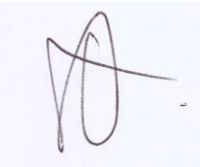
THE PROFILE OF MALE BREAST CANCER PRESENTING TO THE ACADEMIC (TERTIARY) HOSPITALS OF THE UNIVERSITY OF WITWATERSRAND

Kavitha Chetty

Declaration:

I, Kavitha Chetty (Previously: Naidoo), (student number:1032795) declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of general Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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Signed at …….Johannesburg...on …17th……. day……November…….2021.

Acknowledgements:

I would like to sincerely thank my supervisors Prof A. Manell who has painstakingly supported me throughout this process and Dr C Nel. A debt of gratitude to the Surgical Statistics Hub and Prof D. Kruger without whom this dissertation could not have been possible.

Dedication:

To my husband, Lielan Chetty who provided the support to complete this work.

To my sister, Aneka Divyarupa Naidoo who always opened her home to me to write and study.

To my children, Aryanna Emma Chetty and Rahul Obi Chetty who were the ultimate motivation needed to complete this work.

I am forever indebted.

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Abbreviations

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBAH	Chris Hani Baragwanath Academic Hospital
HJH	Helen Joseph Hospital
ER	Oestrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
Ki-67	Ki- 67 proliferation index
BC	Breast cancer
mBC	Male breast cancer
fBC	Female breast cancer
SEER	Surveillance Epidemiology and End Results
USA	United States of America
UK	United Kingdom
RSA	Republic of South Africa
BRAC	Breast cancer gene
CANSA	Cancer Association of South Africa

NHLS	National Health Laboratory Services
TNBC	Triple negative breast cancer
FISH	Fluorescence in situ hybridization
Wits HREC	Human Research Ethics Committee (Medical), University of the Witwatersrand

Contents

1.ABSTRACT

Background:

Male breast cancer, although rare, is a public health concern in South Africa. Studies have shown that there is an increasing trend, internationally, with a more advanced stage of presentation of male breast cancer than female breast cancer.

Objectives:

To identify the profile of male patients presenting with male breast cancer at the academic hospitals of the University of the Witwatersrand.

Methods:

The following is a retrospective review of male patients with breast cancer presenting to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath and Helen Joseph Hospital (HJH) from the period 1 January 2006 and 31 December 2016. Variables captured included: date of birth, race, ER, PR, Ki-67, HER2, hospital name, patient hospital number, specimen episode number and date of specimen logged. Data was collected on a Microsoft excel spreadsheet. Analysis was performed using STATA® Statistics/Data analysis program. Kruskal-Wallis equality of populations rank test, enumerating sample-space combinations, Fisher's exact, Mann-Whitney test, tabulation and observing frequency were performed.

Results:

This series included 154 cases, with most cases being from CMJAH (55.2%). Patients self-identifying as belonging to black race accounted for 79.1% with a median age of 63. The oestrogen receptor status was positive in 93.4% and progesterone in 87.3%; 86,4% of cases were positive for both oestrogen and progesterone receptors. The HER2 receptor status was positive in 13.1% of cases. Analysis of Ki-67 status revealed records for 45 of 154 cases. Of significance is the assessment of the subgroup with a high Ki-67, 34 (75.5%) of all Ki-67 had a value of 14% or above. When assessing intrinsic subtypes, it was reported that 94.8% of patients were a luminal subtype while 5.21% of patients were of the triple negative subtype.

Conclusion:

Although rare, mBC is an important health concern with series indicating an increasing trend in prevalence, with patients presenting at more advanced stages. As precision medicine becomes the standard of care in cancer management, there is a need for further studies and standardisation of receptor subtyping for male patients. All variables including age, race, risk factors, hormonal subtyping and response to treatment must be recorded to tailor mBC care as is routine for fBC.

2.BACKGROUND

Due to the rarity of male breast cancer (mBC), there is significantly less information available compared to female breast cancer (fBC). Most information available either comes from small international studies or has been extrapolated from studies done on fBC.

Current literature indicates an increasing trend in incidence of mBC internationally and that disparities of biology exist based on ethnicity. Further, there is a dearth of documented evidence from Sub-Saharan Africa.

This study hypothesises that there is a difference in incidence and disease profile in the male South African population compared to their western counterparts.

This study aims to examine the male breast cancer cases presenting at the Witwatersrand Academic tertiary hospitals and hopes to provide a foundation for further studies into mBC.

