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THE ROLE OF GEOGRAPHICAL DISTANCE AND REFERRAL PATTERNS ON STAGE AT PRESENTATION IN SOUTH AFRICA - A REVIEW OF TWO SOUTH AFRICAN BREAST UNITS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Masters in Medicine, Surgery

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Declaration

I, Catharina Pothas, student number 1820030, declare that this Research Report is my own work and that I contributed adequately towards research findings stated below which are included in my Research Report.

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Date 2023/05/09

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1. ABSTRACT

Introduction:

Historically breast cancer incidence has been low in Africa but now accounts for most cancer deaths in women in many sub-Saharan African countries. The purpose of this study is to examine the role of referral patterns and geographical distance on the stage at presentation.

Methods:

This retrospective cross-sectional study was undertaken at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) breast units from July 2015 to September 2017. The participants were grouped into both early (I and II) and advanced (III and IV) stage breast cancer. Demographic data (age, residential distance, referral pattern) and histological characteristics (immunohistochemistry and grade) were compared. Bivariate logistic regression models were applied on all variables with a subsequent multivariate analysis on all statistically significant variables.

Results:

Of the 1008 participants enrolled in the cohort, 55% presented with advanced stage disease. Referral pattern was statistically significant on bi- and multivariate analyses with a 50% increased risk of having advanced disease following indirect referral (from secondary hospital or specialist) regardless of other socio-demographic or histological characteristics ($p<0.001$, OR = 1.49, 95%CI 1.13-1.97). Geographical distance had no influence on stage at presentation ($p=0.075$, OR = 1.36, 95%CI 1.03-1.80).

Conclusion:

Referral patterns play an important role as a barrier to care in the South African public sector. Direct referral routes are needed with simple access to specialised breast units.

2. INTRODUCTION

2.1 Background

Worldwide, there is an increasing burden of non-communicable diseases and cancer deaths (1–3). Due to population growth, increased life expectancy, and lifestyle transitions in countries with large low and middle-income populations, an increased cancer burden is predicted over the next few decades (4). In 2025, it is expected that 20 million new cancer cases will be diagnosed worldwide; with the number exceeding 22 million annually within the next two decades (4).

The reported incidence of breast cancer in Africa has been historically low, but there has been a significant increase of newly diagnosed cases in more recent years (5,6). This has been attributed to social and economic development which has resulted in changes such as women postponing childbearing, fewer children per woman, increased obesity rates and disease awareness (5–8). In South Africa, more than 8,000 women were diagnosed with breast cancer in 2012, amounting to about 21.8% of all histologically diagnosed cancers, 35 per 100,000 women (9–11). Lifetime risk for a South African women to develop breast cancer before the age of 74 is 1 in 26 (9).

Breast cancer mortality rates have been gradually declining in high income countries since 1990 due to screening, early detection, increased awareness and improved management options (12). The majority of the mortality burden lies within developing nations as about 70% of breast cancer deaths occur there (13). Breast cancer mortality rates among lower socio-economic patient groups are higher, with most patients presenting at an advanced stage of disease, younger age and potentially more aggressive tumour biology (14–16).

Among the multiple predictors of survival are stage at diagnosis and access to facilities for treatment (17). The potentially unique risk factors associated with breast cancer in the African population remain elusive, as there are very few regulated diagnostic and treatment programs available (18).

2.2 Barriers to care

In the South African public sector, there are many factors that contribute to a delay in breast cancer diagnosis, care, and poorer outcome (19). These factors can be divided into health system and patient related factors (19).

Many factors can influence a patient's decision to seek medical attention including socio-economic status, accessibility of appropriate health care centres and cultural beliefs (20). These barriers also play a role in a patient's adherence to the therapeutic options available in the management of breast cancer, which include surgery, systemic therapy and radiation therapy (20).

Health system related barriers:

The World Health Organisation (WHO) recommends that health systems should have a high capacity to incorporate knowledge and skill development, commitment and efficient management in the prevention and control of non-communicable diseases (1). Early cancer detection and improved access to care are necessary to reduce the higher mortality rates found in low and middle income countries (21).

National population based registration systems are recommended by the WHO to aid in the control and prevention of breast cancer (22). These registration systems are implemented in most developed countries, especially those with the high incidence of breast cancer (22). However among the five countries (Fiji, Bahamas, Nigeria, Macedonia and Pakistan) with the highest mortality burden due to breast cancer in 2012, none of them had a national cancer registry (1).

Information on breast cancer incidence, mortality and prevention is essential for planning healthcare systems (1). Early detection is essential in reducing mortality burden and improving the prognosis of breast cancer (1). This can be achieved by: increasing the level of education in women, especially in developing nations; focusing on health policies aimed at detection and treatment of breast cancers and promoting awareness of risk factors among women (1).

With very few specialised breast units in the South African public sector, exclusively located in peri-urban and urban settings, and a growing population of more than 50 million, dedicated breast units are a scarce resource.

Patient related barriers:

There are many patient related barriers to care. These include factors that are more easily measured and those that are less so. Measurable barriers include demographic groups, socio-economic status, and levels of education. Less easily measured patient factors include variables such as a patients belief system, cultural perceptions and expectations, and personal fears and concerns (19,23).

Additionally, lifestyle factors such as household resources, parity, smoking, drinking, body mass index (BMI) and co-morbidities are among the variables affecting patients' behaviours and access to care. These variables may both aid in access to care and serve as barriers. One study recorded a diagnosis of hypertension being associated with an earlier detection of breast cancer (19). This could be due to opportunistic screening with a patient already presenting to a facility for a known health care problem or due to improved health seeking behaviour within that individual.

