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Characteristics of patients choosing contralateral prophylactic mastectomy for unilateral breast cancer in an urban South African breast cancer clinic

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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 of Master of Medicine

Johannesburg 2021

DECLARATION

I, Phumudzo Ndwambi (0601685M), declare that this research report is my own work. It is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.



13 October 2021 in Johannesburg

DEDICATION

To Nelly Ndwambi, your legacy lives on beyond your wildest dreams.

PRESENTATIONS ARISING FROM THIS STUDY

Presentation of Protocol and provisional results at Wits University Department of Surgery academic meeting 28 February 2018.

ABSTRACT

Background: International trends have shown that female patients with unilateral breast cancer are electing bilateral mastectomies as a method of prophylaxis.

Objectives: The aim of the study was to determine the prevalence of unilateral mastectomies with and without contralateral prophylactic mastectomy (CPM) in one breast clinic service, as well as to identify the demographic and pathological characteristics which predict for the choice of CPM.

Patients and methods: A record review of pathological results and demographic details of female patients of all ages undergoing mastectomy for unilateral breast cancer from 2013-2015 was conducted at the Helen Joseph Breast Care Clinic in Johannesburg, South Africa, to compare patients who underwent a unilateral mastectomy without CPM to those that chose a mastectomy with CPM. The demographic information analysed included race, uniform patient fee scale (UPFS), or 'H' status, and age. The pathology of the breasts was analysed by weight of the breast, histology and TNM stage (early vs late) of the tumour and any histological findings of the contralateral side, as well as having received neoadjuvant therapy.

Results: In total, 299 women who had mastectomies for unilateral breast cancer were included in the study, 59 of whom also had CPM (19.7%). Significantly more White women opted for a CPM compared to Black women (43.5% vs 10.6%, respectively; $p<0.0001$). The women who underwent CPMs had a trend for larger median weight of the breasts and were significantly younger than their unilateral counterparts ($p=0.09$ and $p=0.03$, respectively). There was no significant association for 'H' status, histology of tumour, TNM stage or neoadjuvant chemotherapy that predicted the choice of unilateral mastectomy vs mastectomy with CPM.

Conclusion: The demographic and histopathological characteristics influencing choice of CPM in our local population, although mirroring those of international literature in terms of race and age, are uniquely based on the special socio-economic circumstances of the country. Whether the trend of electing CPM when diagnosed with unilateral breast cancer is likely to increase is uncertain but there is evidence that young, White women of better economic status are more likely to have this procedure. Currently there does not seem to be an influence in the proportion of women electing CPM based on international trends, this is advantageous in that it is in keeping with maintaining a primarily evidence-based indication to performing a CPM on patients with unilateral breast cancer.

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AFFILIATIONS

Department of Surgery at Wits University, Helen Joseph Hospital and Milpark Breast Unit.

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LIST OF ABBREVIATIONS

BRCA – Breast Cancer gene

CPM – Contralateral Prophylactic Mastectomy

SES- Socioeconomic Status

UM- Unilateral mastectomy

UPFS- Uniform Patient Fee Schedule

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INTRODUCTION

Background

Breast cancer is the most frequently diagnosed and leading cause of cancer deaths among women [1]. Over the years there has been an increase in the number of women electing contralateral prophylactic mastectomy (CPM) in unilateral breast cancer [2]. The literature that has reported on the oncological and demographic factors of the women electing CPM, has not included the urban South African setting. Therefore, this study aimed to ascertain the demographic and oncological characteristics of South African patients with unilateral breast cancer that choose CPM and thus appreciate any association that may or may not be present.

In an ever-changing society where the decisions of people's healthcare are dependent on more than basic science, health professionals need to equip themselves with holistic knowledge of the factors that affect our patients' health seeking behaviour and decision making.
In 2018 breast cancer ranked first in number of new cases and third in the number of deaths in South Africa. The International Agency for Research on Cancer reported 14 097 new cases and a 5-year prevalence of 37 662 people across all ages [3]. This illustrates that breast cancer is a prominent and increasing burden of disease in South Africa and thus how it is managed by the relevant healthcare workers is pertinent and should be based on evidence as well as incorporating current trends.

In developing countries, the rapid societal and economic changes are potential reasons for trends in lifestyles shifting towards those similar to high income countries [4]. These lifestyle trends have led to an increase in the burden of cancers associated with reproductive, dietary and hormonal factors such as breast cancer [4].

In women who are diagnosed with unilateral breast cancer, the risk of developing a contralateral breast cancer is three to five times higher than those women who do not have breast cancer, the risk being even higher in women with the mutation in either BRCA1 or BRCA2 gene mutations [5]. BRCA1 and BRCA2 are tumour suppressor genes whose germline mutations pose the greatest risk factor for breast and ovarian cancer by inheritance [6]. The lifetime risk of contralateral breast cancer is 40-65% in women with this mutation and it is in this demographic that CPM has the greatest potential benefit [7].

In women without a detected predisposition, the annual risk of metachronous development of clinically detected contralateral breast cancer is about 0.6% [8]. The cumulative risk increases as the years increase and thus it becomes more significant in patients that are likely to survive for a long time. However over the last two decades there has been a significant increase (3.7% in 1998 to 26.2% in 2011) in patients choosing a CPM that is out of proportion to the reported risks of metachronous cancer [8] and the reason for this should be explored.

The literature published around the demographics, histopathological characteristics and even psychological factors of patients choosing CPM in unilateral breast cancer has identified features associated with this increasing trend. These can be separated into three distinct but often overlapping groups: demographic, histopathological/oncological and psychological. A fourth factor of cosmetic symmetry may also be important in some patients. Many factors identified in the literature are summarised in Table 1.

