 50 years or younger have poor prognosis.[6,7] Reasons for these racial disparities include

lack of access to screening and early detection facilities, preference for traditional medicine over western medicine, as well as lack of knowledge and awareness about the disease.[5, 6, 7, 8, 9]

1.3 Risk factors for prostate cancer

The risk factors for prostate cancer are advanced age, African ancestry and family history.[7, 10] These are not modifiable which makes screening and early detection of paramount importance in reducing mortality associated with this disease. Other risk factors include smoking, alcohol use, infections and exposure to high levels of androgens.[7, 11]

1.4 Prostate cancer diagnosis

Men with prostate cancer can be asymptomatic or present with lower urinary tract symptoms, haematuria or symptoms of advanced disease (back pain, loss of weight or anaemia). Currently, both digital rectal examination and prostate specific antigen (PSA) are used for screening prostate cancer in asymptomatic men. The diagnosis of prostate cancer is confirmed by prostate biopsy. Indications for prostate biopsy are an elevated PSA or an abnormal digital rectal examination.

1.5 Prostate specific antigen

Since its discovery decades ago, PSA has been widely studied and used in prostate cancer. It is a serine protease produced by the prostate gland to liquefy semen coagulum and aid in spermatozoa mobility.[11] It was initially thought to be produced exclusively by the prostate glands, but small amounts have been discovered in other tissues.[11] In men it is prevented from entering circulation by an intact basement membrane. When the integrity of the basement

membrane is compromised due to benign or non-benign diseases of the prostate then it is detectable in blood circulation. Prostate specific antigen exists in two main forms in blood, namely the free form the majority (70 – 80 %) of which is physiologically active and the complexed form which is physiologically inactive.[11, 12] Most of PSA is in the complexed form, about 70-90% is complexed with α1-antichymotrypsin and the remaining with other protease inhibitors such as α2-macroglobulin. [11, 12] The free form of PSA contributes about 10-30% of the total PSA.[12] Total PSA includes both complexed and free forms.

1.5.1 Clinical utility of PSA in prostate cancer detection

Prostate specific antigen is not cancer specific as it is also increased after prostate gland manipulation (digital rectal examination, transurethral ultrasound), urinary tract infection and benign conditions of the prostate such as benign prostate hypertrophy and prostatitis.[11] This affects its diagnostic performance in prostate cancer detection. There are several ways adopted to improve the clinical sensitivity and specificity of PSA in prostate cancer detection which are briefly discussed below.

PSA in combination with digital rectal examination

The performance of PSA in detecting prostate cancer improves when it is used in combination with digital rectal examination than either of them alone. A study by Luboldt et al reported an increase in positive predictive value from 17% to 51% when PSA was used in combination with digital rectal examination than when used alone. [13]

Age-specific reference ranges

The use of age-specific ranges enables early detection in younger men therefore decreasing the number of false negatives. It also accounts for elevated PSA due to increase in prostate volume in elderly men. However, the use of age-specific reference range may miss prostate cancer in elderly men especially in the ranges lower than 6.50 µg/L.[14] The age specific ranges for total PSA are:[14]

- 40 – 49 years old, PSA 0 – 2.50 µg/L
- 50 – 59 years old, PSA 0 – 3.50 µg/L
- 60 – 69 years, PSA 0 – 4.50 µg/L
- 70 – 79 years, PSA 0 – 6.50 µg/L

PSA density

This is total PSA divided by prostate volume as determined by transurethral ultrasound**.** The use of PSA density account for an increase in PSA due to benign prostate hypertrophy in older men. Patients with prostate cancer produce more PSA for the volume of cancer than the same volume in benign prostate hypertrophy.[15] Therefore, the higher the PSA density the higher the risk of prostate cancer. Men with PSA level between 4.00 – 10.0 µg/L and PSA density of more than 0.15 have higher risk of prostate cancer and require prostate biopsy.[15]

PSA velocity

This is the rate of change of PSA. There are different ways of calculating PSA velocity. It can be calculated from at least three PSA levels taken within 18 months.[11] Patients with prostate cancer seem to have an increased PSA velocity compared with those with benign conditions .[16] A PSA velocity of more than 0.75 µg/L/year is suspicious for prostate cancer especially in those men with PSA in the grey zone (PSA 4.00 – 10.0 µg/L) and warrant prostate biopsy.[17]

Prostate specific antigen between 4.00 and 10.0 µg/L is referred to the grey zone or borderline level because both patients with prostate cancer and benign prostate hypertrophy have PSA levels that falls in this range.