3.INTRODUCTION

Male breast cancer is rare and accounts for 0.5 - 1% of all breast cancer cases in the United States of America (USA) and United Kingdom (UK) (1) (2). The first documented cases of mBC appeared in the literature in 1843 and came from the post-mortem finding of five Parisian men from 1830 to 1840 (3). Since then, there has been a gradual increase in the number of reported cases (4). This increasing incidence is supported by data from the Surveillance Epidemiology and End Results (SEER) report from 1973 until 1998 that showed firstly, that incidence had increased from 0,86 to 1,08 per 100,000 population (USA) (3) and secondly, that a racial disparity existed that favoured higher incidences in the Afro-American population compared with the white Hispanic/non-Hispanic population, the converse of which is true in American woman with breast cancer (3). Similar results with regards to increasing incidence are found on review of UK cancer research database. (2).

Studies have further shown that black patients with mBC tend to have a more aggressive course with a different less favourable hormonal receptor expression when compared to their white counterparts (5). Black mBC like black fBC have a poorer 5-year survival rate even when adjusted for stage (4). This may in part be attributed to differences in socio-economic status (6).

MBC, like fBC has been linked to increasing age, with an approximately 10-year older presentation in male counterparts (7). There remain important differences between the

sexes. MBC is almost exclusively hormone receptor positive and is associated with an increased prevalence of BRCA2 germline mutation (8).

On review of data available from African countries, there is a notable increased incidence of mBC compared to the Western population (9). In Nigeria a review of a 20-year series reported a yearly incidence of 1.2 per 100,000 population was reported. It should be noted that the study population however was small, with only 73 cases documented (10). MBC accounts for up to 9% of cancer in men in Tanzania (9), while in Zambia it accounts to 15% of malignancies (9). Data from Uganda has also shown an increasing incidence of 6.2% (11). Male: female ratio in breast cancer is substantially higher in Africa compared to Western countries, particularly in sub-Saharan Africa compared to North Africa (11). Endemic infective agents, namely hepatitis B virus and schistosomiasis, are thought to increase the risk of mBC (12) by impairing liver function and reducing degradation of oestrogen.

The key areas of significance when discussing mBC are risk and prognostic factors. Risk factors may be divided into two key categories: (13) these are: family history/genetics and alternations of the oestrogen: androgen ratio of affected men.

As with fBC, a first degree relative with breast cancer is an identifiable risk factor for mBC (4). This has been reported to increase the risk by as much as 15- 20% depending on the study reviewed (4). When compared to the sporadic occurrence in the general population of 7% (13).The link between fBC and mutations in BRCA1/BRCA2 has been established: 30-86% of inherited fBC are estimated to be linked to an underlying germ line mutation. The incidence of mBC with a genetic mutation has been found to be 4 - 40% (4). The

association of inherited mBC is strongly related to BRCA2 mutation and much less frequently BRCA1 (13).

Alterations of the oestrogen: androgen ratio have been noted in men with mBC. The increase in circulating oestrogens whether exogenous or endogenous has been linked to increased rates of mBC. (13). Obesity results in an increase in endogenous oestrogen. With the global obesity rates having almost tripled in the last 46 years (14). With South Africa (RSA) ranked as 30th in the 2016 global obesity level with 28.3% of the adult population being classified as obese (15).

As with fBC, tumour size and nodal status are the most important prognostic factors in mBC. The hormonal receptor profile of fBC is a key element for treatment planning and influences the rate of disease progression and overall survival. In men, receptor positivity appears to have the same therapeutic significance. Further studies are needed to investigate the response of mBC patients to anti-oestrogen therapy. Currently, males with hormonal receptor positive disease are treated in a similar manner to females with hormonal receptor positive breast cancers (7).

Afro-American men and black African men with mBC frequently present with larger tumours of higher grades, node positive disease and hormone receptor negative status more often when compared to their white counterparts (3). Factors that could contribute to the increasing risk of black men for aggressive diseases include the following : genetic vulnerability, poor socio-economic status (3) and disadvantages in health and education (10). Where there is a background of liver pathology it is hypothesised that elevated circulating oestrogens play a pivotal role (12).

Survivorship is related to bio-psychosocial factors. Biologically, nodal status, the grade of tumour at presentation together with hormonal receptor status are strongly linked to prognosis. Other considerations are that males often present with an advanced disease and are older at presentation, with age being linked to co-morbidities. The social stigma attached to mBC can also be linked to delayed presentation (16). In addition, intolerable side effects of hormonal therapies such as erectile dysfunction and hot flushes has been linked to discontinuation of hormonal therapy. It is therefore likely that the issues related to survivorship are multi-factorial (16).