2.3 Similar previous studies

Few studies have evaluated breast cancer stage at presentation in relation to a patient's distance from the specialised breast unit. A study from CHBAH in Soweto, Johannesburg compared early to advanced stage at presentation (I/II vs. III/IV) to the distance the patient lives from the unit in a peri-urban setting (24). Results indicated that women present to the breast unit at an advanced disease stage when they live further away. Advanced stage at diagnosis increased from 50% for distances <20 km to 62% for distances of 20–29 km and 69% for distances of 30–39 km (24). However in the 9% of patients who lived beyond 40 km, the percentage of advanced tumours (56%) did not increase further with increasing distance from the unit (24).

In another study from Egypt, the stage at presentation at two different urban specialised breast units demonstrated only a weak association with distances from the unit (25).

Patients with longer travel times were more likely to present with an advanced stage at diagnosis (25). They also found that patients referred from another physician to the specialised breast unit was associated with late stage (53.6%) at diagnosis, whereas self-referred patients presented at an earlier stage (38.0%) (25).

2.4 Current referral patterns at CMJAH and CHBAH

The South African National Department of Health's (NDoH) Breast Cancer Control Policy states that the most appropriate regional facilities should be identified and selected as specialist breast units to facilitate rapid assessment of patients and centralise care (26). In the Gauteng healthcare referral pattern, health care professionals at primary care facilities refer patients with breast conditions to a regional hospital, which provide hospital care, limited diagnostic services and can send patients in need of advanced care to a tertiary hospital (26).

CMJAH and CHBAH are both tertiary care hospitals in Gauteng and provide a specialised breast service in the form of specialised breast units. Each unit treats about 20 to 35 patients with newly diagnosed breast cancer each month. In Gauteng there are no regional breast units currently, therefore both the specialised breast units included in this study allow direct referrals from the primary care facilities as well as self-referred patients. This policy aims to minimise barriers to care and avoid diagnostic and treatment delays.

CMJAH breast unit receives breast cancer patients from five cluster hospitals (South Rand Hospital, Bertha Gxowa Hospital, Tambo Memorial Hospital, Edenvale Hospital, Far East Rand Hospital) as well as the numerous associated primary health care clinics. CHBAH breast unit receives patients from multiple primary care clinics in Soweto and surrounding areas as well as regional and district hospitals (Heidelberg Primary District Hospital, Kopanong Primary District Hospital, Sebokeng Hospital, Bheki Mlangeni Hospital and Thelle Mogoerane Regional Hospital). In addition, both units accept referrals from other provinces since many provinces in South Africa have neither dedicated breast cancer units nor provincial oncology units (26).

Both units participate in the ongoing South African Breast Cancer and HIV Outcomes study (SABCHO) which was initiated in 2015. Information on access to healthcare, as well as various other patient and disease related factors are studied (27). A database was established for ongoing prospective data collection for future research and clinical audits.

CMJAH is situated in an urban and CHBAH in a peri-urban setting. An urban area consists of a densely populated area, with administrative or political boundaries, a certain population size or economic function. A peri-urban setting is defined as an urban-rural interface or transition zone adjacent to an urban area (28).

2.5 Aim of the Study

This study examines whether secondary or indirect referral patterns are associated with an advanced stage of diagnosis as compared with primary or direct referral (self-referral, primary care clinic or general practitioner).

We also aimed to determine the influence of residential distance to the tertiary hospital and referral pattern on the stage of presentation. There is no comparative study on the role of distance on stage at presentation in the urban setting and no study evaluating the impact of referral pattern on stage at presentation in South Africa.

2.6 Research Question

Do residential distances or referral patterns to the breast units at CMJAH and CHBAH influence the stage at presentation of breast cancer?

2.7 Hypothesis

Patients who live further away from specialised breast units or presented via a secondary hospital, will present with an advanced stage of breast cancer.

Patients living closer to specialised breast units and patients who present by self-referral or by referral directly from primary clinics or general practitioners will present at an earlier stage.

2.8 Objectives

Primary objective: To evaluate the influence of referral pattern and geographical distance on the stage of breast cancer at presentation to CMJAH and CHBAH breast units

Secondary objective: To identify other clinical and patient socio-demographic factors associated with advanced stage breast cancer at presentation, such as patient age, ethnicity (self-assessed) and breast cancer intrinsic sub-type.

3. STUDY METHODS

The Strengthening and Reporting of Observational Studies in Epidemiology Statement (STROBE) guidelines checklist for cross-sectional review studies were implemented for the compilation of this research report (29). In conjunction, PubMed was used for the literature review.

3.1 Methodology and design

Study design: Retrospective cross-sectional study

Study sites: CMJAH and CHBAH breast units.

Study population / participants: Consecutive consenting participants diagnosed with primary invasive breast cancer at CMJAH and CHBAH breast units from July 2015 to September 2017.

Sampling: Retrospective data from female patient records for those previously enrolled in SABCHO study from the CMJAH and CHBAH specialised breast units during the period 1 July 2015 to 31 September 2017.

Inclusion criteria: We included the following data collection sets from participants previously enrolled in the SABCHO study (ethics approval number M150351 dated 6 May 2015)

- female patients of any ethnicity
- South African residents for five years or longer
- ≥18 years of age
- newly diagnosed with primary invasive breast cancer at CHBAH or CMJAH
- informed consent signed

Exclusion criteria:

- previous cancer diagnosis other than non-melanoma skin cancer or non-invasive cervical cancer

- previous breast cancer
- in-situ disease only
- received systemic radiotherapy or chemotherapy treatment for more than one month
- received endocrine treatment in the past: tamoxifen, raloxifene, toremifene, exemestane, letrozole, anastrozole, fulvestrant or megestrol

Study groups: The patients were grouped into stage at presentation (early-stage and advanced: locally advanced and metastatic) to allow comparison of distance and referral patterns.

Measuring tool: Patient records were accessed via the clinical databases of the respective breast units.

Data collection: Two data sheets per section of study were used. The first data sheet contained patient name, folder number and study number. This information has been kept strictly confidential. The second data sheet was de-identified and contained extractable data.