Percentage free PSA

This is calculated as free PSA divided by total PSA and expressed as a percentage. Both free and complexed PSA are measured separately, and results expressed as a percentage free PSA. Men with prostate cancer have more complexed PSA than free PSA therefore the lower the %free PSA the higher the risk of cancer.[18] The use of %free PSA improves clinical specificity in PSA levels between 4.00 and 10.0 µg/L .[18] There is no agreement on the cut-off that should be used. Some recommend prostate biopsy when %free PSA is less than 15%.[19] Percentage free PSA has been found to perform better in detecting prostate cancer than PSA age specific ranges.[20]

1.5.2 Prostate specific antigen testing

Prostate specific antigen testing improves early detection of prostate cancer in most countries and therefore results in increasing incidences.[21] Countries where PSA based screening is widely available have seen high incidences of prostate cancer but low incidences of advanced disease at presentation.[1, 22] Its increased utilization in these countries has led to prostate cancer stage migration from more advanced disease to detection of organ confined cancer. Similarly, a decrease in PSA testing seem to have being followed by decrease in prostate cancer incidences and it is yet to be determined if this pattern will also affect prostate cancer mortality rates.[23]

The increase in use of PSA observed in countries with high incidence of prostate cancer has enabled early detection of organ confined cancer and early treatment interventions.[1, 24, 25] These increases have been observed in both developed and developing countries.[25, 26] There is limited data from Africa. In a single study from Nigeria, the increase in PSA testing was found to be consistent with increase prostate cancer incidence.[26]

1.5.3 Prostate specific antigen-based screening

The use of PSA to screen for prostate cancer remains a debateable issue as there is conflicting evidence regarding its benefit in reducing prostate cancer mortality. The two major trials conducted to answer this question yielded conflicting results.[21, 27, 28] This led to different medical societies issuing different recommendations on whether to screen for prostate cancer or not.[29, 30, 31] It is important to note that these two studies were conducted in developed countries in Europe and the United States of America where PSA testing is common and the incidences of advanced disease and mortality from prostate cancer are low compared to developing countries.

The benefits of PSA based screening have not been adequately investigated in developing countries where prostate cancer mortality is significantly higher. There is evidence to suggest that it might be beneficial. Ikuerowo et al screened 4110 men, using both PSA and digital rectal examination. A histological diagnosis of prostate cancer was made in 43 men and 17 had locally advanced disease and 15 had metastasis.[32] In a similar study conducted in South Africa, 660 men were screened using both PSA and digital rectal examination, prostate biopsy was obtained in 21 men and showed prostate cancer in 9 men.[33] This study is probably not a true

reflection of the incidence of prostate cancer in the country because very few patients came back to have biopsy taken.

1.6 Study Problem

There is no nationwide screening program in South Africa and majority of PSA based screening is opportunistic. The local guidelines issued by the Prostate Cancer Foundation of South Africa recommend PSA testing for Black African men and men with family history of prostate cancer or breast cancer from age 40 years, all other men from age 45 years and any men with lower urinary tract or other symptoms suggestive of prostate cancer.[34] The foundation guidelines further recommend using age specific total PSA reference ranges.[34]

1.7 Aims and objectives

The aim of this study is to describe the modalities of PSA testing in screening and diagnosis of prostate cancer in Gauteng clinics and hospitals in terms of number of PSA test requests, patient demographic characteristics, type of health care facility (clinic versus hospital), prostate biopsy uptake and PSA level.

The specific objectives were:

1. To establish the number of prostate specific antigen tests requested at the National Health Laboratory Services (NHLS) laboratory at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over the period January 2013 to December 2013.
2. To compare mean age and prostate specific antigen levels between Black African men and men of other racial groups and determine the proportion of prostate specific antigen results in relation to the total prostate specific antigen tests in Black African men under the age of

40, and in other racial groups under the age of 45 and relate these proportions to the category of the requesting health care worker. Categories of healthcare workers are doctors and nurses.

3. To determine the proportion of prostate specific antigen results that falls outside the age-specific reference ranges.

4. To determine how many prostate specific antigen tests that fall above age specific ranges are followed up with a prostate biopsy.

5. To determine the frequency of repeat prostate specific antigen testing per subject.

CHAPTER 2: METHODS

2.1 Study design

This was a descriptive retrospective study using data extracted from the laboratory information system. The study sample included all PSA tests done at the NHLS laboratory at CMJAH during a 12 months' period, from January 2013 to December 2013.