In 2009, South African cases were documented by the Cancer Association of South Africa (CANSA) were reported as 110, accounting for 0.41% of all cancers. (17). A higher rate of incidence was noted in the black population group (0.63%) when compared to their coloured (0.30%), asian (0.29%) or white (0.25%) counterparts (17). In 2015, mBC was ranked 22nd as cause of male cancer compared to 27th in the 1993-1995 summary statistics. (CANSA). Since then, in 2017, incidence of mBC was reported as 194, accounting for 0.49% of all cancers. Again, a higher rate was noted in the black population group (0.80%) (17).

A recent retrospective review of patient records from two hospitals in Johannesburg over a 5-year period (2007 - 2012) revealed that only 23 cases of male breast cancer were identified from a total of 3000 breast cancer cases, of which 44% were of black ethnicity. Invasive ductal carcinoma accounted for 83% of cases. The stages at presentation were Stage 0: 9%, Stage 1: 13%, Stage 2: 52%, Stage 3: 26%. No patients had metastatic disease in this review (18).

4.AIMS AND OBJECTIVES

I. To provide a demographic profile of the adult male patient presenting at the breast clinics at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH) between 01 January 2006 and 31 December 2016.

II. To determine the incidence of male breast cancer seen at CHJAH, CHBAH and HJH breast clinics between 01 January 2006 and 31 December 2016.

III. To determine the receptor profile which include oestrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2) and Ki-67 proliferative marker (Ki-67) of male breast cancer seen at CHJAH, CHBAH and HJH.

5.METHODOLOGY

This was a retrospective descriptive study reporting quantitative statistics. All male patients seen at the breast clinics at CHJAH, CHBAH and HJH for breast cancer related diseases during the period from 1 January 2006 and 31 December 2016 have been included.

Variables captured included: date of birth, race, ER, PR, Ki-67, HER2, hospital name, patient hospital number, specimen episode number and date of specimen logged.

Data collection was performed initially by accessing the mammogram records of the radiology department to include all records of male patients and thereafter were cross referenced with corresponding histology specimens though the NHLS laboratory and thereby compiling a datasheet of variables required. This, however, was met with a few hurdles which resulted in data then being collected from the NHLS database by performing a data extraction. This was performed by the principal investigator.

Patient confidentiality was maintained by assigning each patient a study number for data collection purposes. The patients' names were not captured or stored within the study database. Further, the data was collected and stored on a Microsoft Excel spreadsheet on the principal investigator's laptop that was password protected. Microsoft Excel has been used to provide descriptive statistics for the discussion of the results.

Data analysis was performed using STRATA® by means of descriptive statistics generated from Microsoft Excel. Where analytical statistics are required, data was analysed and mean and standard deviation, and/or median and range reported.

Comparison between groups was facilitated using a t-test or Mann Whitney test for continuous variables, and chi squared test for discreet variables. Statical significance was tested by calculation the P- value and the Fisher's exact due to the number of samples tested.

Written permissions to conduct this study was obtained from several departments namely: Chief Executive Officer and Heads of each Breast Unit and Mammography Departments of the respective hospitals and NHLS.

6.ETHICS

The research protocol was submitted to the University of Witwatersrand Human Ethics Research Committee for review and approval. No study participants have been materially rewarded for participation in the study.

Certificate number: M170267

7.FINANCIAL AND OTHER CONSIDERATIONS

There were no conflicts of interests. All expenses for the study were borne by the principal investigator. Confidentiality of patient data was maintained by the means described above.

8.STATISTICAL ANALYSIS

Data was collected on Microsoft excel spreadsheet. Analysis was performed using STRATA®. Kruskal-Wallis equality of populations rank test, Chi-square testing, enumerating sample-space combinations, Fisher's exact, Mann-Whitney test, tabulation and observing frequency were performed. Assistance with statistical analysis was received via the Surgical Stats Hub.

9.RESULTS

This retrospective descriptive study covers all male patients seen at the breast clinics at CMJAH, CHBAH and HJH for breast cancer related diseases during the period 1 January 2006 to 31 December 2016 and includes 154 male breast cancer cases.

When assessing the series per institution most cases were from CMJAH which had 85 patients (55.2%). CHBAH with 35 cases at 22.7% and HJH with 34 cases at 22.1%.

Race was recorded for 67 patients in this series. With South African black race having a frequency of 53 (79.1%). Followed by South African white race of 10 (14.9%) and South African Indian race of 4(5.9%) in this series.