Study limitations:

- Sources of bias: This study is a secondary analysis of prospectively collected data and therefore bias should be minimal. Other potential source of bias may have occurred as we could not exclude patients that moved to stay with family from more remote sites in South Africa and reported this new residence as their permanent location.
- Some information regarding immunohistochemistry was not always available for all participants, such as Fluorescence In Situ Hybridization (FISH) results for Human Epidermal Growth Factor Receptor-2 (HER2) equivocal results.
- We were unable to determine and include the stage of disease before referral to breast unit.

3.2 Data Analysis

Patients were grouped by stage at diagnosis as early (I/II) or advanced (III/IV). We compared groups concerning demographic data (age at diagnosis, race, residential distance from the specialised breast unit and referral pattern, direct and primary route versus indirect routes via secondary hospitals) and histological characteristics (grading and intrinsic sub-types).

Allred scores on oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 and Ki67 were used as immunohistochemical surrogates for the intrinsic sub-types of breast cancer (30). Luminal A sub-types were defined as ER/PR+, HER2- and Ki67 ≤15%; Luminal B as ER/ PR+ and/or Ki67 >15% and/or HER2 3+/-; HER2-enriched as ER/PR- and HER2 3+; and triple negative as ER/PR- and HER2-.

For distance to hospital, categorical variables were divided into <10km, 10-20km and >20km. These distances were calculated from the address provided by the patient. For referral pattern, variables were direct (self-referral, general practitioner, primary care clinic) and indirect (regional hospital, specialist).

Geographical distance was calculated as a straight line from the respective specialised breast unit to the residential distance of the patient. The coordinates from the patients' stated street addresses were calculated manually with Google Street map services and iTouchmap.com web interface. The linear distance was then calculated using GIS software (ESRI ARC- GIS 9.3 with a Transverse Mercator projection system, central meridian of 29, Hartebeesthoek_1994 as Datum and WGS_1984 as Spheroid) or the Haversine formula (31). (See Appendix B)

Pearson chi square and Fisher's exact tests evaluated the statistical significance of group differences in proportions for categorical variables. Means and medians for continuous variables were computed and Student's t-test and the Wilcoxon rank-sum test were used to determine disparities between groups in means and medians, respectively.

To identify factors associated with advanced stage presentation, we implemented bivariate and multivariate logistic regression models. All variables that are significant at $p<0.1$ on bivariate analysis were assessed in the multivariate analysis, and non-

significant factors were dropped with stepwise backward regression. A two-sided p-value of <0.05 were considered significant throughout. All available data were used in each bivariate analysis. In the multivariate analysis, patients with missing data for included variables were dropped from the model.

We used Stata version 14 (StataCorp Ltd, Texas, USA) to perform this analysis.

3.3 Ethics

This study has been approved by the Human Research Ethics Committee (HREC) at the University of Witwatersrand. Certificate number M1711121, dated February 2018. (See attached Appendix B)

4. RESULTS

Our cohort included 1008 patients from both breast specialised breast unit. Of these, 458 (45%) were early-stage (I/II) and 550 (55%) advanced (III/IV) at presentation to the units.

4.1 Variables

Multiple socio-demographic as well as clinical factors were selected for evaluation to identify factors that may affect stage at initial presentation, with the purpose of strengthening results when accounted for on multivariate analysis. These factors are listed in table 1.

Most women were between 40 and 50 years of age with 142 women (14.1%) below 40 years and 183 women (18.2%) above 70 years old. In terms of ethnicity, Black Africans made up the majority (84.0%), with 491 (89.3%), making up those presenting at an advanced stage.

Marital status was grouped into single, married or in a relationship, divorced and widowed. Only 8.6%, 87 of participants were divorced with most being in a relationship or married (427 women, 42.4%).

Most women, 77.4%, had completed high school or a form of tertiary education. 227 participants (22.6%) have had either informal or primary schooling. Almost half of participants were unemployed (45.9%, 463 women) with only 305 (30.3%) being employed. Household socio-economic score was similar for early and advanced stage presentation.

The majority of the participants (737, 79.1%) were overweight or obese with body mass indices more than 25kg/m^2.

Habits of smoking or drinking were documented in 12.7% and 21.4% of the cohort, respectively.

Regarding co-morbidities, 215 (21.1%) of participants were Human Immunodeficiency Virus (HIV) positive, making up 23.3% (128 participants) of the advanced stage group. 38.3%, 386 of participants were hypertensive.

On histology, the majority of 601 participants (60.2%) had luminal B cancer. Subtypes luminal B, HER2-enriched and triple negative all had higher percentages in the advanced stage group than early stage. Similarly, Bloom and Richardson histological grade 3 was 44.0% of the total cohort but 51.9% of the advanced stage group.

Two hundred and twenty-seven women (22.5%) had prior breast examinations done by a trained medical professional, with even a smaller percentage of the advanced stage group, 20.7% 114 individuals. 47 participants 4.7%, perceived clinic waiting time as a barrier to care.

Geographical distance to unit was divided into three groups namely under 10km, 10-20km and more than 20km. 363 (36.0%) of patients stayed close to the unit (<10km) and 444 (44.0%) stayed more than 20km away. There was a higher percentage (47.3%, 260 participants) of advanced diagnosed patients living more than 20km away.

Most patients (59.4%, 599 participants) presented to the specialised breast units within one month of noting a symptom, with a larger percentage (66.2%) in the early-stage group. 32.5%, 179 of participants in the advanced group took more than 3 months before presenting to the unit. In comparison to the advanced stage group, only 88 (19.2%) of the early-stage group took more than three months to present to the specialised breast units.

Most patients, 781 (77.5%), had three or more visits in the health system before presentation to the specialised breast unit. This was similar in both the early and advanced groups.