2.2 Background on Charlotte Maxeke Johannesburg Academic Hospital National Health Laboratory Service Laboratory

The National Health Laboratory Service (NHLS) laboratory at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is situated in the Johannesburg metropolitan area, South Africa. It is a referral laboratory that serves not only CMJAH but also surrounding healthcare facilities. It receives test requests from approximately 165 clinics and hospitals from Gauteng and other provinces of South Africa. Laboratory data from all South African public hospitals (which are served by the NHLS) are stored at a central location.

2.3 Laboratory analysis of prostate specific antigen

Total PSA in serum samples was measured by two-site sandwich immunoassay, using direct chemiluminometric technology on the SIEMENS Advia Centuar analyser. The assay detects both free-PSA and α1-antichymotrypsin-PSA complex, therefore measures total PSA. Both internal and external quality controls of the assay were within acceptable limits. The NHLS laboratory at CMJAH report PSA results with reference interval of 0 – 4.00 µg/L as recommended by the assay manufacturer. PSA level above 4.00 µg/L is considered high and needing further investigations. The measuring range for assay is 0.01 – 100 µg/L and samples

with values above the measuring range are diluted and retested to obtain accurate results as per manufacturer recommendations. We do not do free percentage PSA at CMJAH NHLS laboratory and therefore this was not analysed.

2.4 Study population

The study subjects were all males who had at least one PSA test done at CMJAH NHLS laboratory including all those PSA requests that were referred from other healthcare facilities in Gauteng province during a 12 months' period, from January 2013 to December 2013. We included all subjects with recorded age, race, requesting healthcare worker name and professional body registration number and type of healthcare facility details done during the study. We excluded females, subjects younger than 10 or older than 90 years, as well as those subjects with no requesting healthcare worker registration number (Health Profession Council South Africa or South African Nurses Council registration number), type of healthcare facility or gender information.

The subjects' age was required for categorizing their PSA results according to age specific reference intervals. Although PSA testing is only recommended in males, gender information was necessary to ensure that PSA results being analysed were for male subjects only.

The requesting healthcare workers were categorised as doctors or nurses. They were identified by their profession regulatory body registration number i.e. Health Profession Council of South Africa (HPCSA) for medical doctors and South African Nursing Council (SANC) for nurses. All healthcare facilities were categorized as either hospital or clinic.

Study subjects' race was categorized as Black African and Other. Information on other racial groups was not available from data retrieved from the NHLS Corporate Data Warehouse, those that were clearly identifiable as Black Africans were categorised accordingly, the rest were grouped into category "Others" which included White, Coloured and Indians.

The study subjects were then divided into four age categories. Age category 1 which included all men less than 40 years to Category 4 which consisted of all men aged 60 years and above. High PSA levels were described as either PSA result above the age specific reference ranges or over 4.00 µg/L for all age groups (see table 2.1).

Table 2.1 Subjects age categories and PSA age specific reference ranges

Age categories	**Age (years)**	**PSA age specific reference ranges (µg/L)[34]**
1	Less than 40	
2	40 – 49	0 – 2.50
3	50 – 59	0 – 3.50
4	60 and above	0 – 4.00

2.5 Data collection

PSA results were identified by requests from clinics and hospitals in Gauteng province done at the NHLS laboratory at CMJAH from January 2013 to December 2013. Information on patients' gender, age, race, PSA test result, category of requesting healthcare worker, type of healthcare facility and prostate biopsy results were recorded on Microsoft Excel spreadsheet. Subjects who had more than 5 PSA test repeats, only the first 5 results were considered for

analysis purposes. Data analysis was done for all patients for the first PSA results during the study period. Subsequent PSA results were only used to assess the extent of repeat testing.

2.6 Statistical analysis

Descriptive statistical analysis was performed using Stata 12 software (Statacorp, College Station, Texas, USA). Subjects' age was found to be normally distributed (Gaussian) and therefore reported as mean and standard deviation and comparison between the means of the racial groups was by Student t-test. Skewness and Kurtosis test was used to assess normality for the PSA results and this was found to display a non-Gaussian distribution. Therefore, non-parametric data analysis was performed. This data was reported as median and interquartile range and comparison of PSA result between two groups using Mann Whitney test. Categorical data was reported as proportions and percentages. The chi squared test was used to compare proportions between racial groups. P value of less than 0.05 was accepted as statistically significant.

2.7 Ethical consideration

This study was approved by the University of Witwatersrand Human Research Ethics Committee (medical). Clearance certificate number M140249 (Appendix A).