Age was recorded for 149 patients with a median age of 63. The data set was unevenly distributed: the 25th percentile being 52 and the 75th percentile being 70. The oldest patient in the series was 98 and the youngest 24. In Figure 1 it is seen that most patients were in the 60 – 64 age group and that the graph roughly follows the bell curve pattern. (Figure)

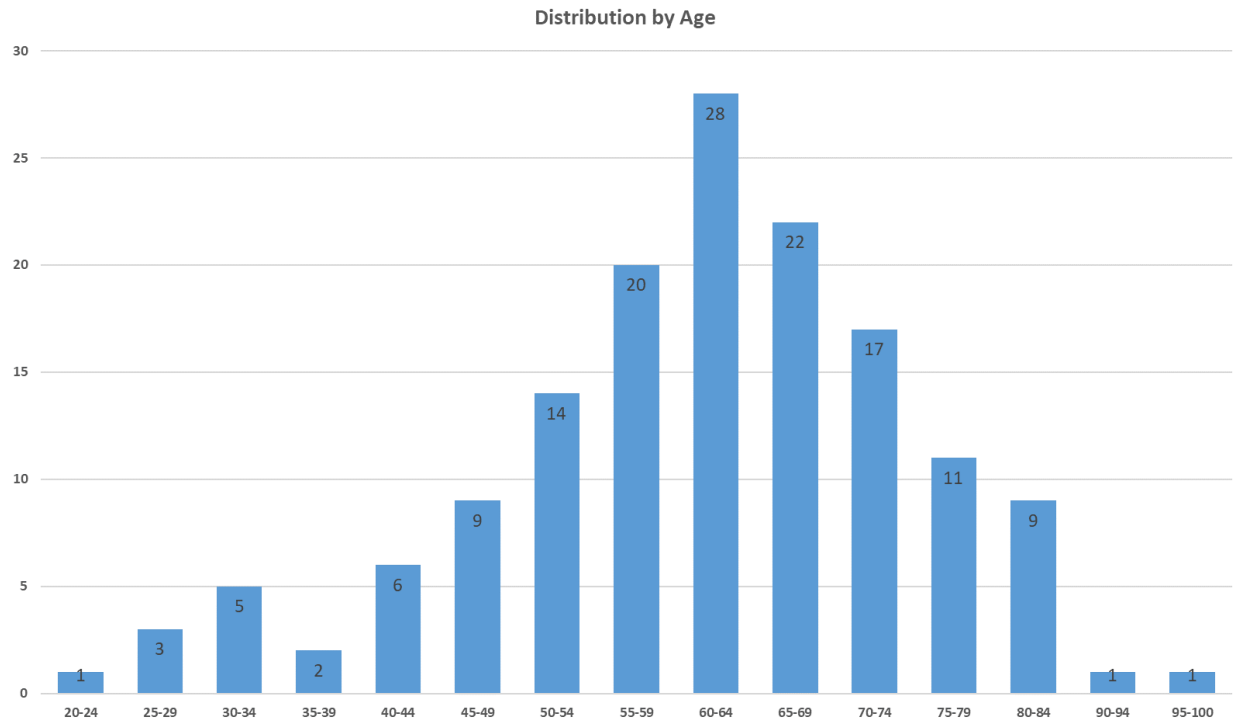

Figure I Distribution per Age

When considering age per institution CMJAH had 83 patients, with a median age of 63. CHBAH had 32 patients, with a median age of 63 and HJH had 34 patients with a median age of 58. Although a trend towards younger age at HJH was observed this was not statistically relevant and therefore no association with age and hospital of origin could be made.

Oestrogen receptor status was recorded for 107 patients. Of the 107 patients, 100 were positive, this accounted for 93.4% of patients. Progesterone receptor status was recorded for 103 patients. Of these 90 were positive, this accounted for 87.3 % of cases. Oestrogen and progesterone receptor status were both available in 103 patients.

Of these 103 cases, 89 were positive for both, accounted for 86,4% of cases.

HER2 receptor status was recorded for 91 patients. Of these 12 patients were positive this accounted for 13.1% of patients.

Ki-67 status was recorded for 45 patients. Of significance was the assessment of the subgroup with a high Ki-67, as defined as 14% or above (19). 34 (75.5%) of all Ki-67 had a value of 14% or above.

Subtype analysis assessment was possible for 96 cases. It was identified that 94.8% of patients were of luminal subtype and 5.21% of patients were triple negative. Luminal subtype was further subdivided into luminal A and luminal B based on HER2 and/or Ki-67. (20) There appeared to be a higher proportion of luminal B compared to luminal A subgroups. Insufficient data was available for further analysis of these subgroups.

No association could be made with regards to oestrogen receptor profile based on hospital. The hospitals had similar percentage of occurrence: CMJAH (92.8%), CHBAH (96.4%) and HJH (91.3%).