Table 1. Factors associated with the increasing trend of contralateral prophylactic mastectomy.

Demographic	**Histopathological/Oncological**	**Psychological**
Young age (<45) [8,9,10,11]	Stage 1-2 [4,9,12,13,15]	Fear of recurrence [13,16,17,18]
White [8,9,10,11,13,14]	Invasive lobular [8,10,11,12,13]	Perceived benefit [16,17]
High Socio-Economic Status [8,12,13]	Small tumour size (<2cm) [9]	Influence by family/friends [17,18]
Family History [7,9,13]	Node negative [9]	Over-estimation of risk [16,17,19]
	ER/PR negative [9]	
	Radiation [9]	
	First primary tumour [9]	
	Neoadjuvant chemotherapy [12,15]	
	BRCA 1/2 [12,13]	

Elsayegh et al explored the benefit of CPM in women with unilateral breast cancer and a germline BRCA1/2 mutation and found that the risk of developing a metachronous contralateral cancer was reduced by 91% [10]. The tumour characteristics associated with increased CPM rates were clinically higher tumour stage, multicentric primary tumour, invasive and in situ lobular histology and recent year of diagnosis [10]. This supports the trend to choose CPM among women with the BRCA mutation as the evidence toward benefit is substantiated. In addition, the increase in the trend of CPM was also studied by Argawal et al and in this study there was found to be a 300% increase from 1997 to 2005 with young age, family history, White ethnicity and the availability of immediate reconstruction being the predictors of this choice. This study delved into the fact that later year of diagnosis, lower stage, smaller tumour size, node negative status, first primary cancer, higher median county income and higher percentage of women with greater than 12 years education all independently increased the odds of a CPM. Among patients who underwent reconstruction, younger age, White race and later year of diagnosis had higher odds of CPM [9].

Similarly, in Grimmer et al.'s 2015 report from the National Cancer Data Base in the USA, White women had a higher proportion of high socioeconomic status and were 15% more likely to have a private medical insurance and thus choose CPM compared to their low SES counterparts who were Black, Asian and Hispanic. The rate of patients younger than 45 choosing CPM also increased from 3.7% in 1998 to 26.2% in 2011[8].

The aforementioned three articles show that varying results can occur with different population samples even though similar aspects are explored. This further emphasizes a need to identify the specific characteristics unique to the environment that we work in.

Lizarraga et al explore the risk of developing a contralateral breast cancer looking at some of the demographics and tumour characteristics that we included in our study. This specific breakdown is important as it indicates to the health professional whether the patient choosing the procedure is justified in their reasons outside of the genetic risk and thus aids in the counselling, advice and reassurance of said patient. They found that in terms of age those most at risk for a contralateral breast cancer were those younger than 30 years [20]. Also, White women were more likely to choose CPM than Black women however it is in these young women that once diagnosed with an index breast cancer have a 20% to 50% higher incidence of metachronous contralateral disease even though the baseline risk is lower [20].

Covelli's group questioned women on the psychological aspects of their breast cancer diagnosis. All the patients reacted to the news of the diagnosis with shock and fear. The women

said that despite being counselled that breast conserving treatment versus unilateral mastectomy were equivalent in terms of long-term survival they felt that the odds of survival were increased if all the breast tissue was gone. The dominant theme amongst the women was "taking control of cancer" and they perceived that extensive surgery in the form of a CPM meant "not going through this again" and longer survival. These women described the healthcare team as a source of information, but valued stories from personal experiences by family and friends. Women who were non-carriers of the genetic mutation when answering a questionnaire, estimated the 5-year risk of contralateral breast cancer at 15% (instead of 0.6 %) [8]. It was this misconception that led to the increase in choice of CPM [16].

The modern patient has increased access to information, thus there is an increased influence in the decision-making relating to the management of their diseases and conditions. A recent study shows that this influence mainly involves the breast surgeon, plastic surgeon and medical oncologist rather than TV, internet, articles and magazines [21]. The awareness and acceptance of this means that the healthcare professional needs to understand characteristics of their patient population that are likely to be associated with electing certain procedures, such as CPM in the case of this study. It is also vital to have the knowledge of which cohort of patients are likely to benefit from CPM in line with the existing evidence available.
Determining the reasons behind the trend of choosing CPM is important to address potential issues in patient counselling and/or peri-operative support in the future. Long-term survival after breast cancer means that surgical decisions have long-lasting consequences for patients.

This study addressed the understanding of the demographic and histopathological characteristics of women choosing CPM at an urban breast cancer clinic.

Objectives

The aim of the study was to determine the prevalence of unilateral mastectomies (UM) with and without CPM in one breast clinic service; as well as to identify the demographic and pathological characteristics which predict for the choice of CPM.

METHODS

Study design

The study was a retrospective, descriptive study of patients undergoing mastectomy for unilateral breast cancer, comparing those patients choosing an UM with those choosing mastectomy with CPM. A record review of histological results and demographic details for enrolled participants was carried out at the Helen Joseph Breast Care Clinic in Johannesburg, South Africa. The clinic is a specialist breast-care clinic where an open-access system allows all patients to attend without previous appointment or referral for breast examination and investigation. The information pertaining to the patient details and chosen surgery is captured in a database once a diagnosis is made.

Patient selection

Female patients of all ages who underwent a mastectomy for unilateral breast cancer from 2013 to 2015 were included in the study.