CHAPTER 3: RESULTS

A total of 21 032 PSA tests were done for 18 022 subjects at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) National Health Laboratory Services (NHLS) laboratory during the 12 months' period of January 2013 to December 2013. Five hundred and twenty four subjects were excluded from the analysis for the following reasons: 268 were excluded because subjects did not have either recorded age or gender or both, 18 subjects under the age of 10 were also excluded as their age was deemed incorrect due to potential transcriptional error, and 78 male subjects over the age of 90 were excluded from the analysis for the same reason,138 female subjects were excluded because PSA testing is not recommended in females, 22 subjects were excluded because there was no information on the requesting healthcare worker and therefore could not be categorised. After these exclusions, a total of 17 498 male subjects with 20365 PSA results including repeat requests data were analysed.

3.1 Study population demographics

The study subjects' demographics are presented in table 3.1. Of the entire study population, 79 % (n=13 795) were Black Africans while 21 % (n=3703) belonged to Others. The mean age of Other men was significantly higher as compared to that of Black African men (mean 61.9 years SD 12.6 vs. mean 55.5 years SD 13.3, $p<0.001$). Only 10% (n=1786) of all subjects were under the age of 40 and most were 60 years and older (44%, n= 7747). Majority of PSA requests came from clinics compared to hospitals (62% vs 38%). Nurses requested slightly more PSA tests than doctors (51% vs. 49% $p<0.001$).

Table 3.1 Study subjects' demographics

Variable	Black Africans n=13 795 (79%)	Others n =3703(21%)	All subjects n =17 498(100%)
Age Categories			
1	1612 (12)	174 (5)	1786 (10)
2	2767 (20)	437 (12)	3204 (18)
3	3920 (28)	841 (23)	4761 (28)
4	5496 (40)	2251 (60)	7747(44)
Type of healthcare facilities			
Hospitals	4453 (32)	2244 (61)	6697 (38)
Clinics	9342 (68)	1459 (39)	10 801 (62)
Requesting healthcare worker			
Doctors	5843 (42)	2698 (73)	8536 (49)
Nurses	7952 (58)	1010 (27)	8962 (51)

Age categories: 1=less than 40 years, 2=40 to 49 years, 3=50-59 years, 4≥60 years

Significantly more Black African under the age of 40 had PSA test done compared to Other under the age of 45 (p-value< 0.001). When we looked at the category of healthcare worker who carried out the PSA tests in Black African men under the age of 40 years, nurses requested 80% of those tests. In Other men under the age of 45, nurses requested slightly more tests compared to doctors (table 3.2).

Table 3.2 PSA test requests by healthcare worker category for Black African men under age of 40 and Others under age of 45

Healthcare worker category	Black Africans men under 40 years n (%)	Others under 45 years n (%)	P-value
Doctor	319 (20)	174 (48)	
Nurses	1293 (80)	186 (52)	
Total	1612 (100)	360 (100)	<0.001

3.2 PSA results

3.2.1 PSA results for all subjects

A total of 20 365 PSA tests were performed on 17 489 men during the study period. Of these, 2876 were repeat tests. The median PSA result for all subjects was 0.97 µg/L (IQR 0.54 – 2.39 µg/L). Analysis of PSA results according to age categories (table 3.3) showed that PSA median increased with increasing age. It ranged from PSA median of 0.66 µg/L (IQR 0.44-1.00 µg/L) in men less than 40 years to 1.68 µg/L (IQR 0.72-5.38 µg/L) in men 60 years and older. Most of the PSA results were between 0 and 4.00 µg/L and only 17% (n=3018) were above 4.00 µg/L.

Table 3.3 Summary description of PSA results for all subjects

Variable	**PSA median (IQR)/ n (%)**
PSA by age categories Median µL (IQR µL)	
1	0.66(0.44-1.00)
2	0.68(0.46-1.08)
3	0.89(0.53-1.75)
4	1.68(0.72-5.38)
PSA above age specific range n (%)	
40 – 49 years old	173(5)
50 – 59 years	600(13)
≥ 60 years	2370(31)
PSA result n (%)	
>4.00 µg/L	3018(17)
≤4.00 µg/L	14 488(83)

Age categories: 1=less than 40 years, 2=40 to 49 years, 3=50-59 years, 4≥60 years.
IQR=Interquartile range, n=number

3.2.2 PSA repeats frequency

We assessed the frequency of PSA test repeats per subject. Majority of patients (89%) had one PSA test and only 0.6% (113) had 5 PSA tests over the 12-month period included in this analysis as shown in figure 3.1.