Referral patterns were divided into direct and indirect referral. Direct is considered a self-referral, from a general practitioner or from a primary care clinic. Indirect referral patterns are from another hospital or a specialist. Patients presented almost equally from either referral pattern, however there was difference between the two stages.

56.6% (311 of 550 participants) of the advanced stage group followed an indirect referral pattern. Also, 56.1% (257 women) of the early-stage group followed a direct referral pattern.

Table 1: Different variables relevant to advanced stage presentation of breast cancer at CMJAH and CHBAH specialised breast units

	Stage at presentation			Pearson Chi square	p-value
	Early	Advanced	Total		
	N=458 (%)	N=550 (%)	N=1008 (%)		
Age group				16.2068	**0.003**
< 40	57 (12.4)	85 (15.5)	142 (14.1)		
>= 40 to < 50	103 (22.5)	139 (25.3)	242 (24.0)		
>= 50 to <60	91 (19.9)	142 (25.8)	233 (23.1)		
>= 60 to <70	105 (22.9)	103 (18.7)	208 (20.6)		
>= 70	102 (22.3)	81 (14.7)	183 (18.2)		
Total	458	550	1,008		
Ethnicity				21.6370	**<0.001**
Of African ancestry	360 (78.6)	491 (89.3)	851 (84.4)		
Others	98 (21.4)	59 (10.7)	157 (15.6)		
Total	458	550	1,008		
Marital status				1.7009	0.637
Single	107 (23.4)	140 (25.5)	247 (24.5)		
In a relationship / married	190 (41.5)	237 (43.1)	427 (42.4)		
Divorced	43 (9.3)	44 (8.0)	87 (8.6)		
Widowed	118 (25.8)	129 (23.5)	247 (24.5)		
Total	458	550	1,008		
Highest level of education				7.4236	**0.006**
Completion of Informal / Primary schooling	85 (18.7)	142 (25.9)	227 (22.6)		
Completion of high school / any tertiary education	370 (81.3)	406 (74.1)	776 (77.4)		
Total	455	548	1,003		
Employment status				13.7442	**0.001**
Unemployed	196 (42.8)	267 (48.5)	463 (45.9)		
Employed	128 (27.9)	177 (32.2)	305 (30.3)		
Retired	134 (29.3)	106 (19.3)	240 (23.8)		
Total	458	550	1,008		

Household socio-economic score					**<0.001**
(score 0-6), median (IQR-Interquartile range)	4 (3-5)	4 (2-5)	4 (2-5)		
Body mass index (BMI)				4.1702	0.124
Underweight and normal	77 (18.0)	118 (23.4)	195 (20.9)		
Overweight	112 (26.2)	120 (23.8)	232 (24.9)		
Obese	239 (55.8)	266 (52.8)	505 (54.2)		
Total	428	504	932		
Alcohol consumption				3.3414	0.068
No	348 (76.0)	444 (80.7)	792 (78.6)		
Yes	110 (24.0)	106 (19.3)	216 (21.4)		
Total	458	550	1,008		
Smoking				3.4959	0.062
No	390 (85.2)	490 (89.1)	880 (87.3)		
Yes	68 (14.8)	60 (10.9)	128 (12.7)		
Total	458	550	1,008		
HIV status				2.7244	0.099
Negative	371 (81.0)	422 (76.7)	793 (78.7)		
Positive	87 (19.0)	128 (23.3)	215 (21.3)		
Total	458	550	1,008		
Hypertensive				1.5656	0.211
No / Unknown	273 (59.6)	349 (63.5)	622 (61.7)		
Yes	185 (40.4)	201 (36.5)	386 (38.3)		
Total	458	550	1,008		
Intrinsic sub-type				18.7126	**<0.001**
Luminal A	106 (23.4)	73 (13.4)	179 (17.9)		
Luminal B	263 (58.1)	338 (62.0)	601 (60.2)		
HER2-nriched	25 (5.5)	43 (7.9)	68 (6.8)		
Triple negative	59 (13.0)	91 (16.7)	150 (15.0)		
Total	453	545	998		
Bloom-Richardson histological grade				38.2897	**<0.001**
1	41 (9.6)	16 (3.1)	57 (6.0)		
2	239 (56.0)	232 (45.0)	471 (49.9)		
3	147 (34.4)	268 (51.9)	415 (44.0)		

Total	427	516	943		
Knowledge of breast cancer					**<0.001**
score (0-9), median(IQR)	7 (5-8)	6 (3-7)	7 (5-8)		
Prior clinical breast examination				2.2292	0.135
None/self	345 (75.3)	436 (79.3)	781 (77.5)		
Clinician	113 (24.7)	114 (20.7)	227 (22.5)		
Total	458	550	1,008		
Clinic waiting time as a barrier				1.9421	0.163
No	432 (94.3)	529 (96.2)	961 (95.3)		
Yes	26 (5.7)	21 (3.8)	47 (4.7)		
Total	458	550	1,008		
Distance to unit				5.1934	0.075
<10km	178 (38.9)	185 (33.6)	363 (36.0)		
10-20km	96 (21.0)	105 (19.1)	201 (19.9)		
>20km	184 (40.2)	260 (47.3)	444 (44.0)		
Total	458	550	1.008		
Time to presentation to the health system				23.3451	**<0.001**
< 1 month	303 (66.2)	296 (53.8)	599 (59.4)		
1-3 months	67 (14.6)	75 (13.6)	142 (14.1)		
>3 months	88 (19.2)	179 (32.5)	267 (26.5)		
Total	458	550	1,008		
Number of visits prior to presentation to the tertiary hospital				0.2228	0.895
0-1	26 (5.7)	35 (6.4)	61 (6.1)		
2	75 (16.4)	91 (16.5)	166 (16.5)		
>= 3	357 (77.9)	424 (77.1)	781 (77.5)		
Total	458	550	1,008		
Referral pattern				16.0227	**<0.001**
Direct: - Self-referral - General practitioner - Primary care clinic	257 (56.1)	239 (43.5)	496 (49.2)		
Indirect: - Another hospital - Specialist	201 (43.9)	311 (56.5)	512 (50.8)		
Total	458	550	1,008		

4.2 Bivariate analysis

The referral pattern was statistically significant between indirect referral patterns (patient referred from another hospital or specialist) and an advanced stage at presentation; p<0.001 on bivariate analysis (Odds ratio (OR)=1.66, 95%, confidence interval (CI) 1.30-2.14). Of the 1008 participants 512 (50.8%) has an indirect referral pattern. Patients who follow the indirect referral pattern were 66% more likely to present with advanced breast cancer as compared to those who have a direct referral pattern (self-referral, primary care clinic, general practitioner).