Data acquisition

Patients were identified from the breast theatre book as having had a mastectomy, either a unilateral mastectomy (UM group) or mastectomy with CPM (CPM group). The hospital number of each patient identified was used to retrieve the demographic information from the hospital administrative system which informed the age and sex.

The hospital's billing system, the Uniform Patient Fee Schedule (UPFS) is the same that is used for all public sector hospitals in South Africa [22]. Patients are classified as full paying or subsidized patients. The subsidized patients are further categorized into the categories : H0, H1 and H2 based on their ability to pay for the service acquired. H0 patients are fully subsidized based on specified criteria eg, referral from primary care facility. Patients qualifying for partial subsidization are categorized as H1 and H2. The default classification for a person without income is H1. Subsidization depends on the assessment of income by the means test. We used "H" status as an indicator of socioeconomic status based on the ability to pay the hospital fees, the patients fell into either H0, H1or H2 [22]

Each patient's pathology report was retrieved from the National Health Laboratory System's 'Labtrak' system and the information recorded included the following:

- The number of specimens received.
- The weight of the breast; in the case of two breasts, the CPM breast was recorded.
- Histology of the CPM side.
- The use of neoadjuvant chemotherapy.
- Stage of breast cancer.

Ethical approval

Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), clearance number M170475, and hospital CEO approval was obtained from Helen Joseph Hospital in Johannesburg, South Africa.

Statistical analyses

The data was captured in Microsoft Excel and later exported into SPSS (originally, Statistical Package for the Social Sciences and now called Statistical Product and Service Solutions) software for data analysis. Descriptive statistics, included frequencies, means and standard deviations (SD) or median and interquartile ranges (IQR) are reported, as appropriate, to summarize the data. The Mann Whitney U test was conducted to assess whether the median age and weight differed significantly between the UM or CPM groups. The Chi-square or Fisher's Exact test of association was used, as appropriate, to determine associations between categorical variables according to UM or CPM groups. A p-value less or equal to 0.05 was considered statistically significant.

RESULTS

A total of 299 patients had mastectomies for unilateral breast cancer during the study period, of whom 59 (19.7%) had CPMs. The demographic and clinical information, including age, race, 'H' status and breast weight, are summarised in Table 2. There was a significant difference in the age of patients choosing unilateral versus CPM, with the unilateral patients being significantly older than the CPM patients (p = 0.03). The majority of patients in the study were Black (57.1%), followed by patients of White (23.2%), Coloured (14.4%) and Indian (5.4%) descent. Overall, there was a highly significant difference in patients who chose unilateral mastectomy vs CPM across racial groups (p<0.0001). Specifically, from Figure 1 only 10.6% of Black patients choose a CPM compared to 43.5% of White patients (Bonferroni corrected p-value<0.001). The women who underwent CPMs had a trend for larger median weight of the breasts, although this did not reach statistical significance (p=0.09).

Table 2. Patient demographics by CPM status

Parameter	All (n=299)	UM (n=240)	CPM (n=59)	P-value
Age (yrs), median (IQR)	56.0 (44.0 – 65.0)	56.0 (45.5 – 66.0)	53.0 (41.0 – 62.0)	0.03*
Breast weight (g), median (IQR)	586 (371–933)	577 (355-860)	655 (462-1020)	0.09
Race, n (%)				
Black	170 (57.1%)	152 (63.6%)	18 (30.5%)	<0.001**
Coloured	43 (14.4%)	35 (14.6%)	8 (13.6%)	
Indian	16 (5.4%)	13 (5.4%)	3 (5.1%)	
White	69 (23.2%)	39 (16.3%)	30 (50.9%)	
H Status, n (%)				
H0	22 (7.4%)	17 (7.1%)	5 (8.5%)	0.82
H1	276 (92.3%)	222 (92.5%)	54 (91.5%)	
H2	1 (0.3%)	1 (0.4%)	0 (0%)	

Abbreviations: IQR, interquartile range; CPM, contralateral prophylactic mastectomy; UM, unilateral mastectomy.
*Mann-Whitney U test. **Chi2/Fisher's exact test.