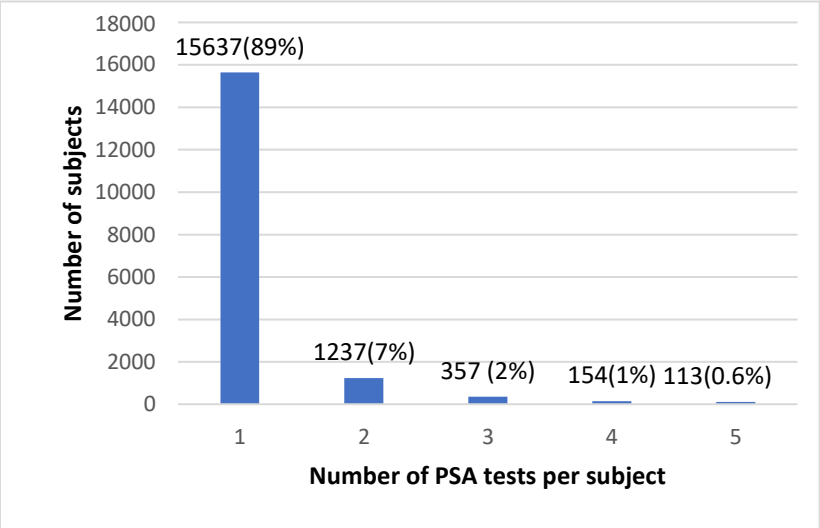

Figure 3.1. Frequency of PSA repeats per subject

3.2.3 Comparison of PSA results by race

PSA medians

When comparing PSA median results of Black African men and Other men, there were no significant differences except in age categories 3 and 4 where Other men had lower PSA median than Black African men (table 3.4).

PSA proportions

The proportions of men with PSA above 4.00 µg/L also differed between the two race categories, 19 % (n=695) out of 3703 of Other men had PSA level above 4.00 µg/L compared to 17% (n=2315) out of 13 795 Black African men (p=0.005) as shown in table 3.4

Table 3. 4 Comparison of PSA results by race

Variable	Black African	Others	P-value
PSA by age categories Median µL(IQR µL)			
1	0.66(0.44-1.00)	0.67(0.41-1.02)	0.84
2	0.68(0.46-1.08)	0.68(0.45-1.12)	0.76
3	0.90(0.54-1.75)	0.85(0.5-1.74)	0.03
4	1.79(0.76-6.03)	1.53(0.63-4.17)	<0.001
PSA above age specific range n (%)			
40 – 49 years old	155(6)	20(5)	0.381
50 – 59 years	492(13)	108(13)	0.818
≥ 60 years	1784(33)	587(26)	<0.001
PSA result n (%)			
>4.00 µg/L	2322(17)	696(19)	0.005
≤4.00 µg/L	11 473(83)	3007(81)	

Age categories: 1=less than 40 years, 2=40 to 49 years, 3=50-59 years, 4≥60 years.
IQR=Interquartile Range, n=number

We determined the proportions of men with PSA above the age specific reference range. There were more men in age category 4 that had PSA above their age specific reference range compared to the other age categories. Only 5% of all men in age category 2 had PSA level above the age specific reference range compared to 31% in age category 4 (table 3.3).

The proportions of Black African men and Others with PSA levels above the age specific reference ranges were also compared. More Black African men aged 60 and above had PSA level above the age specific reference range compared to Other men of the same age category ($p<0.001$) as shown in table 3.4.

3.2.4 PSA result and prostate biopsy

Of all men (n=17 498) who had PSA tests, only 2% (n=423) had prostate biopsy (table 3.5). When we looked at the PSA levels of all men who had prostate biopsy, the median PSA for Other men was significantly lower (3.70 µg/L) than for Black Africans (7.40 µg/L, p = 0.0002). Significantly more Other men had prostate biopsy than Black African men (4% vs 2% p<0.001) as shown in table 3.5.

Table 3.5. The number of men who had PSA results and prostate biopsy by race, age categories and PSA levels

Variable	Prostate biopsy n (%)	No prostate biopsy n (%)	All subjects
Race			
Black African	276(2)	13 519(98)	13 795
Others	147(4)	3557(96)	3703
Age categories			
1	2 (0.1)	1784(99.9)	1786
2	6(0.2)	3198(99.8)	3204
3	52(1)	4709(99)	4761
4	363(5)	7384(95)	7747
PSA above age specific range			
40-49 years	3(2)	170(98)	173
50-59 years	33(6)	567(94)	600
≥60 years	213(9)	2157(91)	2370
PSA			
>4.00 µg/L	245(8)	2773(92)	3018
≤4.00 µg/L	178(1)	14 303(99)	14 480

Age categories: 1=less than 40 years, 2=40 to 49 years, 3=50-59 years, 4≥60 years

Prostate biopsy uptake also differed across all four age categories as depicted in table 3.5. More men in age category 4 had prostate biopsy than men from other age categories. Only 0.2% of men in age category 2 had prostate biopsy compared to 5% in men age category 4.