Even though there was an increase amount of advanced presentation with patients living more than 20km away (OR=1.36, 95%CI 1.03-1.28) this was marginally significant on bivariate analysis (p=0.074). Sub-grouping and analysing separately for the breast units at CMJAH and CHBAH also did not show a statistically significant correlation between stage at diagnosis and distance to unit.

On bivariate analysis, women younger than 40 years were more likely to present with advanced breast cancer as compared to those older than 70 (OR=1.87, 95%CI 1.20-2.93, p=0.003). A woman younger than 40 years was almost twice as likely to have stage III or IV disease as someone older than 70.

Women of African ethnicity were almost 30% more likely to present with advanced stage disease as compared to other ethnicities (p<0.001, OR=2.26, 95%CI 1.56-3.27).

Level of education was also significant as patients with informal schooling or primary school completion were more likely to present with advanced stage breast cancer as compared to those with a higher level, completed high school or tertiary education (OR=1.52, 95%CI 1.12-2.06, p=0.006).

Employment status showed that unemployed women had a 72% higher chance of having advanced stage disease as compared to those that were previously employed and are now retired (OR=1.72, 95%CI 1.26-2.36, p=0.001). It also demonstrated that women who are employed had a similar increased presentation of advanced stage disease as compared to retired women (OR=1.74, 95%CI 1.24-2.46, p=0.001). This

links in with findings regarding age at presentation mentioned earlier, as retired women tend to be of more advanced age.

Histological sub-typing was significant on bivariate analysis. Triple negative breast cancer and HER2-enriched breast cancer were both significantly more likely to present with advanced disease as compared to luminal A breast cancers, 1.24 and 1.50 times more likely respectively (OR=2.24, 95%CI 1.49-3.49, p<0.001, and OR=2.50, 95%CI 1.41-4.44, p<0.001). Luminal B breast cancers were also at increased risk, 87% higher than luminal A breast cancers but not to the same extend (OR=1.87, 95%CI 1.33-2.62).

Higher histological Bloom-Richardson grade was associated with advanced presentation with grade III disease being more than three times as likely to be advanced stage disease as compared to those with grade I histological grade (OR=4.67, 95%CI 2.53-8.61, p<0.001). In keeping with that those with grade II disease were more than twice as likely to have advanced stage breast cancer as compared to grade I disease (OR=2.49, 95%CI 1.36-4.56, p<0.001).

Marital status, body mass index, alcohol consumption, smoking, co-morbidities such as a positive HIV status or hypertension had no influence on stage at presentation on bivariate analysis. Clinic time as a barrier as perceived by the patient was not associated with advanced stage disease. The number of visits in the health system for the presenting problem prior to coming to the breast unit also had no statistically significant influence on the stage at presentation.

Table 2: Bivariate analysis of selected variables linked to advanced presentation of breast cancer at CMJAH and CHBAH

Variable	Bivariate analysis	
	OR (95%CI)	p-value
Referral pattern		**<0.001**
Direct: - Self-referral - General practitioner - Primary care clinic	1.00 (reference)	
Indirect: - Another hospital - Specialist	1.66 (1.30-2.14)	

Distance to unit		0.074
<10km	1.00 (reference)	
10-20km	1.05 (0.75-1.49)	
>20km	1.36 (1.03-1.80)	
Age group		**0.003**
< 40	1.88 (1.20-2.93)	
>= 40 to < 50	1.70 (1.15-2.50)	
>= 50 to <60	1.96 (1.33-2.91)	
>= 60 to <70	1.24 (0.83-1.84)	
>= 70	1.00 (reference)	
Ethnicity		**<0.001**
Of African ancestry	2.27 (1.60-3.22)	
Others	1.00 (reference)	
Highest level of education		**0.006**
Completion of Informal / Primary schooling	1.52 (1.12-2.06)	
Completion of high school / any tertiary education	1.00 (reference)	
Employment status		**0.001**
Unemployed	1.72 (1.26-2.36)	
Employed	1.79 (1.24-2.46)	
Retired	1.00 (reference)	
Intrinsic sub-type		**<0.001**
Luminal A	1.00 (reference)	
Luminal B	1.87 (1.33-2.62)	
HER2-enriched	2.50 (1.40-4.44)	
Triple negative	2.24 (1.44-3.49)	
Bloom-Richardson histological grade		**<0.001**
1	1.00 (reference)	
2	2.49 (1.36-4.56)	
3	4.67 (2.53-8.61)	

4.3 Multivariate analysis

Factors associated with advanced stage breast cancer on bivariate analysis were further analysed with multivariate analysis. These included age, ethnicity, intrinsic sub-typing, Bloom-Richardson histological grade, knowledge of breast cancer and level of education.

Referral pattern was statistically significant on multivariate analysis. Patients with an indirect referral pattern were 50% more likely than direct referral patterns to present with advanced disease (OR=1.49, 95%CI 1.13-1.97, p<0.001).