Progesterone receptor profile based on hospital, seemed to show a trend towards higher percentage of cases positive at HJH (95.6%) as opposed to CMJAH (88%) and CHBAH (83%). However, the Fisher's exact was 0.418 and no association could be made.

With regards to HER2 status, testing was not consistently applied. However, it is noted that 24% were positive at CHBAH, 9% at CMJAH and 9% HJH.

The median value Ki-67 per hospital were: 27 at CMJAH, 22 at CHBAH and 20 at HJH. Although a trend to a higher KI67 was noted at CMJAH, this was not statistically significant with a probability of 0.095. On further analysis, when considering Ki-67 of 14 or above a higher percentage of this subgroup were noted from CMJAH (86.6%), CHBAH (78.5%) and HJH (62.5%). However, the Fisher's exact was 0.28 and therefore these findings were not statistically significant.

When analysing the KI67 subgroup (14 and above) it is noted that the mean age was 58 years, which is lower than a mean age of 62 in the patients with Ki-67 less than 14%. This indicates a trend for younger patients to have a higher KI67 and therefore a more aggressive tumour, however this was not statistically significant.

The mean age of patients who had a positive oestrogen receptor status was 61.8 (which was higher than the group with negative receptor status of 58.1(not statistically significant). Similarly, the mean age of patients with a positive progesterone receptor status was 61.9 which was higher than the group with a negative receptor status of 57 (not statistically significant).

With regards to subtype and age, the observed number of cases of triple negative BC was 5 and the observed cases of luminal BC was 90. The median age in the triple negative group was 56 compared to the median age in the luminal group of 64. This shows a possible indication that triple negative subtype occurs in younger patients, however, this hypothesis was not borne out with an exact probability of 0.44 making the above finding insignificant.

On subtype based on hospital of origin no association was found.

	ER	PR	HER2	KI	Luminal	Triple Negative
Freqency of Positive Receptor Status	93%	87%	13%	75%	95%	5%
Age (50th Percentile)	64.00	64.00	64.00	64.00	64.00	56.00
CHBAH	27%	24%	50%	32%	27%	20%
CMJAH	52%	51%	33%	38%	48%	60%
HJH	21%	25%	17%	30%	25%	20%

Table I Analysis of Hormonal and Subgroup

Analysis of race was consistent with the areas the hospitals serve. That is, in terms of black race: 96.3% were seen at CHBAH, 76% at CMJAH and 57% at HJH. With white race: 0% were seen at CHBAH, 19% at CMJAH and 31.5% at HJH. Indian race: 3.7% were seen at CHBAH, 4.7% at CMJAH and 10.5% at HJH.

10. LIMITATIONS

Several limitations were identified with regards to this study.

Ethics approval was delayed due to two of the three hospitals which had lost the applications for data access and from poor follow-up by the principal investigator. This resulted in a need for re-application for ethics approval, which was subsequently granted. This too took an extended amount of time to achieve.

It should be noted that once ethics was approved and data collection had started, the HJH mammogram books from the period studied had been damaged in a flood and paper records were unobtainable. Subsequently, data needed to be sourced directly from NHLS which resulted in further delays for permission and extraction of correct data sets required.

Further challenges were due to the time frame studied and the transition in data accessing platforms from DISA to TRACKLAB within NHLS. Furthermore, DISA was not directly accessible by the principal investigator.

It is useful to acknowledge that over the time observed, a shift in clinical practise with greater utilization of a targetted approach in treating breast cancer occurred. Therefore, a more consistent testing of immunohistochemistry occurred later in the period studied. Older data sets have a significant amount of hormonal receptor status missing.

Race was not consistently captured which, in view of the established link between race and breast cancer, was a significant shortcoming in data collection. The incidence was

not possible to calculate as the true denominator value was unobtainable from hospital records a further significant short-coming.

Finally due to the retrospective nature of this study follow-up in terms of treatment pathways, response to therapy and overall survival was notably not possible.

11. DISCUSSION

On analysis of the above findings it is noted that the median age of patients in this series was 63. This is in line with global and RSA data, indicating an average age of presentation approximately 10 years older than their female counterparts (7).

This reflects two dynamics that are at play. Firstly, that age is an important risk factor, with mBC affecting an older population. Secondly, that mBC patients are often delayed in their health seeking behaviour, which has implications in terms of stage at presentation, overall survival and 5-year mortality rates. Health promotion campaigns may go a long way in disseminating information and thereby breaking down some barriers to health seeking behaviour.

Most male breast cancers were oestrogen positive (93.4%) in this series. This reflects global trends and points to the underlying risk factors in terms of oestrogen imbalance as well as confirms possible treatment pathways i.e., hormonal therapy (21)The significance of both oestrogen and progesterone positive receptor status has implications of increased response to hormonal treatment option. Thus, this series shows that 86.4% of patients would have had an increased benefit from hormonal therapy.

Ki-67 rate is one of the pivotal biomarkers in terms of predicting aggressiveness i.e., having a high prognostic value and predictive value in terms of response to therapy.

There are, however, several challenges when considering the Ki-67 rate calculation and interpretation. A full exposition of the controversies surrounding Ki-67 is beyond the scope of this discussion. However, it is worth noting issues with regards to standardisation in

terms of testing, tissue fixation, different antibody clones used, different scoring systems, as well as consensus guidelines with regards to defining cut-off values i.e., what constitutes high or low (22) show great variation globally.

This data series demonstrates that 75.5% of patients have a KI67 of 14 or above and therefore an increased proliferation rate suggesting that peri-operative chemotherapy is a viable option for a significant number of male patients. Although not statistically significant, the data shows a trend towards cancer in younger patients having a higher KI67 and therefore a more aggressive tumour.

Triple negative breast cancer (TNBC) is characterised by the lack of expression of oestrogen, progesterone receptors and HER2 gene over-expression and in fact describes a heterogenous subgroup. TNBC comprises of a particularly interesting subgroup of mBC primarily because of its risk factors, limited treatment strategies and paradoxical response to chemotherapy (23). The range of frequency of TNBC depends on the populations studied with some female West African studies, show very high rates reaching of 50% or more. (24) In South Africa, one series showed a range of between 14 - 16% of fBC which were TNBC. (25) When assessing the frequency of TNBC, it is noted that in the current series there was a rate of 5.21%. This was much lower than expected in view of the established link between race and TNBC. It is likely that both a small sample size as well as the diverse genetic make-up of South Africans may have influenced the lower rates.

MBC management is by and large informed by fBC. Since the 1970s, the management of breast cancer has become increasingly targeted.

	FBC: Soweto Series	MBC: Series
Total	1092	154
Age at diagnosis		
25–39	166	11
40–49	253	15
50–59	278	34
60–69	203	50
70–79	130	28
80–103	62	11
Year of diagnosis		
2006–2007	148	13
2008–2009	391	33
2010–2012	553	55
ER		
Positive	614	100
Negative	352	7
Missing	126	47
PR		
Positive	499	90
Negative	462	13
Missing	131	51
HER2/neu		
3+	245	12
2+	192	14
0–1+	490	66
Missing	165	62
Triple-negative		
Yes	196	5
No	753	90
Missing	143	59

Table II Comparison of Female Breast Cancer: Soweto Series and Male Breast Cancer Series

On review of a South African series of female breast cancer from Soweto of 1092 during the period of 2006 -2012; several interesting comparisons may be drawn of note the majority of cases occurred 10 years younger in the female cohort which is in line with

international series. The oestrogen receptor positive cases were higher in males at 93,4% compared to 63,5%. The progesterone receptor positive cases were also higher in males at 87,3% compared to 51,9%. And finally that triple negative breast cancer was much higher in females at 20,6% compared to 5,26%. (26)

With the landscape of treatment anchored in a patient centred multidisciplinary approach, there is an increasing awareness of the pivotal role that rigorous standardised pathological testing plays in decision making with hormonal receptors, biomarkers and genetic testing informing treatment pathways and pharmaceutical advances. Anti-oestrogen drugs and HER2 inhibitors already have established benefits and significantly improving overall survival (27). The future of treatment is likely to depend on precision medicine and genetic testing to improve the standard of care.

On analysis it is noted that HER2, KI67 or FISH studies were not consistently applied during the period studied in this series. There was a more consistent testing from 2013 onwards. Although understanding and therapeutic approach to breast cancer has changed, it is important to be aware that routine complete hormonal and biomarker testing is not yet the standard of care across South Africa (28).

12. CONCLUSIONS

mBC is a rare disease entity with significant implications for those afflicted. Internationally there is an increasing trend in the incidence and multiple risk factors have been identified. It is imperative that to fully understand and treat the burden in South Africa, incidence in high-risk groups be identified so as to utilise appropriate screening protocols, that routine standard of care histopathology testing be performed and targetted treatment pathways are developed.

13. APPENDIX

14.1 Data Table

Unbid	Hospital	Age	Gender	Race	Subtype C	ER	PR	HER2	KI67
P0001	CHBAH	24	M	B	Luminal A	Y	N	N	N
P0002	HJH	35	M	W	Luminal B	N	Y	Y	Y
.....									
P0250	CMJAH	45	M	I		N	Y	N	Y

14.2 Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Kavitha Chetty (Naidoo)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170267

NAME: (Principal Investigator)	Dr Kavitha Chetty (Naidoo)
DEPARTMENT:	Surgery Breast Clinics at: Helen Joseph Hospital Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Incidence and Profile of Male Breast Cancer Presenting to the Academic (Tertiary) Hospitals of the University of Witwatersrand
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Aylwyn Mannell
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/09/2019

This clearance certificate is valid for 6 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 on the 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 **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

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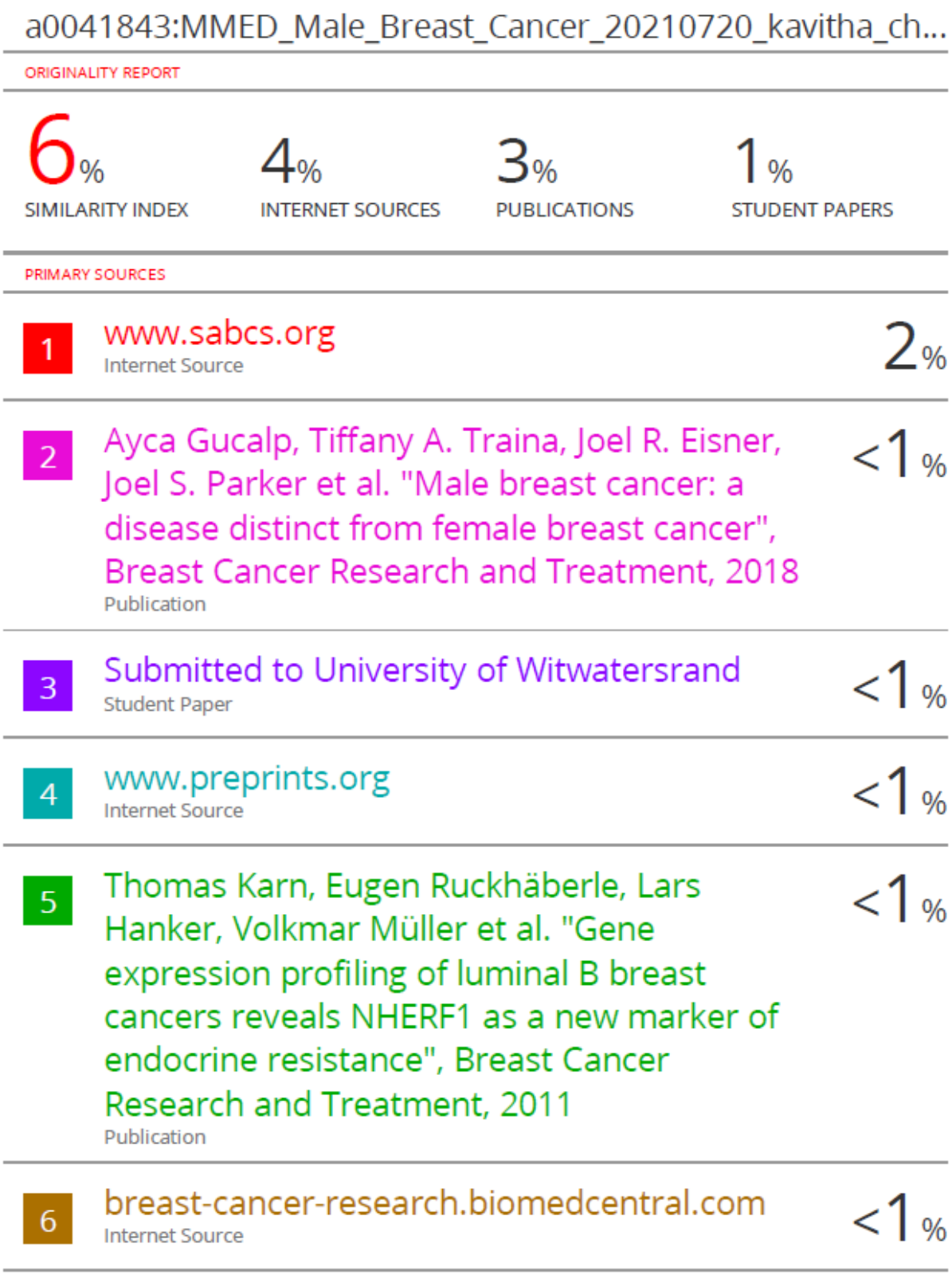

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14. REFERENCES

1. Rebecca , Kimbeley , Ahmedin. Cancer Statistics. Cancer Journal for Clinicians. 2016;: p. 1-41.
2. http://www.cancerresearchuk.org/. [Online].; 2021 [cited 2021 September 17. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero.
3. Humphries , Jordan , Speirs. Obesity and male breast cancer: provocative parallels? BMC Medicine. 2015;: p. 13:134.
4. Weiss , Moysich , Swede. Epidemiology of male breast cancer. Cancer epidemiology, biomarkers and prevention. 2005;: p. 20-24.
5. Hui , Verkooijen , Chia , Kee-Seng , Bouchardy , Eero , et al. Incidence and Outcome of male breast cancer: an international population- based study. Journal of Clinical Oncology. 2011;: p. 1-6.
6. Schwartz B. Race, socioeconomic status and stage at diagnosis for five common malignancies. Cancer Causes Control. 2003;: p. 762-766.
7. Nikolay , Philomena , Nagpal. some aspects of the endocrine profile and management of hormone dependant male breast cancer. the oncologist. 2007;: p. 798-807.
8. Yadaza IB. Male Breast Cancer. Journal of Brest Health. 2016.
9. Contractor. Male breast cancer: is the scenario changing. World J Surg Oncology. 2008;: p. 58-68.
10. Ihekwaba FN. Breast cancer in men in black Africa: a report of 73 cases. J R Coll Surg Edinb. 1994;: p. 344-7.
11. Ndom H. A meta-analysis of male breast cance in africa. The Breast. 2012.
12. Adamu , Yahaya , Adamu , Iliyasu. Management and outcomes of male breast cancer in Zaria, Nigeria. International Journal of Breast Cancer. 2012;: p. 1-6.
13. Gradishar WJ. Breast cancer in men. Uptodate. 2020.
14. WHO. World Health Organization. [Online].; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

15. ProCon.org. ProCon.org. [Online].; 2020. Available from: https://obesity.procon.org/global-obesity-levels/.

16. Ruddy , Winer. Male breast cancer: risk factors, biology, diagnosis, treatment and survivorship. Annals of Oncology. 2013;: p. 24:1434-43.

17. www.cansa.org.za. [Online].; 2021 [cited 2021. Available from: https://cansa.org.za/files/2021/01/Fact-Sheet-on-Breast-Cancer-in-Men-NCR-2017-web-January-2021.pdf.

18. Rayne , Schnippel , Thomson , Reid , Benn. Male Breast Cancer Has Limited Effect on Survivor's Perceptions of Their Own Masculinity. American Journal of Men's Health. 2016.

19. Yip CH. Role of KI657 in Breast Cancer - Important for Management. Asian Pacific Journal of Cancer Prevention. 2016.

20. Inic Z. Difference between Luminal A and Luminal B Subtypes According to Ki-67, Tumor Size, and Progesterone Receptor Negativity Providing Prognostic Information. Clin Med Insights Oncol.. 2014.

21. Alfonso. Male breast cancer: correlation between immunohistochemical subtyping and PAM50 intrinsic subtypes, and the subsequent clinical outcomes. Diagn Pathol. 2017; 12: 20. 2017.

22. Acs B. Ki-67 as a controversial predictive and prognostic marker in breast cancer patients treated with neoadjuvant chemotherapy. 2020.

23. Yin L. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Research volume. 2020.

24. Antoine. High Incidence of Triple-Negative Tumors in Sub-Saharan Africa: A Prospective Study of Breast Cancer Characteristics and Risk Factors in Malian Women Seen in a Bamako University Hospital. Oncology. 2012.

25. Prodehl L. Triple Negative Breast Cancer in South Africa; 2011.

26. Herbert Cubasch MJRHJSAINAKNBEvdBVM&JSJ. Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa. Breast Cancer Research and Treatment. 2013.

27. Kiven. High Incidence of Triple-Negative Tumors in Sub-Saharan Africa: A Prospective Study of Breast Cancer Characteristics and Risk Factors in Malian Women Seen in a Bamako University Hospital. Oncology. 2012.

28. Toma A, Neitz S. Quality of Histopathological Reporting in Breast Cancer. JCO Glob Oncol. 2021.

29. Bhagwandin. Carcinoma of the male breast in Zambia. East Afr Med Journal. 1972;: p. 176–9.

30. Crew , Neugut , Wang , Jacobson , Grann , Raptis , et al. Racial disparities in treatment and survival of male breast cancer. Journal of clinical oncology. 2007;: p. 1089-98.