We looked at the age at biopsy and PSA level above age specific reference range and found that more men in age category 4 who had PSA level above the age specific range had prostate biopsy than men in other age categories. Since the laboratory gives a reference range of 0 – 4.00 µg/L, we looked at the proportions of men with a PSA above the cut off value of 4.00 µg/L who had a prostate biopsy. Of all men with PSA level above 4.00 µg/L, only 8% (n=245) had prostate biopsy.

There was a significant difference in the proportion of Black African men with PSA above the age specific reference ranges who had a prostate biopsy compared to Other men who had PSA level above age specific reference range and prostate biopsy. This difference was present across all age groups. Prostate biopsy uptake for Other men was significantly higher across all age groups (table 3.6) compared to Black African except in age 60 and above where the difference did not reach statistical significance. However, Black African men between age 40 – 49 had the lowest prostate biopsy uptake of 0.7%. When we compared proportions of all Black African men and Other men with PSA level above 4.00 µg/L and prostate biopsy, more Other men had prostate biopsy (10%) than Black African men (7.5% p=0.033).

Table 3.6. Comparison of Black African and Other men who had prostate biopsy by PSA level

Variable	**Black African n (%)**	**Others n (%)**	**P-values**
PSA above age specific Ranges			
40 – 49 years	1 (0.7)	2 (10)	p=0.002
50 – 59 years	22 (5)	11 (10)	p=0.018
≥ 60 years	153 (8)	60 (10)	p=0.227
PSA > 4.00 µg/L	175 (7)	70 (10)	p=0.033

3.3 Prostate cancer and prostate biopsy

A total of 423 men had prostate biopsy, 49% (n=209) had negative results for prostate cancer while 51% (n=214) had positive results for prostate cancer. Of those who had positive prostate biopsy results, 70% (n=150) were Black African and 30% (n=63) were of other racial groups. Significantly more Black African men who had a prostate biopsy (54% i.e. 150 out of a total of 276) had prostate cancer compared to 43 % (63 out of 146) Other men (p=0.03) figure 3.2. When we compared the Gleason score between the two racial groups, the difference was not statistically significant (7.5 versus 7.3, p = 0.362)

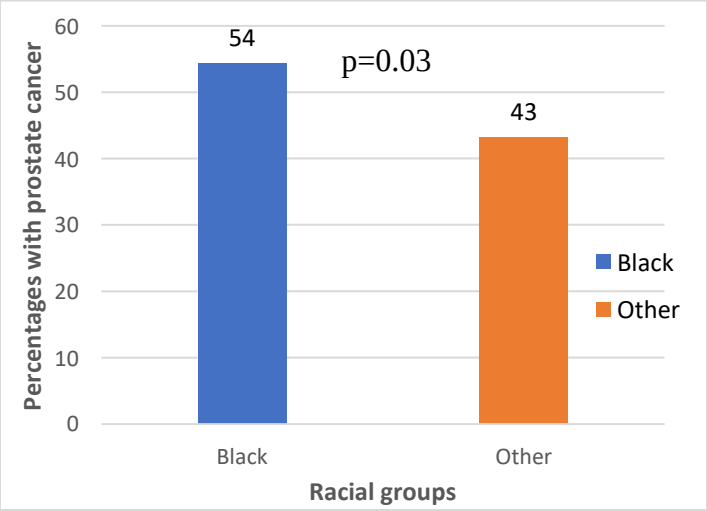

Figure 3.2. Percentage of Black African and Other men diagnosed with prostate cancer on prostate biopsy

CHAPTER 4: DISCUSSION

This study was aimed at describing the modalities of PSA testing in screening and diagnosis of prostate cancer in Gauteng health facilities during a one-year period.

The major findings were:

1) Black African men had lower prostate biopsy uptake and more prostate cancer compared to men of other racial groups.

2) The median PSA level for Black African men from age 50 and above was significantly higher than Other racial groups.

3) PSA testing is a common practice in our primary health facilities especially for Black African men across age all age groups.

4.1 Biopsy uptake and prostate cancer

The finding of low biopsy uptake and more prostate cancer diagnosis amongst Black African men in the current study is in keeping with findings of other studies in the country. A studyby Heyns et al found that only 19% of Black African eligible for prostate biopsy had biopsy compared to 47% of Coloured men.[35] Most Black African men did not come back to have biopsy taken in that study. In another study done by the same authors consisting of predominantly white and coloured men, biopsy uptake for Black African men was 53% which was lower compared to 87% for White men and 67% for Asian men.[36] Reasons for this low turnout for biopsy include migration to other cities or rural areas, lack of knowledge on the prostate cancer, preference for traditional medicine over western medicine and lack of transport to healthcare facilities.