Table 3: Multivariate analysis of referral pattern of breast cancer at CMJAH and CHBAH

Variable	Unadjusted		Adjusted*	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Referral pattern		**<0.001**		**<0.001**
Direct: - Self-referral - General practitioner - Primary care clinic	1.00 (reference)		1.00 (reference)	
Indirect: - Another hospital - Specialist	1.66 (1.30-2.14)		1.49 (1.12-1.97)	

*Adjusted for age, ethnicity, level of education, intrinsic sub-type, histological grade, prior knowledge of breast cancer and time to presentation to the health system.

5. DISCUSSION

5.1 Discussion of results

Referral patterns and geographical distance:

The most notable finding of this study is related to referral patterns. Referral patterns had a significant influence on stage at initial presentation with patients indirectly referred (from a secondary hospital or another specialist) at a 50% higher chance of having advanced stage disease, regardless of other factors associated with delayed presentation. Ironically, avoiding the established health system patterns results in improved patient care.

Current referral patterns in the public sector prescribe that a woman with a primary health care problem, such as a breast lump, will present to her clinic first. She will then be referred to a regional facility which may delay her access to care (26). Since direct referral to specialised breast units, including primary care clinics, is associated with earlier stage disease at presentation, this study motivates for better access to primary care facilities across the country as well as direct access to specialised breast units.

There is a clear need for streamlining the care of a patient to minimise delays and facilitate the earlier access to a specialised breast unit. Simplified referral dictates that patients should be directly referred to a specialised breast unit from all access points in the health care system, such as the primary care clinics, general practitioners, or other hospitals. A policy should be implemented in which all patients presenting with a breast lump above a certain age would be referred directly to the next clinic at the specialised breast unit.

Access can be further simplified by allowing an open-door policy at all breast units. With an increasing patient burden the unit will subsequently grow to meet the needs of the population being served. Public awareness should be improved regarding these available services. As most other disciplines with specialised units do not follow an open-door policy most of the population would not be aware that the units are available free of referral.

Further research is required to identify potential causes for advanced presentation from indirect referrals. Since the number of previous visits before presentation to tertiary hospital was not statistically significant, it is unlikely to have been due to referral to multiple hospitals before arriving at either specialised breast units. Other potential contributing factors could include time delays for investigations outside of the specialised breast unit. For example, a histology specimen may be sent from the regional centre to the hospital where the specialised breast unit is located. This sample would not be fast-tracked, and results would be checked again at the referring facility only to refer the patient to the specialised unit again. With limited resources, patients would also experience delays in obtaining radiological investigations whereas in a specialised breast unit there is a dedicated mammography unit. Additionally, the delay could also be due to time in between visits.

Geographical distance did not demonstrate a statically relevant relationship to the stage at presentation in this study. This contrasts with a previous study from CHBAH that showed women who presented to the breast unit with advanced stage disease lived further away (24). The initial CHBAH study's cohort included patients enrolled from 2006 and 2012 (24). Distances were divided into <20km and >20km and was found to be significant if the patient lived >20km; a cumulative effect was also noted with and increased risk for advanced disease for every 30km (24).

Even though the majority of our study's cohort included patients from CHBAH, the CMJAH population contributes significantly to the study. Urban settings such as CMJAH are different from peri urban CHBAH and therefore distances could be more easily accessible for a patient from within an urban setting due to improved access to transport (28). However sub-grouping and analysing separately for the breast units at CMJAH and CHBAH also did not show any correlation between stage at diagnosis and distance to unit for the <10km, 10-20km and >20km distances.

An option that has not been explored is adjusting distances to a linear model, comparing to the stage at presentation, which could show a relative risk increase with increasing distance. Another possibility is that socio-demographic improvements,

advances in technology and transport systems mean that distance simply does not play the role it previously did.

Other factors predicting stage at presentation:

Age, ethnicity, level of education and employment status were all socio-demographic factors that were relevant to stage at initial presentation. Additionally, histological factors in terms of Bloom-Richardson grading and intrinsic sub-typing also influenced the stage at presentation.

Tumour biology in younger women tend to be more aggressive, as demonstrated in this cohort. Hereditary breast cancer plays a bigger role in younger patients as compared to luminal cancers in the older population. Furthermore, a lack of health seeking behaviour and screening can contribute to a delay in diagnosis. There is a need for further investigation of this vulnerable group, considering their unique risk factors and strategies to detect cancer earlier.

BMI, smoking, and alcohol usage were not statistically significant on bivariate analysis. These are considered risk factors for breast cancer but are not relevant to the initial stage at presentation in this cohort (6,32–35). Most of this cohort (79.1%) were overweight or obese and therefore BMI could not be compared on bivariate analysis and could not be associated with stage of disease.

Most of the cohort, 781 (77.5%), had three or more visits in the health system before presentation to the specialised breast units. This was similar in both the early and advanced groups. Even though there was no statistically significant difference in number of prior visits and stage at presentation, it is concerning to note that a patient has potentially unnecessary visits putting strain on the health system and delaying definitive management.

Decreasing stage at presentation and centralised care:

Patients clearly experience barriers to care in our urban and peri-urban setting in Johannesburg with most women (55.0%) presenting with advanced disease. However, these figures are lower in comparison to previously reported data. A study conducted at

CHBAH looking at breast cancer presentations between 2006 and 2012 indicated that 60% of patients presented with advanced stage breast (38). Furthermore, a 2001 study from Johannesburg indicated that 77.0% of patients of African descent presented with advanced disease (36,37).

The decrease in stage at presentation could be indicative of the functioning breast units at CMJAH and CHBAH as well as socio-economic development, patient awareness and health seeking behaviour despite an increasing cancer burden. A study conducted at CHBAH demonstrated a significant improvement in proportionate early-stage presentations 30% to 50% over a 6 year period from 2007 to 2012 (38).

Although these findings are encouraging, they still fall way short of an up to 90% early-stage presentation reported by high income countries (1,39). Here the lack of population-based screening methods needs to be taken into consideration as this results in only symptomatic patient presentations, and therefore a more advanced stage at presentation. This differs from high income countries where disease detected on screening result in patients often presenting while still asymptomatic.