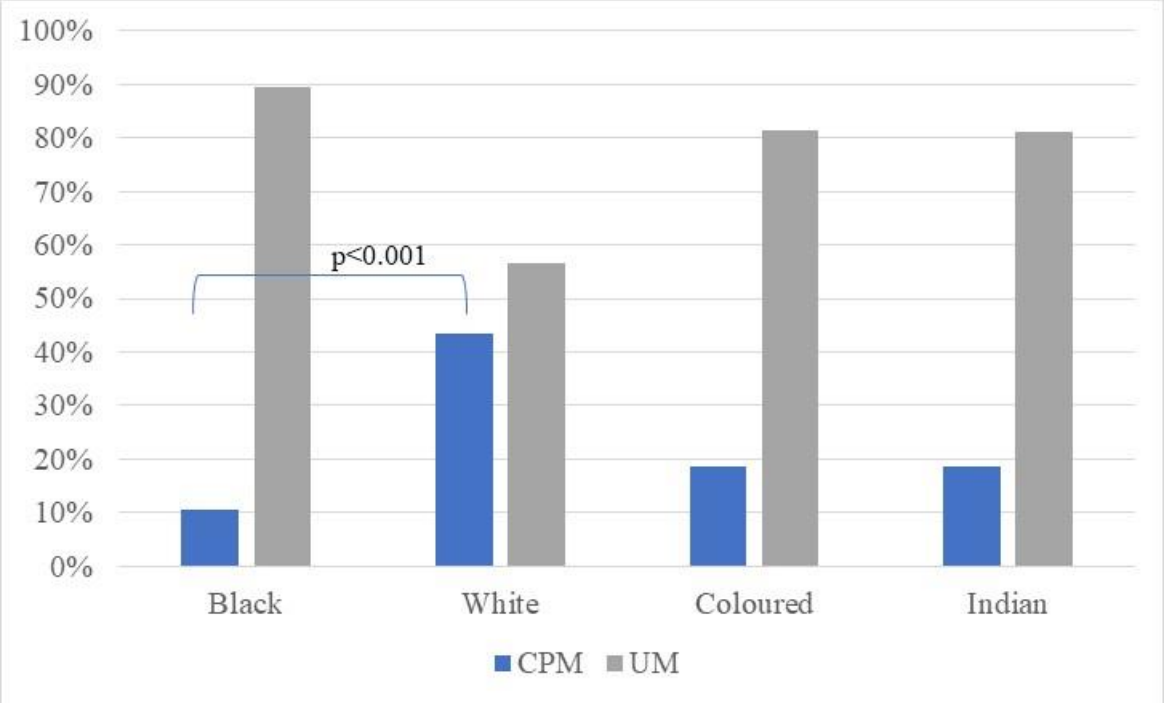

Figure 1. Contralateral prophylactic mastectomy (CPM) vs unilateral mastectomy (UM) according to race.

The histopathology of the breasts, including breast weight, primary tumour histology, histology of the contralateral side and TNM staging of tumour, is shown in Table 3.

Table 3 Histopathology of the breast according to CPM status

Parameter, n (%)	All (n=299)	UM (n=243)	CPM (n=59)	P-value
Histology of tumour				
Ductal Carcinoma In Situ	18 (6.0)	15 (6.3)	3 (5.2)	
Invasive Ductal Carcinoma	230 (77.2)	184 (76.7)	46 (79.3)	0.69
Invasive Lobular Carcinoma	10 (3.4)	7 (2.9)	3 (5.2)	
Other subtypes	40 (13.4)	34 (14.2)	6 (10.3)	
Histology of CPM				
Ductal carcinoma in situ	1 (1.7%)	-	1 (1.7%)	-
No Invasive Malignancy	47 (81.0%)	-	47 (81.0%)	
NA	10 (17.2%)	-	10 (17.2%)	
TNM stage	*n=298*			
Stage 0-2a (early)	129 (43.3%)	98 (41.0%)	31 (52.5%)	0.14
Stage 2b-4 (late)	169 (56.7%)	141 (59.0%)	28 (47.5%)	
Neoadjuvant chemotherapy	*n=211*			
Yes	161 (76.3%)	133 (54.7%)	29 (49.2%)	0.59
No	50 (23.7%)	42 (17.3%)	9 (15.3%)	

Abbreviations: CPM, contralateral prophylactic mastectomy; UM, unilateral mastectomy.

There was no association between being in either the UM or CPM group by each of the following variables: UPFS Status (p-value = 0.854), Histology of tumour (p-value = 0.69), TNM stage (p-value = 0.4) and neoadjuvant chemotherapy (p-value =0.516).

The population that had CPM were predominantly White with the difference in mean weight of the breast being larger than the UM counterparts and the median age being younger. Pathologically most of the population had invasive ductal carcinoma; were T2 N +, thus either Stage IIb or IIIa, and had had neoadjuvant chemotherapy. Of this group only one patient was found to have a contralateral malignancy. As seen from Figure 1, most patients were of low socioeconomic status (H1).

DISCUSSION

International trends are influential in patients' decision-making from both a patient and a health professional's point of view. In the era of increased access to information, health professionals must not be deterred from practising evidence-based medicine. There always, however, lies a caveat to applying blanket medicine to diverse communities.

This study has achieved baseline statistics of the prevalence of UM vs CPM mastectomies in the South African public hospital setting and thus we are now able to assess whether our population is following international trends of an increase in the CPM as a procedure.

The international community has studied the demographic of the patient population that elects a CPM, a procedure otherwise not indicated based on low potential risk of a contralateral breast cancer. Patients in whom the procedure is acceptable are those with a higher risk than the average population, namely BRCA 1/2 mutation carriers. Even with this, the modern patient is known to elect the CPM despite oncological indication for this.

The Department of Health provides a public and private health service in South Africa. The average citizens that access the public health service are of a lower socioeconomic standing [23]. Adequate, evidence-based health care is provided to all patients despite their socioeconomic status and the necessity in stratifying patients according to 'H' status serves to allow them to be billed according to their affordability. In this study we would not expect to see a discrepancy between the UM and CPM populations based on socioeconomic standing as the majority of this population is of similar economic standing.

The international trends showed that White women were more likely than any other race to have CPM. The same trend was demonstrated in our study. This could be influenced by the varying levels of education and access to information among the patients. Owing to the country's Apartheid history, large discrepancies in equality still exist. The White population of the country had access to better basic human needs including education and health care prior to the country establishing democracy [23]. Almost three decades, or 27 years, after South Africa established a democratic republic it may be expected that equilibrium of equity would be on the horizon if not yet achieved. The unfortunate reality is that the public system that affords basic healthcare to South Africans is still comparatively under-resourced and thus in roads to catching up on past inequities are often slow or halted.

The relevance of this is evident in that despite there being only 23.2% of White women in the total population, more than half the CPM procedures were performed on this ethic group (50.9%). The previous and ongoing advantage afforded to this group of women in terms of access to information and increased ability to understand and interrogate the treatment options is likely to have played a role in this trend; although because these choices do not reflect current evidence-based recommendations for CPM, it is possible that there are also other culture-specific influences that this study does not elicit. Having these baseline statistics coupled with the attempts by government to decrease the inequality and inequity gaps by affording the general population basic education and healthcare, future statistics will be able to demonstrate whether the ratio of patients electing the CPM mastectomy is truly reflective of the total population. The findings of which can further be interrogated.

We hypothesized that women with bigger breasts would more likely be the ones choosing a CPM procedure and, despite the CPM group having a larger median weight of the breast, this did not reach statistical significance. This is consistent with the literature reviewed that also did not find this factor to be influential in deciding on CPMs.

A higher percentage of patients post neoadjuvant chemotherapy still opted for UM which, although not statistically significant, is different to the international trend which demonstrated neoadjuvant chemotherapy as a factor that favoured CPM [12, 15]

The stage at presentation is higher in the South African setting compared to the rest of the world [24] and in this study the highest percentage of patients were found to have late stage breast cancer 2b-4. It can, however, be noted that the population that underwent CPM mastectomies had the highest percentage early stage (stage 0-2a) compared to the late stage (stage 2b-4). This is consistent with literature findings that showed that lower stage tumours were found in patients that had chosen CPM.

The most prevalent histology of the total population was invasive ductal carcinoma and that was reflected in both CPM and UM procedures. The literature, however, found that patients choosing CPM had invasive lobular carcinoma as the prevalent histology. The incidence of contralateral breast cancer is higher for invasive lobular carcinoma and thus the preservation of that breast is less frequent [25]. When looking at the patients in the current study with invasive lobular carcinoma in isolation, only 30% (n = 3/10) had a CPM from which we can deduce that the CPM association with the biology of the tumour did not play a major role in influencing the decision in this group of patients. This may be because, unless researched, this

knowledge is common to the health practitioner who, in line with the ethical considerations of the evidence, would not routinely advise this even in a discussion of the risk of contralateral involvement of invasive lobular carcinoma[26]

A history of neoadjuvant chemotherapy has been associated with electing CPM. In this study the analysis of this factor was hindered by a large percentage (29.5%) of the population that did not have the timing of their chemotherapy documented. Of the patients with documentation, 76% had neoadjuvant chemotherapy. In this population, unlike the trend in international literature, there was only a small percentage (17.9%) that had CPM. This percentage was similar to the group who had CPM without neoadjuvant chemotherapy (17.6%).

Limitations of the study and alternative approaches

The limitations in the study arose from incomplete or misconstruable file records. The inclusion of UPFS, or 'H' status, to depict the patient's socio economic status may also have caused limitation with regards to the accuracy of the information collected as well as the fact that in the setting of the study it did not determine the quality or limit the options of treatment that the patient received. The setting of an urban clinic gives a false sense of the origin of the patients seen, patients often that travel far due to the increased access to healthcare in urban areas and this may be increased in the setting of walk in clinic thus rural patients may be included in the study. To gain access to public healthcare, a local address is used to specify the drainage area to which a patient shall be managed and often patients from rural areas use a relative or acquaintance's address to gain access. This gives a false impression of location unless interrogated.

CONCLUSION

The demographic and histopathological characteristics influencing choice of CPM in the South African context, although having some similarities to those in international literature, are unique to the special socio-economic circumstances in the country. The future of this procedure in our context will likely show a slow uptake as it has been demonstrated that fewer factors were associated with electing CPM in as compared to those same factors that lead to the international increasing trend. The factors are less likely to apply to the cultural and racial diversity in a South African healthcare setting currently which is advantageous in that it is in keeping with maintaining a primarily evidence-based indication to performing a CPM on patients with unilateral breast cancer. With continuation of monitoring of the characteristics, as well as increasing access to information, a unique set of characteristics may emerge based on the cultural and racial diversity of South Africa.

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APPENDIX 1: Approved Protocol

Characteristics of patients choosing bilateral mastectomy with no reconstruction in an urban African breast cancer clinic: a descriptive study.

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Abstract

In an ever-changing society where the decisions of people's healthcare is dependent on more than simply science, health professionals need to equip themselves with holistic knowledge of the factors that affect our patients' health seeking behaviour and decision making. Breast cancer is the most frequently diagnosed and leading cause of cancer deaths among women. Over the years there has been an increase in the number of women electing contralateral prophylactic mastectomy in unilateral breast cancer. Factors commonly associated with this increasing trend young age, Caucasian ethnicity, family history, high socio-economic status, low tumour stage, small tumour size, invasive lobular carcinoma, fear of recurrence and availability for reconstruction. Recommendations based of the clinical outcome in mortality for women who should be offered contralateral prophylactic mastectomy are those with BRCA 1/2 gene mutation. The literature that is focused on the oncological and demographic factors is not available for the urban South African setting and it is the intention of this study to ascertain the demographic and oncological characteristics of the patients that choose this procedure and thus appreciate any correlation that may or may not be present. Psychological factors, albeit important, will not be the focus of this study. The results of this retrospective study may, however, lead to a prospective study that aims to ascertain these influences.

Title

Characteristics of patients choosing bilateral mastectomy with no reconstruction in an urban South African breast cancer cohort: a descriptive study

Degree registered

MMed, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand

Supervisors

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Specific Aims

Aim 1:

To determine the prevalence of unilateral mastectomy and bilateral mastectomy in one breast clinic service, with and without reconstruction.

Rationale: The rate for contralateral prophylactic mastectomy (CPM) is described as increasing in international literature but unknown in our practice

Hypothesis: Contralateral prophylactic mastectomy without reconstruction (CPMWR) is commonly chosen by patients, and the most common cause of bilateral mastectomy

Expected outcomes: A baseline level by which to measure future trends and define the procedure as a common one.

Aim 2:

To identify the demographic and pathological characteristics which predict for the choice of CPMWR

Rationale: Determining the presence of characteristics of patients making the decision for CPMWR will ensure appropriate counselling for patients pre-operatively

Hypothesis: Women with big breasts or those after primary chemotherapy may prefer CPMWR

Expected outcomes: An information session with counsellors to highlight predictive factors for CPMWR; a peer-reviewed article (provisionally titled "The demographic and histological characteristics of patients choosing bilateral mastectomy with no reconstruction in Johannesburg, South Africa" for Clinical Breast Cancer journal)

Nomenclature

There is no standardised way to describe bilateral mastectomy for unilateral cancer. For non-specialist readers, bilateral mastectomy is the most easily understood phrase for this surgery. However, this can be used to describe procedures for both unilateral and bilateral cancers.

Therefore, the nomenclature ‘contralateral prophylactic mastectomy’ has been adopted and used to describe a bilateral mastectomy for unilateral cancer.

In this protocol, bilateral mastectomy refers to all bilateral surgeries; contralateral prophylactic mastectomy (CPM) refers to cases of unilateral breast cancer where patients have chosen a bilateral procedure

Literature review

The International Agency for Research on Cancer published their latest statistics that show that breast cancer was among the most commonly diagnosed cancers worldwide. It is the most frequently diagnosed and most common cause of death in women with the incidence and mortality having increased by 20% and 14% respectively from 2008 to 2012 [1].

In developing countries as a result of the rapid societal and economic changes, the trends show that lifestyles are shifting towards those similar to industrialised countries [1]. This has lead to an increase in the burden of cancers associated with reproductive, dietary and hormonal factors [1]. It is clear that breast cancer is increasingly becoming a burden on society and further understanding of the varying aspects of the disease is required so as to better manage these patients [1].

The modern patient has the ability to access information which has shown to be influential in the decision-making relating to the management of their diseases and conditions with more influence by breast surgeon, plastic surgeon and medical oncologist than TV, internet, articles and magazines [2]. The awareness and acceptance of this means that the healthcare professional needs to understand characteristics of their patient population that are likely to be associated to electing certain procedures, in the case of this study contralateral prophylactic mastectomy (CPM). It is also vital to have the knowledge of which cohort of patients are likely to benefit from CPM from an evidence-based point of view.
In women who are diagnosed with breast cancer, the risk of developing a contralateral breast cancer is three to five times higher than those women who do not have breast cancer, the risk being even higher in women with the germline BRCA1/2 mutations. The lifetime risk is 40-65% in this group of women and it in in this demographic that CPM has the greatest potential benefit [3].

Without a detected predisposition, the annual risk of metachronous development of clinically detected contralateral breast cancer is about 0.6%. As the cumulative risk increases over years it becomes more significant in patients that are likely to survive for a long time. In addition but out of proportion to the documented risks of metachronous cancer however, over the last two decades there is a significant increase in patients choosing a CPM, with the rates increasing from 3.7% in 1998 to 26.2% in 2011.[4]

The literature published around the demographics, histopathological characteristics and even psychological factors of patients choosing CPM in unilateral breast cancer has identified features associated with this increasing trend. These can be separated into three distinct but often overlapping groups: demographic, oncological and psychological. A fourth factor of cosmetic symmetry may also be important in some patients. Many factors identified in the literature are summarised in Table 1.

Table 1: Factors associated with the increasing trend of contralateral prophylactic mastectomy

Demographic	**Histopathological/Oncological**	**Psychological**
Young age (<45) [4,5,6,7]	Stage 1-2 [1,5,8,9,11]	Fear of recurrence [9,13,14,15]
White [4,5,6,7,9,10]	Invasive lobular [4,6,7,8,9]	Perceived benefit [13,14,]
High Socio Economic Status [4,8, 9,]	Small tumour size (<2cm) [5]	Influence by family/friends [13,15]
Family History [3,5,9]	Node negative [5]	Over-estimation of risk [13,14,16]
	ER/PR negative [5]	
	Radiation [5]	
	First primary tumour [5]	
	Neoadjuvant chemotherapy [8,11]	
	BRCA 1/2 [8, 9,]	

The decision to undergo reconstruction should be discussed with all women who have a mastectomy. A study by Nelson et al showed that reasons for reconstruction included having the desire to look natural, feel feminine, to be able to wear many types of clothes and to 'get my life back'[3]. The availability of reconstruction, particularly to achieve symmetry, has been cited as important in the choice of undergoing CPM after unilateral breast cancer. It is important to note that the decision for breast reconstruction is complex and surgeons and patients alike should be aware of the factors that influence contralateral symmetrisation. Rizki et al explored these factors by dividing them into four categories namely Optimisation of symmetry, patient satisfaction and motivation, technical consideration and financial and political implications [17]. Studies have found that implant based reconstruction was found to be associated with better symmetrisation and the rates of implant reconstruction after bilateral mastectomy (most commonly mastectomy with CPM) increased from 28.2 to 43.5 percent while the rate of autologous reconstruction decreased from 32.2 to 27.3 percent [6].

Hoskin et al found that patients who opted for immediate breast reconstruction (IBR) after unilateral mastectomy were twice as likely to choose contralateral mastectomy and reconstruction [8]. Patients less than 50 year old with primary breast surgery showed consistently high rates of bilateral mastectomy with IBR (~60%) between 2009 and 2014 [8]. Those younger than 50 years old with neoadjuvant chemotherapy showed increase use of bilateral mastectomy with IBR to more than 80% by 2014 and a corresponding sharp decrease in bilateral mastectomy without IBR [8] . The subgroup which preferred unilateral mastectomy without IBR was older than 60 years old with stage II or III disease undergoing primary surgery [8].

A study by Argawal also linked reconstruction to choice of CPM. It showed that reconstruction rates after a bilateral mastectomy for breast cancer increased from 18.7 to 46.5 from the year 2000 to 2010 [5]. However, the study also found that despite the increase in the rate of reconstruction, in the sample of 157,042 women with unilateral cancer, 9.1% chose bilateral mastectomy (with CPM) without reconstruction and only 7.8% underwent CPM with reconstruction. This choice of CPM without reconstruction is further seen in the sub-analysis of women choosing CPM, where 53.9% did not undergo reconstruction at all [5]. The

demographic of the women elected reconstruction were younger, White and earlier stage of breast cancer. In a study by Freedman et al, Hispanic women, unmarried women and those with college degrees were noted to have been more likely to have reconstruction [11].

Although determining the psychological factors related to a choice of CPM are beyond this scope of the current study, they may be as important as demographic or oncological factors. Kwong et al looked at the psychology of a cohort of women who chose CPM. 75% admitted to the constant worry about the risk of contralateral breast cancer prior to the procedure, a risk that was diminished by the surgery but still overestimated with one woman citing as much as 50% perceived risk of recurrence [16]. Similarly Covelli et al described that the news of the diagnosis was met with shock and fear. The women expressed that despite being counselled that breast conserving treatment versus unilateral mastectomy were equivalent in terms of long term survival they felt that the odds of survival were increased if all the breast tissue was gone [13].

The dominant theme amongst the women was "taking control of cancer", they perceived that extensive surgery in the form of a CPM meant "not going through this again" and longer survival. It was also found among this cohort that they all described the healthcare team as a source of information but valued stories from personal experiences by family and friends. Women who were non carriers of the genetic mutation, when answering a questionnaire, estimated the 5 year risk of contralateral breast cancer at 15%. It was this misconception that led to the increase in choice of contralateral prophylactic mastectomy [13].

There is clear evidence indicating the increasing trend of contralateral prophylactic mastectomy but the medical justification behind this trend is lacking with the benefit being in patients with positive gene mutations. Determining the reasons behind this trend is important to address issues in patient counselling and support peri-operatively. Long-term survival after breast cancer means that surgical decisions have long-lasting consequences for patients. This study will address the first part of understanding this patient group, by describing the demographic and oncological characteristics of women choosing CPMWR , and lay a foundation for further quantitative and qualitative investigations

Methods

Study design

Study overview: The main study will be a retrospective, descriptive study of patients undergoing mastectomy comparing those choosing unilateral mastectomy with those choosing mastectomy with CPM, both with or without reconstruction. A record review of radiological and histological results, with demographic details for enrolled participants will be carried out.

Study site: This study will be conducted at the Helen Joseph Breast Care Clinic (government hospital) in Johannesburg, South Africa.

Study population: All female patients of all ages who have undergone mastectomy with or without reconstruction. Exclusion criteria are:

- Absent patient file *and* absent radiology or histology reports

Study period: From January 2013 to December 2015, or until accrual of adequate sample size that will render statistically significant results (>150). If this accrual is not attained the recruitment period may be increased.

Study procedures

Method: *Patient data collection*

The patients will be identified from the breast theatre book as having had a breast cancer surgery and those with mastectomy or mastectomy with CPM included.

The hospital number of each patient identified will be used to retrieve the demographic information from the hospital administrative system as is given on admission of every patient entering the hospital. This will be done with assistance from administrative personnel eg. Clerk. The information that will be recorded from this demographic sheet will be:

- Age
- Race
- Socioeconomic status (SES) 'H status'.

The hospital number of each patient will then be entered in the National Health Laboratory System's Labtrak to retrieve the pathology report. The information that is available on the pathology report that will be recorded will be:

- The number of specimens received; this will be used to compare with the information from the theatre book to accurately record whether the patient indeed had unilateral or bilateral mastectomy
- The weight of the breast; in the case of two breasts, the CPM breast will be recorded
- The histological characteristics of the affected breast; sub-type, grade, receptor status
- Histology of the CPM side
- The use of neo-adjuvant chemotherapy
- stage of disease at presentation (TNM and stage as assessed clinical or radiologically [where both are obtained radiological stage will be included])

As there is often missing information in hospital records, the above information will be supplemented with information from the patients' hospital files, radiology reports and oncology records.

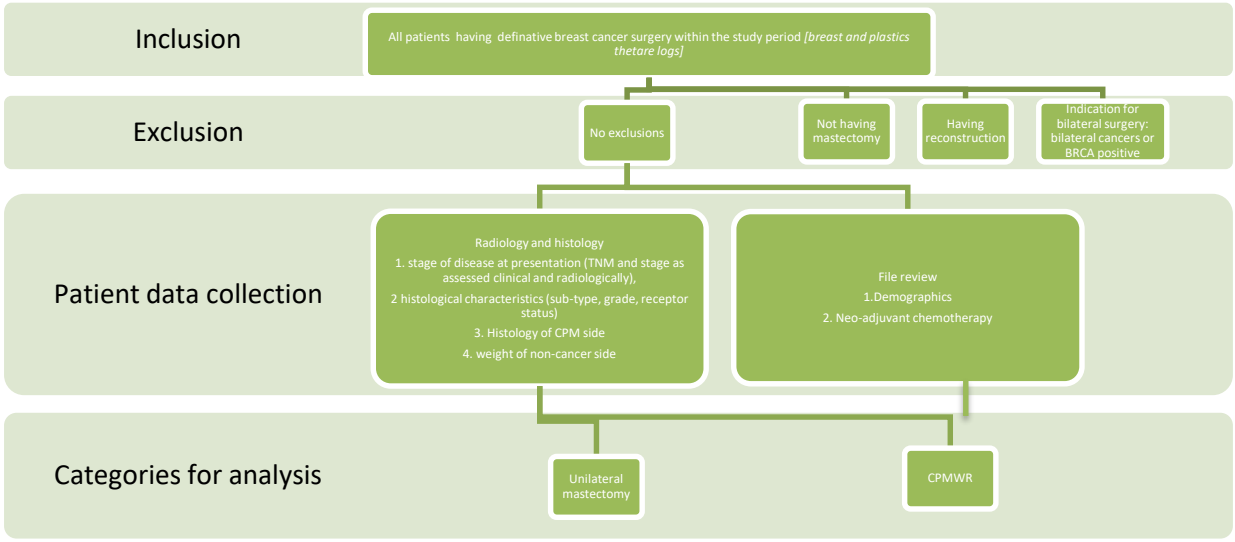
The hospital file will be retrieved from Helen Joseph records department, the radiology report from the Helen Joseph radiology department and the oncology report from the Charlotte Maxeke Johannesburg Academic Hospital oncology department if required.

The data will be collected in a CRF on the REDCap (Research Electronic Data Capture) system. A de-identified dataset will be used for data analysis. Variables on the CRF are as follows:

Study number	Age	Race	H status	Unilateral/Bilateral mastectomy	Weight	Histology of tumour	Histology of CPM	TNM stage	Neoadjuvant chemotherap

Consent: This is a retrospective study and as such individual informed consent should not be required.

Summary of study methods



Data analysis

Data collection: The data will be administered in the REDCap (Research Electronic Data Capture) system. A de-identified dataset will be used for data analysis.

Data analysis: Data collected will be separated and responses grouped into categories.

- Patient characteristics will be analyzed using frequencies and proportions. Some variable will be converted to categorical variables and also presented as counts and proportions.

- For comparing independent numerical variables the Student's t-test or One-way ANOVA test will be used. Non-parametric tests will be used for data that is not normally distributed. Most of the variables will be categorical variables. Two-sided difference of proportions will be compared across categorical variables using Pearson chi2 test and p-values presented. A p-value <0.05 is considered statistically significant.

- Coefficients will be presented for the categorical variables where appropriate with 95% confidence intervals and choice of BMWR will also be analyzed using linear regression. Modified Poisson regression will used to estimate the incident rate ratio and 95% confidence intervals to understand the relative risks of BMWR according to patient characteristics.

- All statistical analysis will be carried out in Stata v13.1 (College Station, Texas) or similar statistical package.

- Pertinent comparisons would be: Age; Subtype; Weight of breasts; Neo-adjuvant chemotherapy; tumour size; and Stage of disease.

Limitations and alternative approaches

The limitations in the study will arise from incomplete or misconstruable file records. The inclusion of 'H status' depicting socio economic status could cause limitation with regards to the accuracy of the information collected as well as the fact that in this setting it does not determine the quality of treatment the patient receives.

Timeline

	2015 Q4	2016 Q1	Q2	Q3	Q4	2017 Q1	Q2	Q3
Literature Review	x	x						
Protocol assessment					x			
Ethics application					x			
Recruitment and study					x	x	x	
Data cleaning and analysis						x	x	
Manuscript prep							x	x
Thesis preparation							x	x
Submission of degree							x	x

Budget

	Year One Oct 2016-17	Year Two Oct 2017-18	Total
Personnel	0	0	
Equipment	0	0	
Transport/travel	450	450	
Other direct costs	0	0	
			900

Dissemination of findings

Results of analyses will be disseminated as widely as possible in South Africa, where information on the epidemiology of breast cancer and other breast conditions is limited. The study sites and the Department of Health will receive a report with the results. We will submit the results for presentation at relevant conferences in South Africa and/or internationally. As stipulated by the University of the Witwatersrand, a journal manuscripts will be submitted to an appropriate, peer-reviewed national or international journal for publication.

Conclusion

The future of breast cancer and breast cancer surgery is dynamic and it is up to the health professionals involved to be all encompassing when it comes to our management of this prevalent disease. Best medical care is better achieved when the health care professional understands what type of patient and patient pathology is likely to make certain surgical management decisions.

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APPENDIX 2: Datasheet

Study no.:		
Age, years:		
Race:		
'H' Status:		
Mastectomy:	Unilateral	Bilateral
Weight, grams:		
Histology of tumour:		
Histology of CPM:		
TNM stage:	Early (0-2a)	Late (2b-4)
Neoadjuvant chemotherapy:		
Other/notes:		

APPENDIX 3: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr P Ndwambi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170475

NAME: (Principal Investigator)	Dr P Ndwambi
DEPARTMENT:	School of Clinical Medicine Department of Surgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Characteristics of patients choosing bilateral masectomy with no reconstruction in an urban African breast cancer clinic: a descriptive study
DATE CONSIDERED:	05/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S Rayne
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/12/2017

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 on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 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 **April** and will therefore be due in the month of **April** 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