A local study has shown that when Black African men, present with prostate cancer at a younger age, it is usually at an advanced stage[6]. Efforts to reduce incidences of advanced disease in the country will benefit from the targeted high-risk groups having access to further investigations and treatment. However, even when they have access to further investigations such as prostate biopsy, a local study has shown that they do not come back for additional tests.[33]

The public sector serves most of our population, most of whom cannot afford private healthcare. Public hospitals are overwhelmed with very high caseloads and financial constraints with lack of equipment and inadequate human resources namely urologists. This service is often the only option for majority of Black South Africans. Therefore, low biopsy uptake may also be due lack of resources at the public healthcare facilities. Our results also exclude those patients who may have been diagnosed with advanced disease by other clinical means such as digital rectal examination and imaging for metastasis and not have had prostate biopsy.

Advanced prostate cancer diagnosis

Advanced prostate cancer diagnosis is defined by a high PSA (≥20.0 µg/L), a Gleason score of more than 7 or the presence of metastasis. In this study we found that of all men who had prostate biopsy, Black African men had significantly high PSA level which is in keeping with other studies.[8, 37] However, there was no difference in Gleason scores between Black Africans and other racial groups. The finding of similar Gleason scores is not in keeping with the findings of other studies in the country. The reasons for this disparity in our study could be due to the small number of biopsies or disease stage at the time of biopsy in both racial groups. We

did not review patients file to find out the details on patients' clinical presentation and assess if there were any differences.

4.2 Racial disparities in terms of PSA levels

We found that Black African men's PSA levels were significantly higher from age 50 and above. This agrees with other studies conducted in the world and country which found higher PSA levels amongst black men. [8,32,38] In a study by Ikuerowo et al done in Nigeria found the median PSA of 1.50 ng/ml and 95th percentile of 10ng/ml.[32] The authors concluded that PSA level in Nigerian men is higher compared to their Caucasian counterparts. In a similar study done in South Africa found the mean PSA amongst Black African men to be higher than Other racial groups.[37] Reasons for the high PSA levels amongst African men include high prostate volume and infections. However, in this study there was no difference in PSA levels in the younger age groups (<50 years). This could be due to small sample size in the younger age group in our study as majority of our study participants were older (≥ 60 years and above).

In the current study, we found that there was racial disparity in terms of abnormal PSA depending on which cut-off we used. When using the standard PSA cut-off of 4.00 µg/L, more other men had PSA above this cut-off than Black African. However, when we used the age specific reference ranges, more Black African men from age 50 and above had PSA above their age specific reference ranges than Others. This is an important finding as NHLS laboratories still use the standard PSA 0-4.00 µg/L reference interval. The few studies conducted in Africa and South Africa used the standard PSA cut-off of 4.00 µg/L to screen for prostate cancer irrespective of age or race. However, prostate cancer is detectable even in men with PSA below

4.00 µg/L.[39] Of the 2950 men with PSA below the 4.00 µg/L, 15.2% were found to have prostate cancer on prostate biopsy.[39]

There are no studies comparing PSA standard cut-off and age specific reference ranges for prostate cancer screening in our country. A study conducted in the Cayman Islands by Jyoti et al on 165 Afro Caribbean men, using the cut-off of 4.00 µg/L showed that most patients with benign prostate disease had PSA below this cut-off and only three patients with PSA below the 4.00 µg/l were found to have prostate cancer.[40] They concluded that majority of patients with prostate cancer in their population can be excluded when their PSA levels are below 4.00 µg/L. Further studies are required to compare the diagnostic performance of the standard PSA cut-off of 4.00 µg/L and age specific reference ranges between the different racial groups in our population.

Although local guidelines recommend the use of age specific reference ranges for PSA[34] the evidence is conflicting on the use of age specific reference ranges for PSA in prostate cancer screening. Some studies have found it reduces the number of false negatives in younger men and false positives in older men.[41, 42] A study by Catalona et al comparing PSA age specific reference, PSA density and percentage free PSA in prostate cancer detection found age specific PSA cut-offs missed 20% to 60% of cancers in men older than 60 years of age.[20] Polaski et al had also argued that the use of age specific reference ranges had not been approved or recommended by the assay manufacturers.[43]There is evidence to suggest that percentage free PSA may perform better at detecting prostate cancer however free PSA measurement is not widely available for our population. Future studies looking at the predictive value of percentage free PSA can guide us as to its utility in our population.