The need for specialised care at dedicated specialised breast units is apparent and patients with earlier access and direct referral patterns present at an earlier stage. With very few specialised breast units in South Africa, exclusively located in peri-urban and urban settings, and a growing population of more than 50 million, dedicated breast cancer care is a scarce resource.

It is important that more centres are established to allow access to more patients and this will reduce costs to the health system, allow patients to get different therapeutic and investigatory services at one central location and promotes specialisation and research opportunities (40). Benefits demonstrated in first world studies include an increase in earlier stage presentation, breast conserving surgeries and improved survival in advanced stage diagnoses (40,41).

5.2 Recommendations

- An open referral policy allowing for direct referral of a patient from a primary health care sitting, as well as allowing self-referral. As numbers grow in patients, the units will grow to meet the needs.
- More specialised breast units would provide improved access with units spaced out.
- Limit work up at the regional breast facility until those units at smaller hospitals are better equipped to deal with breast pathology.
- Educate health care professionals about availability of specialised breast units.
- Educate the community and improve public awareness. Women need to know that there are specialist breast units available, where they are and the services available.
- Simplified access to primary care facilities, which can then refer the patient to the specialised breast units.

5.3 Further research opportunities

- Patients' perspectives should be considered with what they regard as causes for delays in their diagnosis, work-up or management.
- Investigation of other barriers to care and potential strategies to overcome these. Time to referral of patient from a secondary hospital, delays in initial work up done at a secondary hospital, limited access to primary health clinics and general understanding of these systems should all be investigated as reasons for delayed presentation from indirect referral patterns.
- Research into appropriate and effective screening methods and the application thereof in the South African setting.

- It is important to identify modifiable factors that can contribute to better stage at presentation in future studies.

6. CONCLUSION

Referral pattern plays an important role in stage at presentation at specialised breast unit in the public sector in Johannesburg, with those following an indirect referral pattern presenting at an advanced stage of disease.

More work is needed to assure swift access to care, with plans to minimise delays for patients presenting to a breast care facility. This study demonstrates that current referral patterns need to change with easier direct access to specialist breast units.

7. REFERENCES

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and Mortality and Epidemiology of Breast Cancer in the World. Asian Pac J Cancer Prev. 2016;
2. Adeloye D, Sowunmi OY, Jacobs W, David RA, Adeosun AA, Amuta AO, et al. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. J Glob Health. 2018;
3. Wang H, Naghavi M, Allen C, Barber RM, Carter A, Casey DC, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
5. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J cancer. 2019;
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;
7. Brinton LA, Figueroa JD, Awuah B, Yarney J, Wiafe S. NIH Public Access. 2015;144(3):467–78. Available from: http://files/124/Brinton et al. - 2015 - NIH Public Access.pdf
8. Manuscript A. Europe PMC Funders Group The Global Burden of Cancer 2013. JAMA Oncol [Internet]. 2015;1(January 2014):505–27. Available from: http://files/7/Manuscript - 2015 - Europe PMC Funders Group The Global Burden of Cancer 2013(3).pdf
9. Singh E, Sengayi M, Urban M, Babb C, Kellett P, Ruff P. The South African National Cancer Registry: an update. Vol. 15, The Lancet. Oncology. England; 2014. p. e363.

10. De Cock KM, Jaffe HW, Curran JW. The evolving epidemiology of HIV/AIDS [Internet]. Vol. 26, AIDS. AIDS; 2012 [cited 2020 Oct 25]. p. 1205–13. Available from: https://pubmed.ncbi.nlm.nih.gov/22706007/

11. Wadler BM, Judge CM, Prout M, Allen JD, Geller AC. Improving breast cancer control via the use of community health workers in South Africa: A critical review. J Oncol. 2011;

12. Dubey AK, Gupta U, Jain S. Breast cancer statistics and prediction methodology: a systematic review and analysis. Asian Pac J Cancer Prev. 2015;16(10).

13. Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment options, herbal medicines, and socioeconomic determinants. Breast Cancer Research and Treatment. 2017.

14. Moodley J, Cairncross L, Naiker T, Momberg M. Understanding pathways to breast cancer diagnosis among women in the Western Cape Province, South Africa: A qualitative study. BMJ Open. 2016;

15. Edge J, Buccimazza I, Cubasch H, Panieri E. The challenges of managing breast cancer in the developing world - A perspective from sub-Saharan Africa. South African Medical Journal. 2014.

16. Dickens C, Duarte R, Zietsman A, Cubasch H, Kellett P, Schüuz J, et al. Racial comparison of receptor-defined breast cancer in Southern African women: Subtype prevalence and age - Incidence analysis of nationwide cancer registry data. Cancer Epidemiol Biomarkers Prev. 2014;

17. Downing A, Prakash K, Gilthorpe MS, Mikeljevic JS, Forman D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. Br J Cancer. 2007;

18. Brinton LA, Figueroa JD, Awuah B, Yarney J, Wiafe S, Wood SN, et al. Breast cancer in Sub-Saharan Africa: opportunities for prevention. Breast Cancer Res Treat. 2014 Apr;144(3):467–78.

19. Joffe M, Ayeni O, Norris SA, McCormack VA, Ruff P, Das I, et al. Barriers to early presentation of breast cancer among women in Soweto, South Africa. PLoS One.

2018;

20. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. J Clin Oncol. 2001 Sep;19(18 Suppl):125S-127S.