4.3 The number of PSA tests in healthcare facilities

In a country with no nationwide screening program, the number of PSA tests in this current study reflects a high utilization of PSA testing. This finding is not in keeping with other studies done in the country. A study by Tindal at el done in the rural province of Limpopo and urban city of Pretoria found that of all patients who were referred to the urology clinic, only 3% were referred due to an elevated PSA test[8]. It is important to note that majority of subjects in that study were from the rural areas of Limpopo which reflect low PSA testing in rural areas of South Africa. However, our study was done in the urban relatively well-resourced Gauteng province hence the high PSA testing could be because of increase disease awareness and access to screening facilities amongst Black African men or inappropriate PSA test use by healthcare workers. Men in urban areas may have better access to clinics and hospitals and are exposed to awareness campaigns via media platforms than men in rural areas. Also, men in rural areas may have higher preferences to traditional medicine than western medicine and therefore not visit healthcare facilities when they have health issues. Studies done in developed countries have shown that even in the absence of nationwide screening programs, PSA based opportunistic screening does occur.[25]

4.4 Age of PSA testing

In our study we found that the mean age for Black African men was lower compared to other racial groups. Although there are no studies that have looked specifically at the age of PSA testing, previous studies looking at prostate cancer prevalence have shown that Black African men present at an older age and with advanced disease.[8,35,37] The younger age of Black African men in our study may suggest that this group is becoming more aware of their increased risk of prostate cancer or an increase utilisation of PSA in our primary health facilities to screen for

prostate cancer. However, the increase in knowledge of prostate cancer is not in keeping with the finding of a study by Mofolo et al conducted in the Free State which found that more than half of men interviewed had no knowledge of prostate cancer.[9] Of note is that their study consisted of a significant number of young Black African between ages 34 - 44 years.

The number of even younger (less than 40 years of age) Black African men who had PSA test is also a concern. Although we do not know the clinical features of these patients on presentation, this practice points to possible inappropriate use of PSA test by healthcare professionals and lack of awareness of the local guidelines. In a resource scarce country like South Africa where healthcare budgets are often exceeded, one needs to consider the cost implications of inappropriate PSA tests use.[44] The current cost of PSA at the National Health Laboratory Services (NHLS) laboratories is R112.14 per test. It is not only the cost of prostate specific antigen test, but also the cost of downstream procedures that needs to be considered. Ma et al found that downstream procedures such as prostate biopsy contributed 72% of the overall cost of PSA based screening.[45]

Limitations

This study had a number of limitations. Firstly, due to the retrospective nature and large sample size, we could not verify if patient details were correctly and appropriately recorded as on request forms. Secondly, patient files were also not reviewed to determine reasons for PSA test requests. Thirdly, not all patients had recorded race information, therefore those that were clearly identifiable as Black Africans were categorised accordingly. For the rest we manually assigned race based on other demographic details such as name, surname as well as geographic location. We compared our results with census data and race imputation program and found

very similar numbers of Black Africans and Other patients. For Other racial group (Coloured, Asian and Whites) the results were the same (21% of population study), for Black African we got 79% compared to 71% from census data and imputation program. This discrepancy is most likely due to the fact that the race imputation categorised 9% as unknown while we had two race categories namely; Black Africans and Others. The 9% unknown were most likely manually assigned to the Black African race category.

Recommendations

This is the first study using big data to investigate PSA testing in our population. We recommend:

- Further studies to compare PSA testing between rural and urban areas and look at the diagnostic performance of PSA test in our population.
- Since there is evidence to suggest that lack of PSA testing may contribute to Black African men presentingwith advanced aggressive disease, we recommend PSA testing for this high-risk group as per local guidelines however resources must be made available for further investigations of abnormal PSA results.
- Education for healthcare workers at clinics regarding local guidelines for PSA testing including indications for testing and causes of false positives to minimise the risk of inappropriate PSA use.
- NHLS laboratory make documentation of self-reported race mandatory on the laboratory request form as this information is important for public health policy and health promotion intervention.

CONCLUSION

PSA testing is a common practice in our primary healthcare facilities. The numbers of PSA tests done differ by age and race of patients. Black African men had lower biopsy uptake even though they were likely to be diagnosed with prostate cancer on biopsy.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATE

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140249

NAME: (Principal Investigator)	Dr Mpho Reginah Maphayi
DEPARTMENT:	Chemical Pathology NHLS Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Patterns of Prostate Specific Antigen Testing in Gauteng Clinics and Hospitals, South Africa
DATE CONSIDERED:	28/02/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr JA George

APPROVED BY:

Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 24/03/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

yearly progress report

Principal Investigator Signature

26/03/2014
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APPENDIX B: TURNITIN REPORT

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