21. Yip CH, Buccimazza I, Hartman M, Deo SVS, Cheung PSY. Improving outcomes in breast cancer for low and middle income countries. World J Surg. 2015;

22. WHO. Cancer Breast cancer : prevention and control. World Heal Organ. 2014;

23. Akuoko CP, Armah E, Sarpong T, Quansah DY, Amankwaa I, Boateng D. Barriers to early presentation and diagnosis of breast cancer among African women living in sub-Saharan Africa. PLoS One [Internet]. 2017 Feb 1 [cited 2022 Feb 20];12(2). Available from: https://pubmed.ncbi.nlm.nih.gov/28192444/

24. Dickens C, Joffe M, Jacobson J, Venter F, Schüz J, Cubasch H, et al. Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: A South African public hospital case series of over 1,000 women. Int J Cancer. 2014;135(9):2173–82.

25. Stapleton JM, Mullan PB, Dey S, Hablas A, Gaafar R, Seifeldin IA, et al. Patient-mediated factors predicting early- and late-stage presentation of breast cancer in Egypt. Psychooncology. 2011 May;20(5):532–7.

26. CLINICAL GUIDELINES FOR BREAST CANCER CONTROL AND MANAGEMENT 2. [cited 2022 Feb 19]; Available from: www.doh.gov.za

27. Cubasch H, Ruff P, Joffe M, Norris S, Chirwa T, Nietz S, et al. South African Breast Cancer and HIV Outcomes Study: Methods and Baseline Assessment. J Glob Oncol [Internet]. 2017;3(2):114–24. Available from: http://ascopubs.org/doi/10.1200/JGO.2015.002675

28. UNICEF, UN General Assembly. Convention on the rights of a child. United Nations, Treaty Series. 1989.

29. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Int J Surg.

2014;

30. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999;

31. G van Brummelen. Heavenly Mathematics: The Forgotten Art of Spherical Trigonometry - Glen Van Brummelen - Google Books [Internet]. New Jersey: Princeton University Press; 2013 [cited 2019 Aug 4]. Available from: https://books.google.co.za/books?id=0BCCz8Sx5wkC&pg=PR7&redir_esc=y#v=onepage&q&f=false

32. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer [Internet]. 2015;136(5):E359–86. Available from: http://files/142/Ferlay et al. - 2015 - Cancer incidence and mortality worldwide Sources, methods and major patterns in GLOBOCAN 2012(2).pdf

33. Reynolds P. Smoking and breast cancer. Journal of Mammary Gland Biology and Neoplasia. 2013.

34. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, et al. Alcohol, tobacco and breast cancer - Collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. Br J Cancer. 2002;

35. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet (London, England) [Internet]. 2008 [cited 2022 Feb 19];371(9612):569–78. Available from: https://pubmed.ncbi.nlm.nih.gov/18280327/

36. Lince-Deroche Sarah Rayne ii N, Craig van Rensburg Carol Benn ii iii, Sithabiso Masuku Pearl Holele iv iii, Helen Joseph Hospital iii. S A H R 2 0 t h E d i t i o n.

37. Fregene A, Lisa A, Newman MPH, Newman LA. Breast Cancer in Sub-Saharan Africa: How Does It Relate to Breast Cancer in African-American Women? 2005;

Available from: www.interscience.wiley.com

38. Murugan N, Dickens C, Pisa P, McCormack V, Joffe M, Jacobson J, et al. Down-staging of breast cancer in the pre-screening era: Experiences from Chris hani Baragwanath academic hospital, Soweto, South Africa. South African Med J. 2014;

39. Unger-Saldaña K, Miranda A, Zarco-Espinosa G, Mainero-Ratchelous F, Bargallõ-Rocha E, Miguel Lázaro-Leõn J. Health system delay and its effect on clinical stage of breast cancer: Multicenter study. Cancer [Internet]. 2015 Jul 1 [cited 2022 Feb 20];121(13):2198–206. Available from: https://pubmed.ncbi.nlm.nih.gov/25809536/

40. Kemeny MM. The effect of centralizing breast cancer care in an urban public hospital. J Community Support Oncol. 2017 Sep 1;15(5):e263–7.

41. Chu KC, Tarone RE, Kessler LG, Ries LAG, Hankey BF, Miller BA, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst [Internet]. 1996 Nov 6 [cited 2022 Feb 20];88(21):1571–9. Available from: https://pubmed.ncbi.nlm.nih.gov/8901855/

Appendix A: List of abbreviations

BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ER	Oestrogen Receptor
FISH	Fluorescence In Situ Hybridization
HER2	Human Epidermal Growth Factor Receptor-2
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IQR	Interquartile range
NDoH	National Department of Health
PR	Progesterone Receptor
SABCHO	South African Breast Cancer and HIV Outcomes
STROBE	Strengthening and Reporting of Observational Studies in Epidemiology
WHO	World Health Organisation

Appendix B: Haversine's formula

Haversine's formula is used to calculate a linear distance between two points on a sphere.

$$d = 2r \arcsin\left(\sqrt{\operatorname{hav}(\varphi_2 - \varphi_1) + \cos(\varphi_1)\cos(\varphi_2)\operatorname{hav}(\lambda_2 - \lambda_1)}\right)$$
$$= 2r \arcsin\left(\sqrt{\sin^2\left(\frac{\varphi_2 - \varphi_1}{2}\right) + \cos(\varphi_1)\cos(\varphi_2)\sin^2\left(\frac{\lambda_2 - \lambda_1}{2}\right)}\right)$$

- d: linear distance calculated between patient's residential address and specialised breast unit
- r: radius of the Earth (average 6371km)
- latitude φ1: Patient's residential address, latitude
- longitude λ1: Patient's residential address, longitude
- latitude φ2: specialised breast unit, latitude
- longitude λ2: specialised breast unit, longitude (31)

Appendix C: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Catharina Pothas et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1711121

NAME: (Principal Investigator)	Dr Catharina Pothas et al
DEPARTMENT:	Surgery Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Role of Geographical Distance and Referral Patterns on Stage at Presentation in South Africa - A Review of Two South African Breast Units
DATE CONSIDERED:	Ad Hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M150351 Dr Herbert Cubasch
SUPERVISOR:	Dr Sarah Nietz
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/02/2018

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 Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES