Factors influencing delay in presentation and their impact on cancer stage in women with a diagnosis of breast cancer in South Africa

Factors influencing delay in presentation in women with a diagnosis of breast cancer in South Africa and their impact on cancer stage at presentation – [original title]

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand,
in fulfilment of the requirements for the degree of Doctor of Philosophy

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Johannesburg, 2018

Declaration

I, Sarah Louise Rayne, declare that the work contained in this thesis is my own work, except to the extent indicated in the acknowledgement sections.

This thesis is being submitted for the degree of Doctor of Philosophy, at the University of Witwatersrand, Johannesburg, South Africa.

This work has not been submitted for any other degree or examination in this or any other university.

Sarah Louise Rayne (PHD Candidate)

Thursday, 31 January 2019

Publications

The following peer reviewed publications are included as part of this thesis (order of publication):

1. Rayne S, Schnippel K, Wright K, Kruger D, Firnhaber C, Benn C. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa. J Glob Oncol 2016;3:125–34. doi:10.1200/JGO.2015.002691.

2. Rayne S, Schnippel K, Benn C, Kruger D, Wright K, Firnhaber C. The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa. J Cancer Educ 2017. doi:10.1007/s13187-017-1234-3.

3. Rayne S, Schnippel K, Kruger D, Benn C, Firnhaber C Delay to diagnosis and breast cancer stage in an urban South African breast clinic. Submitted to South African Medical Journal S Afr Med J 2019;109(3): doi:10.7196/samj.2019.v109i3.13283

4. Rayne S, Schnippel K, Grover S, Kruger D, Benn C, Firnhaber C The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa. Submitted to South African Journal of Surgery *In press*

5. Rayne S, Schnippel K, Grover S, Fearnhead K, Kruger D, Benn C, Firnhaber C. Unraveling the South African Breast Cancer Story: The Relationship of Patients, Delay to Diagnosis, and Tumor Biology With Stage at Presentation in an Urban Setting. Journal of Surgical Research. 2019 Mar 1;235:181-9. doi: 10.1016/j.jss.2018.09.087

Presentations

The following reviewed abstracts have been accepted for presentation as part of this thesis (order of meeting):

1. **Rayne, S.,** Kruger, D., Wright, K., and Benn CA. "Under-estimating psycho-social issues in young women with breast cancer in South Africa, may seriously impact their ability to make informed treatment choices"

   Winner of best oral presentation (student): Wits Health Sciences Research Day, September 2014

2. **Rayne, S.,** Kruger, D., Wright, K., and Benn CA. "Under-estimating psycho-social issues in young women with breast cancer in South Africa, may seriously impact their ability to make informed treatment choices" European School of Oncology Breast Cancer in Young Women Conference, Dublin, November 2014

3. **Rayne, S.,** Schnippel, K., Kruger, D., Wright, K., Firnhaber, C., and Benn, C. "Understanding the fears expressed by patients with a breast cancer diagnosis in urban South Africa" AORTIC (African Organisation for Research and Training in Cancer) conference, Marrakesh, Morocco, November 2015

4. **Rayne S**, Schnippel K, Kruger D, Benn C, Wright K, and Firnhaber C. "The effect of access to information on beliefs of breast cancer patients toward their disease in urban South Africa: A cross-sectional descriptive study" Bert Myburgh Research Forum, November 2016

5. **Rayne, S.,** Schnippel, K., Benn, C., Kruger, D., Wright, K. and Firnhaber, C., "Attitudes and beliefs of breast cancer patients toward their disease in urban South Africa: A cross-sectional descriptive study" European Cancer Congress, Amsterdam, January 2017

6. **Rayne, S.,** Schnippel, K., Benn, C., Kruger, D., Wright, K. and Firnhaber, C., "Attitudes and beliefs of breast cancer patients toward their disease in urban South Africa: A cross-sectional descriptive study" Wits Cancer Research Symposium 2017

7. **Rayne S,** Schnippel K, Fearnhead K, Grover S, Kruger D, Benn C, Firnhaber C "Unravelling the South African breast cancer story: the relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting." 11th European Breast Cancer Conference, Barcelona 2018

Regulations

Formatting and language

As prescribed by the Faculty of Health Sciences style guide the references are presented using the Vancouver format and are numbered in ascending order in the text and are listed in that order in the references. The references are referred to in the text by a number in square parenthesis (i.e. [2]). The references are not listed at the end of every chapter but a complete list is at the end of the thesis.

The results chapters are the published articles and are presented as they were on acceptance / submission. The text formatting has been adapted to match that of thesis, but the structure is that prescribed by the journal. For clarity all tables and figures are embedded, but the thesis has been referenced as one body of work.

The journal articles were submitted in English (United Kingdom) and for consistency this is carried through the thesis.

Permission to publish

There were five journal articles included in the thesis. Where the journal articles are currently published in open access journals with Creative Commons Attribution license they do not require additional permission to be reused or included in this thesis. Where permission is required, it has been sought and obtained (Appendix E). The remaining journal articles are currently under review and permission will be sought once they are accepted if required.

Abstract

Background

Breast cancer is the most common cancer in women in most low- and middle-income countries, and often presents at an advanced stage affecting prognosis irrespective of the care available. Studies from sub-Saharan Africa concerning patients with breast cancer are often presented as a homogeneous group with lack of education, awareness and access commonly cited as reasons for late stage and delay to presentation.

Study Rationale

This study was designed to explore this uniform characterisation of patients with breast cancer in three parts: first define the relationship of their demographic and socio-economic characteristics with their attitudes, fears and beliefs held regarding breast cancer and its treatment; then determine the relationship of socio-economic and psychosocial characteristics with a patient's stage at presentation, and delay to presentation; and finally investigate and understand the heterogeneity of breast cancer molecular biology in this population, and assess its independent contribution to late-stage disease.

Methods

A questionnaire was designed for distribution to breast cancer patients. It included questions about their characteristics, socio-economic circumstances, education, and ability to access care as well as their agreement to statements of knowledge and beliefs about breast cancer. In a pilot study, the questionnaire was distributed to 263 breast cancer patients at two sites (one government and one private health care facility) in Johannesburg.

Using a modified questionnaire including time to access care, patients attending the urban government open-access breast unit over a 14-month period with a new diagnosis of breast cancer were then recruited. The stage at presentation and molecular subtype for participants was recorded. The relationship of clinical stage and delay to presentation to demographic variables, beliefs and molecular subtypes were assessed through univariate and multivariate modified Poisson's regression methods of calculating odds ratio with 95% confidence intervals.

Results

The pilot study found that fears related to treatments were far stronger than those related to socio-economic barriers, and higher in young women under 40 years. Access to information was protective from adverse beliefs about cancer but positive expressions of cure and beating cancer were found equally in all women. Socio-economic status was a strong confounder of race and explained most of the racial differences in levels of fear.

In the final study, 252 women diagnosed with a new breast cancer completed the survey (response rate of 70.8%). Stage 3 (56.0%) was most common at presentation and nearly one third of all patients presented with T4 cancer. Total delay to present at the breast clinic was associated with locally advanced stage at presentation (p=0.021) and most delay occurred between acknowledging a breast symptom and seeking care. Self-reported transport difficulties predicted both advanced stage at presentation and delay to presentation of more than six months.

Invasive ductal carcinoma was most common (92.7%), and the most common subtype was Luminal B (57.9%) followed by Luminal A (21.5%), triple negative (13.9%) and HER2 positive (6.7%). HER2 overexpression remained an independent risk factor for late stage at presentation.

Conclusions

Participant's beliefs about their new breast cancer diagnosis and breast cancer in general were most commonly appropriate, and showed a low level of fatalism, in contrast to other studies in sub-Saharan Africa. Few beliefs or socio-economic factors influenced delay to presentation or stage at presentation, however this study found that tumour biology has a compelling place in understanding the aetiology of late-stage disease.

This thesis has contributed information to the complex interplay that exists between the patient, her environment and the breast tumour biology. It helps us address the issues of access to care, in both patients-related and treatment availability.

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Acknowledgements

To the patients, the participants and co-collaborators in this work: Thank you for your contribution to our better understanding of this disease and your experience.

To my supervisors, for your tireless encouragement and realistic goal-setting.

To the academic staff at the Department of Surgery, University of Witwatersrand, it has been such a pleasure to work in the department and be part of your team.

To my research assistants, Renee and Dorcus who facilitated the collection of accurate collection of much of the data in a busy working environment. Without you this project would not have been possible. Thank you for your attention to detail, empathy and wry observations.

To my parents and brother: it seems like it doesn't end… but thank you for the support, unquestioning faith in me, and for the trajectory set from an early age through love and encouragement that has helped me in my work.

To my wonderful husband: words fail. To the bottom of the ocean, to the moon and back, or just perhaps, to waking up at the weekend and me not going to work. What exciting times.

Finally (and not exhaustively or in a particular order): Deirdre, Carol, Renee, Dorcus, Naomi, Kate, Kirsty, Surbhi, Cindy, Cheryl, Sandra, Susan, Dyanadree, Irma. What a fabulous group of strong role-models and friends I have had the privilege in which to engage in research. My life is better for knowing and working with you all.

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List of abbreviations and definitions

AJCC	American Joint Committee on Cancer
aRR	Adjusted Relative Risk
ER	Oestrogen Receptor
HBM	Health Belief Model
HER2	Human Epithelial Receptor 2
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
IRR	Incidence Risk Ratio
LMICs	Low- and Middle- Income Countries
PR	Progesterone Receptor
RR	Relative risk
T-Ack	Time to acknowledge symptom
T-HS	Time to attend healthcare services
T-BCC	Time to attend breast care clinic
TNM	The Tumour Nodal Metastases system of cancer staging. See below and Appendix B

Excerpt from the American Joint Committee on Cancer (AJCC):

"The TNM Staging System was developed and is maintained by the AJCC and the Union for International Cancer Control (UICC). It is the most commonly used staging system by medical professionals around the world. The TNM classification system was developed as a tool for doctors to stage different types of cancer based on certain, standardized criteria. The TNM Staging System is based on the extent of the tumour (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M)" [1]

Chapter 1: Introduction

Breast cancer remains the most common cancer affecting women worldwide. More than 1.67 million women were diagnosed in 2012, with more than half a million women dying annually from the disease [2]. Low- and middle-income countries (LMICs) carry a disproportionate burden of disease with increased numbers of patients presenting with advanced stage of disease and increased mortality per stage of disease. It is estimated that in the next 15 years the rate of diagnosis will double to 3.2 million women per year [3]. Advances in understanding this global cancer burden has led to advocacy for "all women who develop breast cancer to have an equal opportunity for early diagnosis…and timely access to potentially curative treatment" [4].

In South Africa, and in other LMICs, access to care is dependent on a complex interplay of individual and health systems factors, most of which have been poorly described. Whilst the disease has been characterised by low levels of knowledge and late stage at presentation, assumptions regarding the causes of this are often discussed in literature, health policy or the media without references or objective evaluation. These have included fear of biomedical care, antipathy towards cosmetic 'disfigurement', patriarchal or hierarchical gate-keeping to care, and financial- or transport-related burdens [5–7]. In addition, systematic reviews have viewed Africa, sub-Saharan Africa or LIMCs in general as a homogenous group, either by necessity due to paucity of relevant studies or academic ignorance of geosocial nuances [8–11]. However, growth in country-specific research agendas, the recognition of intra-country population variances and more patient/participant-centred studies have led to a shift of understanding of barriers from either patient or provider related, to a more complex interplay of determinants that encompasses biological, economic, geographical, psychosocial and individualistic factors.

This project was a result of the recognition of the paucity of understanding of the patient's experience of breast cancer recognition and diagnosis in South Africa, and of an unresolved conundrum found by the candidate in her surgical practice, with the patients she cared for: why women with equal economic or geographic barriers should present early with a trauma to the chest, but late with a cancer of the breast; why patients seemingly from the same social and ethnic background should differ in their acceptance or refusal of the biomedical management of their breast cancer; and why a young, urban educated woman might present with the same advanced disease as her elderly illiterate unemployed female counterpart; when all the while the literature tells us these factors are defining determinants of breast cancer in South Africa.

Therefore, to answer, or at least inform this question further, this project aimed to examine the determinants of advanced stage of breast cancer at presentation, through a description of delay to presentation, patient-related factors and the biological characteristics of disease. To address this aim, four main objectives were investigated. **Five** publications were produced to acheive these objectives and they are presented in this thesis. These objectives were:

Objective One: To describe the relationship between patient socioeconomic characteristics with their fears and beliefs concerning breast cancer in an economic cross-section of South African survivors.

Objective Two: To determine the relationship between stage of breast cancer at presentation with structural delays affecting the patient, including work, transport and healthcare access.

Objective Three: To determine the relationship between stage of breast cancer at presentation with psychosocial factors affecting the patient, including their fears concerning breast cancer and beliefs held surrounding its presentation, causes and consequences.

Objective Four: To assess the relative contributions to advanced stage at presentation of patient factors and of tumour biology.

Chapter 2: Literature review

Breast cancer and other conditions of the breast are well researched in high-resource areas such as the United States (USA) and Western Europe. However, information is still lacking on the burden of these conditions in low- and middle-income countries, particularly in sub-Saharan Africa.

Breast cancer is one of the leading causes of death from cancer in women in South Africa as reported by the South African Cancer Registry. The most recent literature regarding this is from 2012 and reports that breast cancer was the leading form of cancer among women in South Africa (21.8%) with an age-adjusted incidence rate of 27.6 per 100,000 persons, corresponding to a lifetime risk of 1 in 33 [12]. These data, however, were not current and may not reflect the current incidence of the disease. In 2009, Statistics South Africa reported that breast cancer was the 9th leading cause of death amongst females aged 50 – 64 years old in the Gauteng Province, accounting for 2.9% of all deaths [13]. However, it is hypothesized by local breast cancer clinicians that breast cancer incidence is under-reported and the mortality figures underestimated.

Barriers to breast cancer care

The optimal and appropriate treatment of breast cancer is dependent on timely presentation and diagnosis. Presentation to a healthcare worker will normally follow a period of time where the patient is aware of the symptom. This variable length of delay may impact on the stage of cancer at presentation which, in turn, will impact on survival. Alarmingly, a delay of more than three months is associated with a more advanced stage at presentation [14,15], which, in turn, is associated with poorer survival [16]. Through delay to presentation and difficulty in accessing treatment many healthcare disparities will affect the outcomes in breast cancer. In the USA it is understood that race, income, education and beliefs all affect access to health care [17–19]. Black women are reported to have decreased survival at every stage of breast cancer when compared to all women [20, 21]. Specifically in the USA, low-income is predictive of poorer outcome because of more common late presentation or inadequate access to quality care, but this is also found in many other studies globally [22–29]. In trying to understand these disparities and their effect on outcome, many studies rely on socioeconomic factors including education, insurance status, work and transportation [18,28,30–32]. These factors may provide physical barriers to access adequate health care, such as the inability to pay for services or transport to facilities, however patients' beliefs, fears and understanding of the disease can provide a transparent, but equally substantial psychosocial barrier to breast cancer care.

To overcome many of these barriers affecting cancer care provision, including its quality and outcomes, multi-disciplinary breast management is imperative [33]. The latter is considered the gold standard for the treatment of all breast disease, in particular breast cancer, and allows peer-review of all patients being treated and easy communication by all the health professionals who are part of the team [33,34]. Multi-disciplinary management of patients with the inclusion of other healthcare professionals and lay care workers allows cognisance of not only the disease process, but also the cultural and social background of the patient and any potential biases this may infer. Understanding different cultural and psychosocial prejudices allows healthcare workers to approach their patients sensitively and address potentially undisclosed concerns. This leads to more effective counselling and education concerning treatment options when cancer has been diagnosed. In addition, at a community level it allows improved targeting of populations at risk of late referral or those that may be missed by health-screening initiatives in breast disease, due to their beliefs and biases.

Breast cancer awareness and the Health Belief Model

Breast cancer is a disease that can affect all women [21,24]. However, perceptions of breast cancer over the last 30 years in South Africa, and in African women are in the process of changing. From being considered a disease of older white women [35], there is now a move in community awareness to recognise that all women can be affected, across racial, menopausal and cultural boundaries. This change has occurred through aggressive community education projects [36–38], targeting of the media in public health campaigns [39, 40], and the founding of several single issue breast cancer advocacy and support groups [41–43]. In pursuing breast care awareness in South Africa, education and support projects often utilise financial or logistical experience and information produced internationally. These are based on American and European models and may include information in English alone or pictures of women with European features and/or celebrities. Although this may be successful in raising awareness within some regions of society, the larger South African population, particularly those attending the public hospital breast care centre, remain unreached [44]. By not targeting and utilising more local languages, differing cultures and belief systems in providing patient information, problems with the diversity of languages, poor literacy rates and even an inherent suspicion of accepting education and advice on breast health from women of a different cultural background will be unresolved. Moreover, before it is possible to better reach women with education and access, we must first determine the presence and impact of these psychosocial barriers on the help seeking behaviour of women with breast cancer.

Most health education programmes and public health initiatives have the Health Belief Model (HBM) at their core and utilise this model to generate effective outcomes [45]. The model was

devised by American public health workers in the 1950s to describe why uptake for Tuberculosis screening was poor and how it could be improved [45,46]. It is summarised by four key constructs which influence an individual's or collective individuals' health-seeking behaviour and include 1) perceived seriousness, 2) perceived susceptibility, 3) perceived benefits, and 4) perceived barriers [45]. Although the four key constructs from this American model can be extrapolated in general, the specific details of each may not fit with the experience in different cultures. Specifically, it assumes that a patient persuaded of the seriousness of their disease will be more likely to present for treatment. There is also an assumption that knowledge of increased susceptibility is associated with increased health-seeking behaviour. In the HBM, knowledge of seriousness and susceptibility together are assumed to lead to increased threat [45]. Again, this model does not allow for personal beliefs, such as perceived protection from a disease, nihilism or disempowerment preventing impetus for care, or the beliefs of the religious or cultural community the patient belongs to.

Reasons for delay in presentation

In Africa, previous studies have investigated the reasons for late presentation of breast cancer and reported that ignorance and fear accounted for women not presenting with palpable breast masses when they are first detected or small [47–49]. In a study from Ghana the major reasons for delay or absconding were fear of mastectomy, herbal treatments or prayer, and financial concerns [50]. A patient may believe they are susceptible to cancer but consider themselves financially burdened by seeking treatment [51, 52]. Although access to health services may be a reason for late presentation [52,53], an alarming number of patients had delayed treatment following erroneous reassurance in other medical consultations [54]. These latter findings further highlight that it is not just patients who should be the target for awareness, but that the education of healthcare professionals in our community are equally important.

Beyond the HBM, health beliefs can be strongly related to psychosocial and religious biases. This was confirmed in many social groups [17,53,55–58] and is reported as affecting health presentation (and delay) to the detriment of the patient. Actively seeking medical treatment can be a sign of spiritual weakness and unbelief in the higher powers' ability to heal [55] and that strong belief in a higher power means an early diagnosis only "gives one a longer time to worry and be sick" [59]. Because of a disparity in outcomes between white (non-Hispanic) and African-American women in the USA, many studies have looked at socioeconomic and cultural factors in relationship to race and found their beliefs varied [60]. Strong beliefs in chance or fatalism may lead women to recognise the presence of the disease but be disinclined to seek care [53,59,61]. Although there was no correlation between years of education and health beliefs, less educated women were less likely to feel in control of their disease [59]. Furthermore, in many diseases

difficulty in the acceptance of biomedical treatment options may lead to a trial of traditional medicine [55]. A study in Nigeria showed that 55% of patients who were using herbal or complementary medicines did not inform their medical doctor, mainly because they were not asked [54]. An implicit or overt disapproval of herbal or traditional methods of healing by medical professionals means that the patient may then default on appointments and disappear to follow up [53]. In many cases the patient will re-present with advancement of disease, which may prevent breast-conserving surgery or indicate metastatic disease. Unfortunately, the subsequent change of treatment or seemingly 'more aggressive' treatment can lead to further distrust of the biomedical model and the practitioners, and confirm a belief that patients who go to hospital will die [53]. Many may delay treatment because of the fear of mastectomy [47], unable to access or unaware of possibilities such as breast conserving surgery.

Understanding the barriers to breast cancer care in South Africa is imperative in improving care and enabling and encouraging women to access healthcare earlier. While little has been studied on psychosocial barriers to cancer diagnosis and treatment in South Africa, studies into adherence of anti-retroviral treatment for HIV/AIDS look at the interplay of beliefs and help-seeking behaviour in HIV in South Africa and indicate some potential barriers which can also be seen in our cancer care. In these studies patients believed that seeking medical treatment was a sign of weakness of religious faith and may often wish to embark on a trial of prayer [53]. Once healing prayer was embarked on, any seeking of medical care signals a doubt in the healing power of their higher power. Charismatic leaders can encourage patients to seek only religious healing and again patients will delay seeking or accepting medical care until advancement of disease [62]. In addition, works on maternal health and HIV in sub-Saharan Africa have also identified similar themes in delay and barriers to care, including transport, work, money and attitudes towards disease such as guilt, denial and shame [63–65].

Defining a population at risk

A severe limitation in extrapolating information from the global breast cancer literature is that patients studied are most commonly from one particular racial or ethnic group. This can be problematic in a new century and in a post-apartheid South Africa, where we should question the influence race alone has on beliefs around breast cancer and receptiveness to treatment, or whether, as in the HBM, universal concerns over welfare, and fear around treatment and death transcends race or culture.

Health surveys among seemingly homogeneous groups (such as Black Africans living in the UK) show great diversity of language, education, diet and health behaviours [66], and therefore assuming help-seeking behaviour or barriers will be standardised within a racial group should be treated with caution. In addition, using such groupings for purposes of drawing socioeconomic

conclusions (such as race as a proxy of medical insurance status or poverty) ignores economically advantaged African patients and the underprivileged and uneducated of other races [66]. Whether beliefs in a higher power or the practice of ancestor worship mean that the primary malignancy is not a result of abnormal cells but part of a curse or disapproval of these entities [55, 59], or whether the attraction of alternative therapies and distrust in mainstream modern medicine influences a patient's decision [27], for many patients the primary cure of the cancer cannot be found in a biomedical model and only after other options are exhausted may medical treatment be sought.

In addition to determining the barriers to seeking help is the inherent question of whether the delay caused by these cultural, psychosocial and socioeconomic barriers impacts on patient prognosis and survival. Although many studies worldwide have looked at this question, systematic reviews of this data indicate that the relationship between delay, advanced stage and prognosis is more complex [15, 67]. Delay appears to be related to survival; however, it is unclear whether that relationship would hold strong if stage of disease is controlled for. Nevertheless, a linear relationship between delay and stage of disease is often erroneously assumed. Therefore, patients whom present later, who may not have an increase in their tumour size, nodal involvement or metastatic status, may not have a decrease in survival. This may be due to the confounding factor of tumour biology which, through differing grades and characteristics, affects time to metastatic spread and ultimately survival. In fact, in one study from the UK those who delayed presentation for more than six months had a longer associated survival [68] which may be in part due to slow tumour progression caused by indolent pathology, not controlled for in the study.

The problem of the 'problem indigent patient'

This study aimed at examining the help-seeking behaviour in breast cancer care of the many diverse groups in urban South Africa. As healthcare workers, we may have our own beliefs and prejudices concerning individuals, groups and their help-seeking behaviour, expecting some women to present early and others to delay, depending on their education, socioeconomic status and culture. Often a dialogue (that may be unspoken) in healthcare workers in South African hospitals is of the 'problem indigent patient', slow to come to the hospital and quick to run to the traditional healer [69]. However, Spurlock et al. (2006) showed that there was no correlation between years of education and disease beliefs [61] and no previous studies in South Africa described a population in South Africa who present late for care, but are devoid of the compromising socio-economic characteristics which impact on their ability to access care . Whether any of these international findings of socio-economic and psychosocial barriers can be extrapolated to women in South Africa is unknown. In addition, the psychosocial barriers to

breast help-seeking behaviour may be different between the different ethnic or economic groups of this country but provide no less of a barrier, albeit traditional medicines in a rural patient or vitamin supplementation in an "educated" urban patient.

There is a considerable lack of understanding of, and research on the extent by which South African patients' psychosocial or socioeconomic influences affect their help-seeking behaviour in breast cancer care. While some of these areas have been investigated in individual groups, there has been no holistic analysis on how (or indeed if) beliefs concerning breast cancer and its care differ by race, culture, education or environment in South Africa. At present much of the discourse around cancer awareness in sub-Saharan Africa and South Africa in particular carries preconceptions concerning different racial groups not founded on evidence-based research.

This study in context

Therefore, in this doctoral thesis I aimed to investigate the diagnosed breast cancer patient's understanding of the breast cancer and the experience of delay, access and care in urban South Africa. In addition, by correlating the delay to presentation to the clinical stage of breast cancer at presentation, this study aimed to determine where factors related to the patient's psychosocial bias (be it individual and/or ethnically related), the delay or difficulty in access to care, and inherent tumour biology affects stage of breast cancer at presentation.

Chapter 3: Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients with Breast Cancer in Urban South Africa.

Reference: Rayne S, Schnippel K, Wright K, Kruger D, Firnhaber C, Benn C. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients with Breast Cancer in Urban South Africa. **J Glob Oncol** 2016;3:125–34. doi:10.1200/JGO.2015.002691

At the time of this thesis submission, Chapter 3 (Paper 1) was published in Journal of Global Oncology. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the University with combined references for clarity. See Appendix A1 for a PDF version of the published article.

Introduction

Breast cancer is the most common form of cancer to affect women in South Africa and was responsible for 20.8% of female cancers and more than 10% of the entire cancer burden [70]. The National Cancer Registry (most recent report, 2009) reports an age-adjusted incidence of 27.6 per 100,000 equating to a lifetime risk of 1 in 33 women [70].

In developed countries, advances in the management of breast cancer over the last fifty years, including screening and early detection programmes, have led to an increase in survival rates. Early stage breast cancer has a survival of more than 95% [71], however late stage disease continues to be responsible for most cancer deaths, through metastatic progression.

Optimal treatment for breast cancer and increased survival relies not just on early detection but early and continued presentation at a centre capable of treating the disease. Thus, healthcare disparities will affect a patient's outcome [16]. In trying to understand these disparities and their effect on outcome, studies often look to socioeconomic factors including education, health insurance status, work and transportation [18,30]. These factors may provide physical barriers in accessing adequate health care. Physical barriers can also become a source of psychosocial stress for the patient causing fears which can also affect timely presentation, treatment and patient choices about their breast cancer care [31].

In addition to physical barriers to access of care and fears related to socio-demographic factors, further stress can be associated with knowledge (or lack of knowledge) of treatment modalities, their associations and side effects.

Understanding the fears associated with breast cancer in South Africa is important in improving care and enabling and encouraging all women to access treatment earlier. By interviewing

women accessing services in both government and private facilities in Johannesburg, we sought to determine the fears experienced by all women with a diagnosis of breast cancer, allowing identification of important universal areas for education and improved care provision.

Methods

This dual centre study included patients with and without medical aid in Johannesburg, South Africa. Medical aid is the system of health insurance in South Africa bought by the end-user which allows access private facilities. Patient without medical aid or with poor coverage are seen in government funded facilities at low- or no-cost. The government clinic is based within a provincial government tertiary hospital and manages approximately 350 new breast cancer diagnoses each year. Only 6% of these patients have medical insurance (unpublished local data). The private facility sees private or medical insurance funded patients and manages approximately 400 new breast cancer cases per year.

From November 2011 to May 2013, patients undergoing treatment for breast cancer in each centre were recruited to complete a questionnaire. The questionnaire was distributed to consenting patients attending for diagnosis, operation or follow-up over a 21-month period. Each patient was offered the choice to complete the questionnaire alone or with the aid of an assistant, who could translate into the patient's preferred language. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The first part of the questionnaire included sections on demographics, socioeconomic status, educational background, work, transport, and religious affiliations. The second part of the questionnaire used a summative scale of 0 (no fear) through 5 (fear under control) to 10 (very fearful) to determine the patients' feelings of fear and concern *at diagnosis* about issues related to their care, social circumstances or prognosis.

Analyses

Patient characteristics were described using frequencies and proportions. Age was categorized as age 40 years and younger, or age 41 years and older. Having dependents was compared to not having dependants. Social status was categorized as being married or unmarried, the latter of which included women who were single, divorced, or widowed. Women who were employed by others or considered themselves self-employed were compared to women who were unemployed or retired. Education was grouped according to highest level of formal schooling completed: primary, secondary, or tertiary. Reported race was collapsed into black and non-black categories, including women who indicated white, indian (asian), coloured, and mixed races. Women who indicated that they sometimes or always had difficulty with transport or taking time off from work were compared to women who indicated they seldom or never had those difficulties. Two-

sided differences of proportions were compared using Pearson chi^2 test. A p-value <0.05 was considered statistically significant.

Responses were categorized as fearful (score greater than 5) or not fearful. Modified Poisson regression with robust error estimation [72] was applied to the data to estimate the relative risk of being fearful according to patient characteristics; risk ratios and a 95% confidence interval (CI) are presented. Univariate and multivariate results adjusted for the patient characteristics described above are presented. All statistical analyses were done in Stata v13.1 (College Station, Texas).

Results

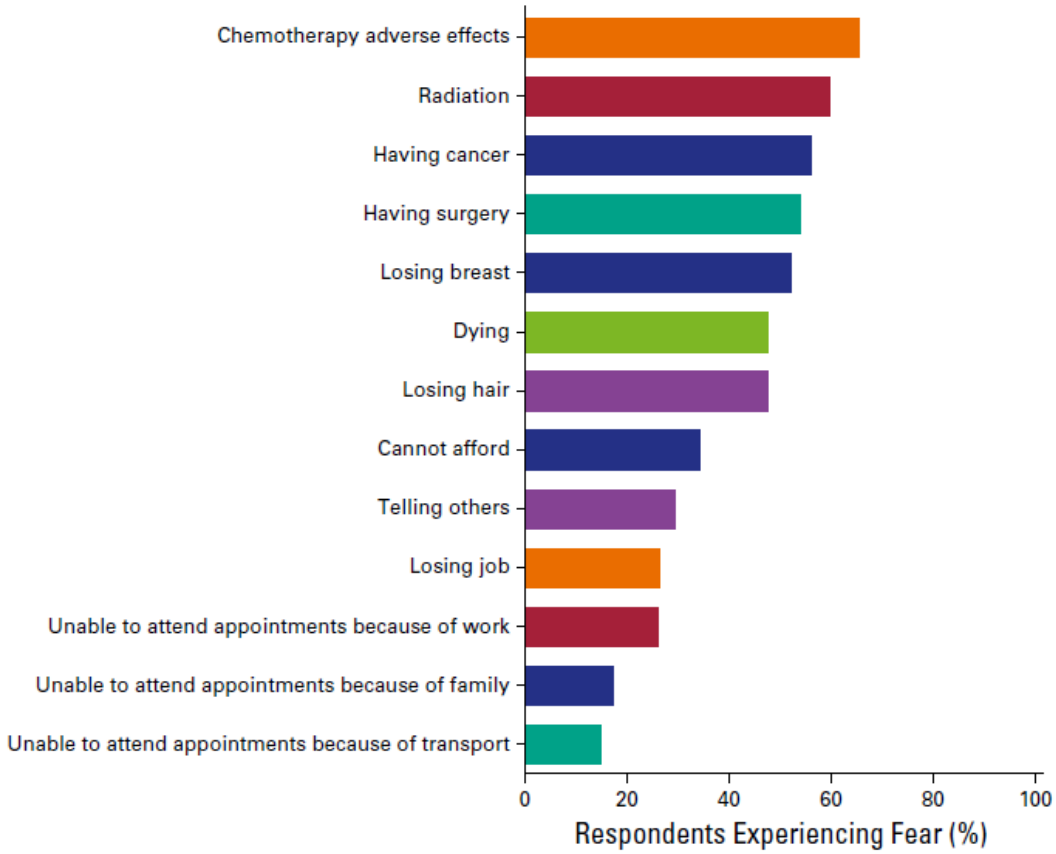
A convenience sample of 263 patients was included. Patient's age ranged from 18 to 86 years with a median of 52 years (IQR: 44-62) with 41 patients who were 40 years or younger at diagnosis (16%). Table 1 lists patient characteristics grouped as either private hospital or government hospital and shows that government patients were more likely to be black (p<0.0001), single and living with others. They were less likely to be employed when compared to private facility patients (52% vs 73%; p=0.001). Significantly more private facility patients had a tertiary education (53% vs 13%, p<0.0001) and 36% of government patients attained primary education only compared to 6% from the private facility. Access to cell phones was extremely high in both groups (97% private facility, 95% government) but computer and internet usage was significantly higher in private patients (87% vs 39%, p<0.0001).

(Ch3) Table 1 Patient characteristics

Description		Private hospital	Government hospital	Total	p-value
		n=93 (35%)	n=171 (65%)	n=263	
Age					
	<=40 years	15 (16%)	34 (21%)	207 (81%)	0.388
	41 years+	77 (84%)	130 (79%)	49 (19%)	
Race					
	Black	7 (8%)	78 (48%)	85 (33%)	<0.000
	Non-black	85 (92%)	85 (52%)	170 (67%)	
Marital status					
	Married	50 (59%)	70 (47%)	120 (51%)	0.081
	Not married	35 (41%)	79 (53%)	114 (49%)	
Formal education					
	Primary	5 (6%)	56 (36%)	61 (25%)	<0.000
	Secondary	37 (41%)	80 (51%)	117 (48%)	
	Tertiary	48 (53%)	20 (13%)	68 (28%)	
Dependants					
	No dependants	18 (20%)	23 (15%)	41 (17%)	0.297
	Any (1 or more)	72 (80%)	132 (85%)	204 (83%)	
Have cell phone					
	Yes	98 (97%)	147 (95%)	265 (96%)	0.484
Use computer					
	Yes	79 (87%)	62 (39%)	141 (56%)	<0.000
Employed, job					
	Yes	67 (73%)	83 (52%)	150 (60%)	0.001
Time off for appointments difficult					
	Yes	12 (13%)	32 (24%)	44 (20%)	0.039
Transport for appointments difficult					
	Yes	8 (9%)	58 (36%)	66 (26%)	<0.000

All fears

Figure 1 illustrates how many patients were fearful (score greater than 5) for each domain included in the questionnaire. The overall pattern demonstrates that fears related to treatments and prognosis were far stronger than those related to socioeconomic barriers. The most common treatment-related fears were related to chemotherapy side-effects (65.4%) followed by radiation and surgery (59.7% and 53.9% respectively). Although some patients feared both surgery and breast loss, the differences between the women who feared surgery and those who feared breast loss was statistically significant ($p<0.001$) as were women who feared surgery and women who feared radiation ($p<0.001$) using the Pearson chi^2 test. Concerns over ability to attend appointments for reasons including transport and work were the lowest.



(Ch3) Figure 1 The percentage of women categorised as fearful (fear score greater than 5) in each described fear

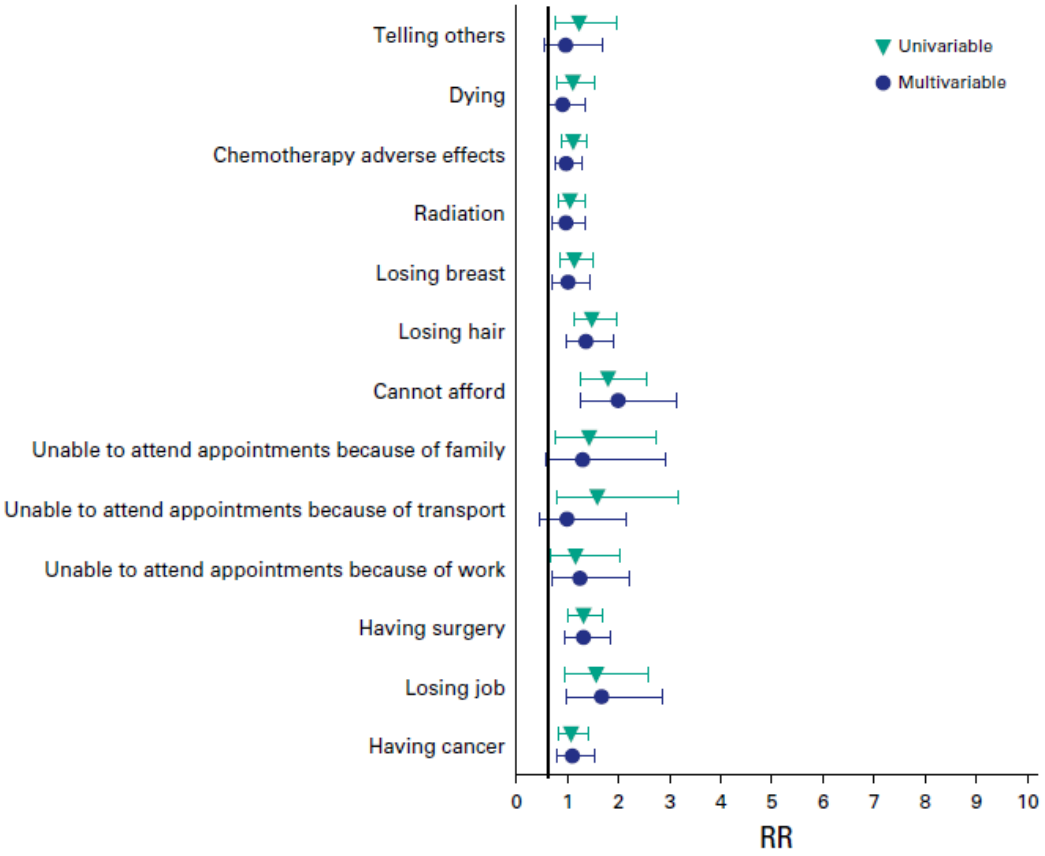
Relative risks of different fears

The relative risk of fearfulness for women under 40 years were uniformly higher than for older women (Figure 2). This was most pronounced in their worry over affording all appointments and treatments (RR: 1.80, 95%CI: 1.26-2.56). Young women also had an increased likelihood of treatment related fears, significantly in fear of hair loss (RR: 1.48 (95%CI: 1.12-2.95) and fear of surgery (RR: 1.31 (95%CI: 1.02-1.68)).

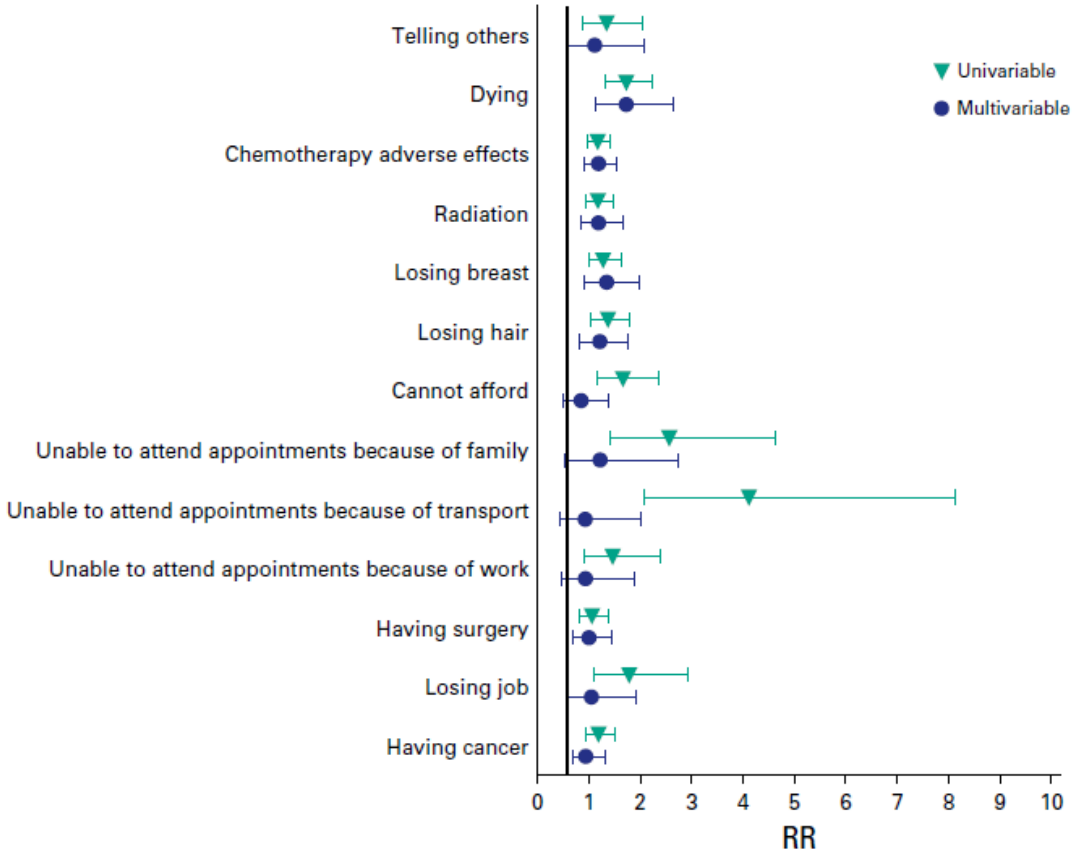
In women of all ages, difficulty with taking time off work (a relative measure of job insecurity) had increased likelihood of fear about job loss (RR: 2.59, 95%CI: 1.59-4.21) and were more likely to fear missing appointments either due to transport (RR: 2.46, 95%CI: 1.52-3.96), or due to family commitments (RR: 2.46, 95%CI: 1.52-3.96). They also feared the side-effects of chemotherapy more (RR: 1.30, 95%CI: 1.07-1.58). A tertiary education was protective against fear of job loss (RR: 0.46, 95%CI: 0.24-0.92) and not attending appointments due to transport and family RR: 0.20 (95%CI: 0.07-0.58) and RR 0.33 (95%CI: 0.14-0.75), respectively.

The fear of dying had a median of 5 and the widest spread of any of the fears with an IQR of 1 to 9; 47.7% of participants indicated they were fearful of dying (a score above 5). Women with dependents were 1.73 times more likely to be afraid of dying (95%CI: 1.03-2.90) as were black women (RR: 1.79, 95%CI: 1.33-2.24). Figure 3 shows that black women experience much more fear towards the physical barriers to care: they were much more afraid of missing appointment due to transport problems (RR: 4.11, 95%CI: 1.42-8.12) or due to family commitments (RR: 2.56, 95%CI: 1.42-4.62) and worried they could not afford to get cancer (RR: 1.66, 95%CI: 1.17-2.37). These results are similar to those experienced by women in the public hospital (Figure 4).

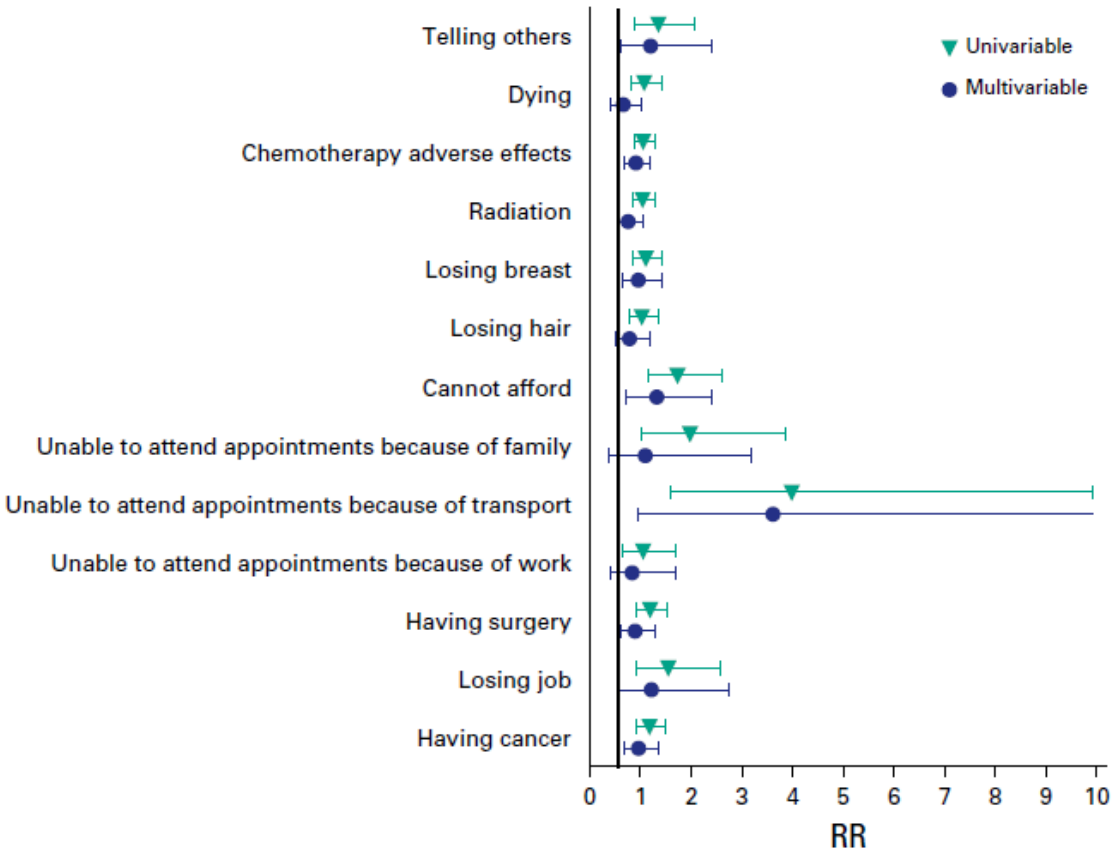
In adjusted regression, where patient characteristics were held constant (Figure 5), black race remained a significant predictor of fear of dying, aRR: 1.73 (95%CI: 1.13-2.64). Socio-economic characteristics such as employment, use of the government hospital, and computer use were not statistically significant predictors of fear of dying. Although being young, black, in a government hospital or with transport difficulties increased the fear of affordability of treatments, none remained significant in the multivariate adjusted model.



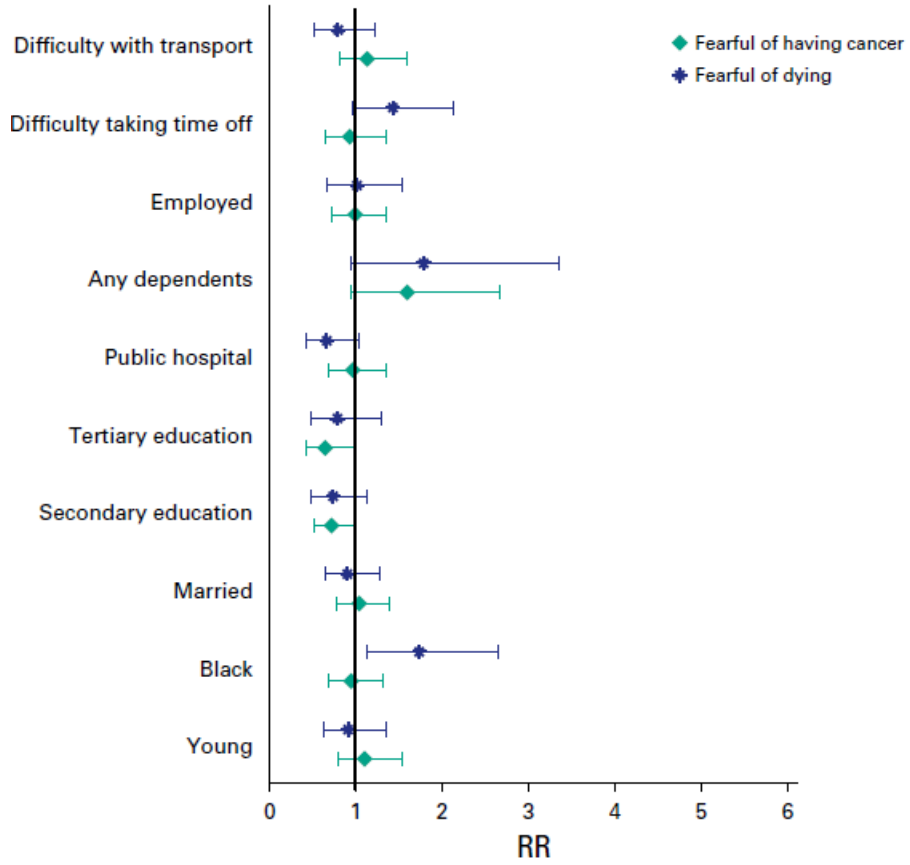
(Ch3) Figure 2 The relative risk of fears in women aged 40 or less shown relative to those above 40 years old.



(Ch3) Figure 3 The relative risk of fears in women of black race shown relative to all other women in the study



(Ch3) Figure 4 The relative risk of fears in women at public sector hospital shown relative to women at private sector hospital



(Ch3) Figure 5 Multivariate analysis of influences on the fears of affordability of appointments and treatment and dying

Discussion

In women with a diagnosis of breast cancer, this study found that breast cancer treatment and its side effects, including the universal fears of cancer and dying were associated with increased fear at diagnosis, but socioeconomic factors including transport, work and financial issues were not. Affordability of cancer treatment was the only socioeconomic factor that was associated with an increased level of concern.

Studies have found that fear can be important in determining delay to treatment [47,50,73,74]. How patients are treated also appears to influence if they continue to attend for care, whether by their physicians [75,76] or due to side effects [50,77,78]. However, the relative contribution of these factors to fear associated with a diagnosis has not been determined. The new findings from the present study suggest that physical obstacles may represent less of a barrier to care than psychological fears associated with treatments in our urban South African setting.

Within this sample different populations emerged, each with unique combinations of concerns. Like many other studies [79,80], we found a significant relationship between younger age and higher cosmetic fears around hair loss, although not loss of the breast. This lack of fear around mastectomy may reflect the options of reconstruction and breast conserving surgery. Younger women also face increased fears over affordability of treatment, having surgery and job insecurities. These differences reflect the pressures these women face in maintaining income after a diagnosis. The loss of hair could also be concerning in this light as it would publicise cancer therapy to employers and colleagues. Studies that have looked at the psychological needs of young women have found that younger patients viewed themselves as different from older patients, with problematic work and relationship issues, fertility decisions and poor support when transitioning into survivorship [81,82]. Our findings are consistent with this and highlight the distinctive support needs of this young group.

In addition, this study highlighted other groups with less psychological resilience around breast cancer treatments including those with job insecurities (increased fear of job loss) and those with dependants (fear of dying) whose additional supportive needs may be overlooked. The near universal fear of cancer, with all its negative connotations, was present in increasing measure in those with dependants. In an economic centre such as Johannesburg, members of the working population are often held responsible for household dependants in addition to supporting an extended family and homesteads in rural areas. It is possible that the demands of close care-giving to family, the economic demands of dependants near and far, and the unexpected nature of cancer can add significant psychological stress to such patients.

The highest scoring fear was in relation to possible radiation treatment. This mirrors other studies which show women have a non-specific fear of radiation [30,83], and possibly fear its relationship to causing cancer. These findings highlight the important role that education of the pre-symptomatic woman (essentially every woman) in how breast cancer is not just diagnosed, but also treated. Education has been shown to reduce fears and improve attendance in diverse global populations [84–86]. including recent successes of HIV/AIDS community education in sub-Saharan Africa where radio and TV soap operas have been used to highlight diseases such as HIV/AIDS with measurable effect [87]. The contribution of recent high profile breast cancer survivors in South Africa can also be used as an opportunity to introduce public discussion of treatment options and successes in breast cancer care [88].

The current study indicated an extremely high ownership of mobile phones in the population studied (89%). This, coupled with the increasing use of internet through smartphones connectivity allows eHealth and mHealth strategies to be employed for education. Already, young patients in South Africa access health information for themselves and family through smartphone

internet access [89], and this has been shown to modify health-behaviour, if not knowledge, in a South African patient population [90]. These forms of education can complement more traditional mass-education initiatives which have been used in breast cancer awareness in low-income, low-awareness areas of the world [91,92] and in South Africa, with layering of messages of education through multi-media [87]. This new finding that breast cancer treatments are a source of fear and potential barrier to care means that introducing management options and expectations into the dialogue of breast cancer awareness and screening should be a practical application following this study for cancer care in South Africa.

The fear of dying in black women was moderated by attendance at a government hospital. This may be a reflection of good social support, closer ties to community and in particular the presence of survivor-navigators in the government hospital, funded by a non-governmental organization. Other studies have also found that having counsellors or navigators present, reassures patients and helps them negotiate the complex medical system and are then likely to receive recommended standard treatment [93]. In addition, navigators are able to identify and resolve intra-personal (defined as beliefs knowledge attitudes and socioeconomic) barriers that affect patients [94]. Securing funding to maintain and increase the number of available navigators is a challenging undertaking in our resource-limited environment, however the potential future outcome of improved patient care highlights the necessity.

In previous studies have shown strong relationships between disparities of access and response to breast cancer care for different races internationally and in South Africa [77,95]. Studies from Africa or of African migrants are often reliant on using cultural beliefs and fears to explain these barriers to care [18,30,31,73,74,95,96], whereas in this study we found that although there were differences between races in their levels of fear, these were related to inherent socioeconomic disparities rather than cultural responses. Black women were more likely to fear hair or breast loss and more likely to experience concerns over socioeconomic obstacles. However, due to the legacy of previous economic/political policies in the country, there remains a significant association between race and socioeconomic status. These socio-economic factors were strong confounders of race in this study and on multivariate analysis, most of the race-fear relationships weakened, demonstrating little inherent racial differences but inherent strong educational and economic drivers of fear. These data provide preliminary support for questioning the existence of culturally-bound reasons for delay and failure in breast cancer treatment and point to more holistic concerns shared by women of all races in all countries.

In all countries, but particularly in post-apartheid South Africa relying on factors such as race to predict fears, attitudes and access is problematic. These data confirm the questioning of the influence race alone has on fears around breast cancer and receptiveness to treatment and in fact

whether universal concerns over welfare, and fear around treatment and death transcend race or culture. Health surveys among other seemingly homogeneous groups show great diversity of language, education, diet and health behaviours [66] and therefore assuming help-seeking behaviour or barriers will be standardised in a racial group should be treated with caution.

Limitations

For practical reasons, an opt-in invitation method was used in this study, and no information is available for those that declined to complete the questionnaire. Although translation was available, there may be a selection bias towards English-speaking patients of all races, and this may confound some of the variables, particularly around education and employment. Therefore, the extent to which this can be generalised to all breast cancer patients is unknown. An additional consideration and scope for further work is that the study was purely quantitative in its approach. Examination of the full scope of fears and attitudes of patients through interviews would increase the range of our understanding of the patient's experience.

The study was cross-sectional in nature and while women were asked to recall the fear experienced at diagnosis, in recollection some of these fears may have been moderated or increased for women who had already started treatment.

In addition, a further limitation as with many studies of breast cancer in sub-Saharan Africa, is that this sample is taken from patients attending an urban specialist centre. Although they would have vital and valid responses for this study particularly regarding access and barriers to care, it is impossible to target patients with breast cancer who fail or refuse to present to medical services at any point in their care. However, many of the patients in this current study would be presenting in the later stages of the disease for final palliative care of fungating wounds or terminal disease symptoms. More studies are required to relate medical details including staging at presentation to psychosocial and socioeconomic characteristics.

Conclusion

Studies on barriers to cancer care in underserved populations have often focussed on the physical barriers that prevent patients from accessing care. Our results show that women are far less fearful of how they will negotiate life during treatment (including work, finances and family commitments) than they were of the planned treatments. Young patients are particularly vulnerable to increased fear when approaching treatment for breast cancer and this group should be targeted with specific support. For all women, the public message of breast awareness should include education about breast cancer treatment and emphasise the importance of treatment for survival.

Chapter 4: The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa.

Reference: Rayne S, Schnippel K, Benn C, Kruger D, Wright K, Firnhaber C. The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa. J Cancer Educ 2017. doi:10.1007/s13187-017-1234-3.

At the time of this thesis submission, Paper 2 was published in Journal of Cancer Education. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university with combined references for clarity. See Appendix A2 for a PDF version of the published article.

Background

In South Africa, breast cancer is the most common cancer to affect women. Breast cancer is responsible for 20.8% of all cancers and one of two leading causes of cancer death, being preceded only by cervical cancer [97]. The most recent figures from the National Cancer Registry (2009) report that the lifetime risk for developing breast cancer in South Africa is 1 in 33 (age-adjusted incidence of 27.6 per 100,000) [97]. In a country and region where the HIV, tuberculosis and other communicable disease burden is extremely high and a maternal peri-natal mortality rate of 154 per 100,000 [98], cancer has often not been prioritised. However recent successes concerning comprehensive roll-out of anti-retroviral treatment and better treatment of the complications of HIV/AIDS has meant that non-communicable disease management has become more relevant for the long-term health of the population. In the last 50 years, advances in breast cancer management globally have led to a universal increase in detection and survival. Despite this, delayed presentation and late stage disease continue to be responsible for a significant disparity between international survival rates and those in South Africa and other low- and middle-income countries (LMICs).

There is a considerable lack of understanding and research as to the extent to which South African patients' psychosocial or socioeconomic influences affect their help-seeking behaviour in breast cancer care. While some of these areas have been investigated in individual groups, such as in black African women [99], there has been no holistic analysis on how, or indeed if, beliefs concerning breast cancer and its care differ by race, culture, education or environment in sub-Saharan Africa. There can be great diversity of culture beliefs and barriers amongst seemingly homogeneous groups [66], and reliance on specific demographic characteristics to predict attitudes in a diverse and changing country like South Africa may no longer be valid.

This study examines the attitudes and beliefs surrounding breast cancer held by women in the many diverse socioeconomic and racial groups in urban South Africa and aims to determine where there are important universal or specific areas for improved education and understanding.

Methods

This study included patients from two specialist breast care clinics in Johannesburg, South Africa. One is a government-funded hospital serving predominantly uninsured patients and managing approximately 350 new breast cancer diagnoses each year. In close geographical proximity is a private or medical insurance funded practice diagnosing and managing approximately 400 new breast cancer diagnoses per annum.

A convenience sample of patients was recruited from all patients undergoing management for breast cancer at either of the two study centres between November 2011 and August 2013. Recruitment was strictly voluntary, encouraged through posters and direct invitation to take part in the study. Consenting participants completed a questionnaire and assistance was provided by breast clinic staff for patients who required translation of the questionnaire into their preferred language or clarification during completion. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The study questionnaire was designed with multidisciplinary involvement from specialists involved in breast cancer care and included general questions and questions specific to our patient population. Demographic information included age, race and ethnic background, first language, marital status, and dependents. Questions on socioeconomic status included educational background, employment, and work and transport logistics. Women were asked whether they affiliated with any religion and the frequency of attendance at religious services. Particular attention was paid to determining participant's interaction with the world around them, including confidence in reading and writing, access and use of newspapers, television, computer, cell phone, and internet, and time spent outside the home. It should be noted that due to the availability of non-text content in traditional media and online, access to information was considered separate to literacy.

Finally women were asked to rate their agreement with 22 statements (Figure 1) which embodied preconceptions pertaining to delays in health-seeking behaviour, based on those previously described in the literature for breast cancer [18,55,61,100] and HIV for Southern Africa [53,60] and from their personal experience in our multidisciplinary team. A eleven-point summative scale was used to quantify responses from strongly disagree to strongly agree.

Analyses

Frequencies and proportions were used to describe patient characteristics and social circumstances were categorised (categories found in Table 1 and 2). Health services accessed were categorised as government or private depending on which facility they attended. Only 8% of patients in the government hospital have medical insurance (unpublished local data), and this is predominantly low-cost plans which exclude care in private facilities. No government patients are treated in the private facility.

Women who were employed by others or considered themselves self-employed (which may be formal or informal work in South Africa) were compared to women who were either unemployed or described themselves as retired. After the initial demographic description (Table 1) self-reported race was then collapsed into black and non-black categories, (non-black including women who indicated white, indian (asian), coloured (a South African statistical group denoting a mixed race), and mixed races).

Responses to statements of belief were categorized as agree (scoring 6 or greater out of 10) or not agree (scoring 5 or below). Two-sided differences of proportions were compared using Pearson chi2 test. A p-value <0.05 was considered statistically significant. Patient characteristics were also tested using a correlation matrix, and no strong correlations were observed. As a result, interaction terms were not included in the analysis.

In order to facilitate analysis, similar attitudes or belief statements were grouped together (Figure 1) and an average score calculated. Four groups were analysed further. Scores from beliefs related to cancer as a punishment and external control i.e. this is a curse from God, this is a curse from others, and this is a punishment – were summed and an average across the three statements analysed for this "punishment" group. The other three groups were negative outlook (e.g. "I will die in hospital"), positive outlook (e.g. "I will beat cancer"), and belief in alternative treatments (i.e. acceptance of non-medical therapies and healing). Women who did not respond to all statements in a particular group were excluded from that group's analysis. Myths about cancer (regarded as factually incorrect) and questions regarding faith in God were not analysed further, because of ambiguity in the interpretation of these questions or ability to group them homogeneously for analysis.

Modified Poisson regression with robust error estimation [7] was applied to the data to estimate the relative risk of agreeing with each of the grouped beliefs according to patient characteristics; relative risk ratios (RR) and 95% confidence intervals (CI) are presented. Using stepwise regression, any patient characteristic that was significant at the $p<0.10$ level in univariate analysis was included in the multivariate model and multivariate results adjusted (aRR) for the patient characteristics described above are presented. The choice of stepwise regression allowed for

inclusion of women in the analysis who did not have complete information (all questions with a response). All statistical analyses were done in Stata v14 (College Station, Texas).

Results

Two hundred and fifty-nine patients consented to complete the questionnaire. The age range of participants was 20 to 86 years with a median of 52 years (IQR: 44-62), 49 participants were categorised as 'young' (≤ 40 years; 18.6%) and 70 participants were classified as 'older' (> 60 years; 26.6%). Table 1 shows the demographic characteristics of the participants, and that approximately two thirds of participants were from the government hospital (64.6%), most were formally or informally employed (57.0%) and most described themselves as either white (47.2%) or black (32.2%). A significantly higher percentage of government patients were black at 47.9% compared to black private patients at 7.6% (p<0.0001)

(Ch4) Table 1. Patient demographic characteristics (n=259)

Characteristic	Description	Count	%
Age	<=40 years	47	18.1%
	41 to 60	135	52.2%
	61 years +	70	27.0%
Hospital sector	Government	166	64.1%
	Private	93	35.9%
Race	Black	82	31.7%
	Coloured	20	7.7%
	Indian	25	9.7%
	White	124	47.9%
Employed, job	Yes	149	57.3%
	No	83	32.1%
	Pensioner (Retired)	16	6.2%

Not reported /missing: Age (n=7); Race (n=8); Employment (n=11)

The social characteristics of participants are summarised in Table 2. Overall the predominant language spoken was English (62.7%) and was indicated as a first language in 24.4% of black and 75.8% of non-black participants (p<0.0001). English was indicated as either a first or second language for 93.3%. Self-reported levels of competency in reading and writing were high at 89.5% and 83.2%, respectively. Cell phone usage was very high (89.7%) and more than half used a computer (56.0%). Forms of social and informational interaction regularly used by participants were television (94.0%), newspapers (43.0%) and internet (35.0%). At the time of this study (2011-2013) most cell phones owned by members in this population *would not* have been smartphones with internet or intensive data capability which can be seen in the difference

between cell phone and internet usage rates. Religious attendance was high with nearly half of all participants (47.5%) attending services at least once a week.

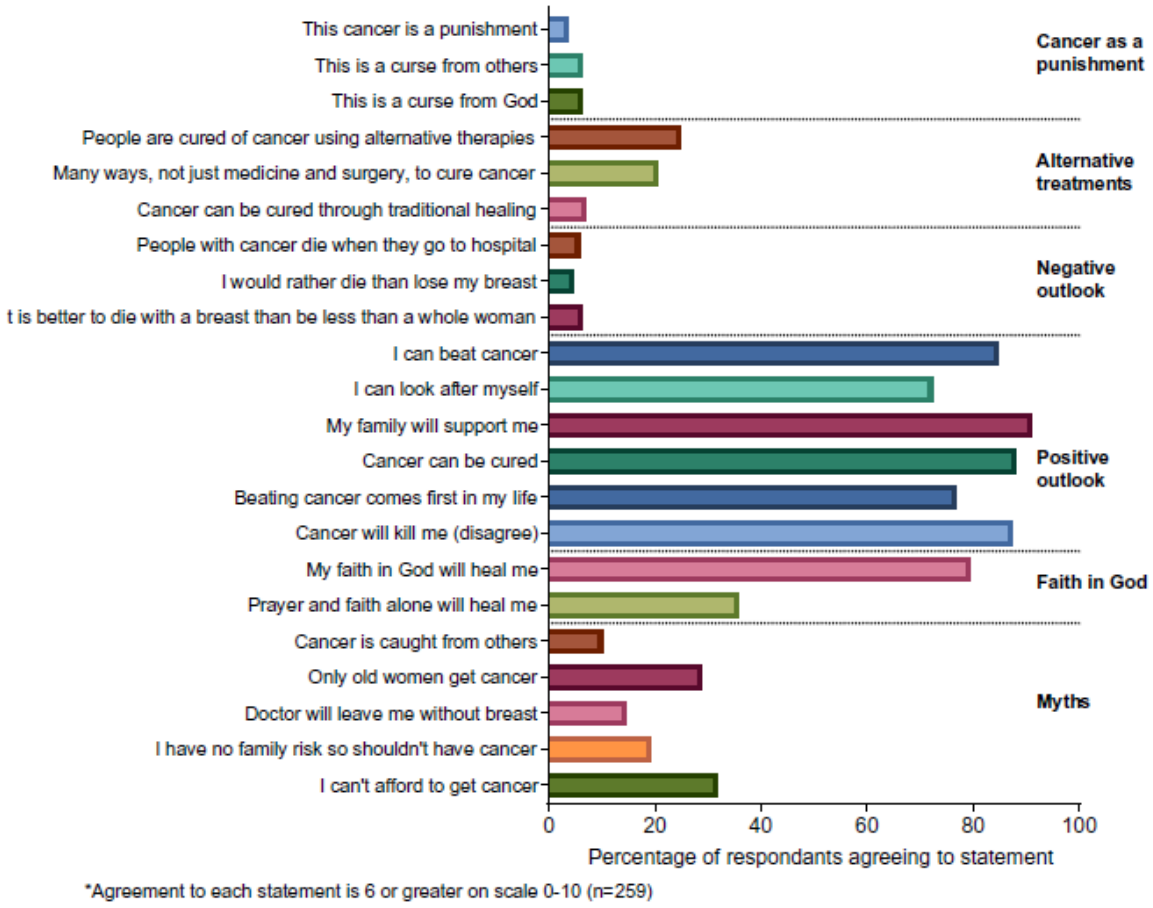
Beliefs

The frequency of patients expressing agreement or belief (a score of 6 and greater) for each statement included in the questionnaire is illustrated in Figure 1. Positive statements of outlook in medical cure and family support were the most commonly believed, followed by beliefs in alternative treatments, both complementary and faith–based. Least believed were statements regarding cancer as a punishment or curse either by God or others.

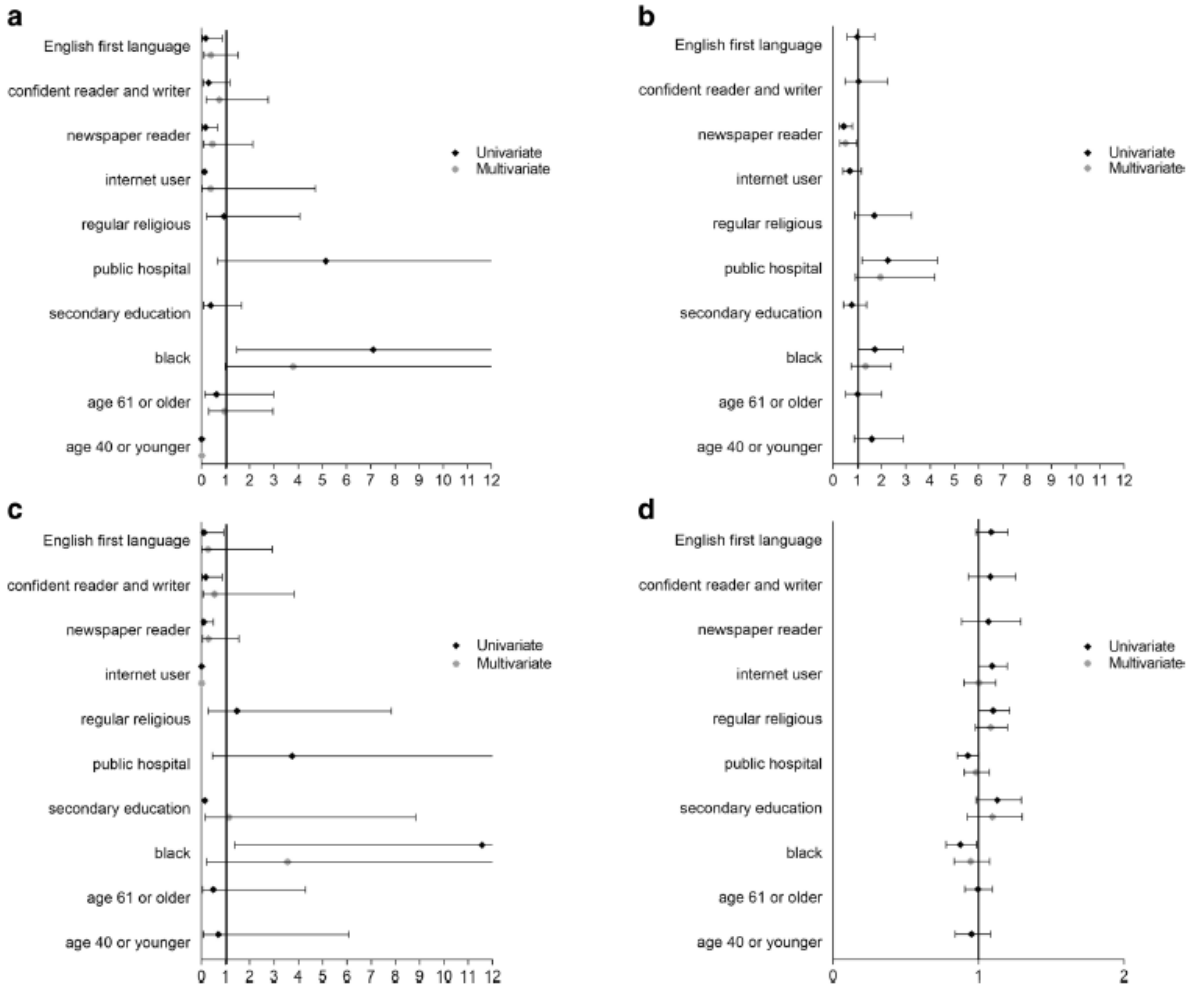
(Ch4) Table 2. Social characteristics of study participant (n=259)

Characteristic	Description	Count	%
First language	English	163	62.9%
	Afrikaans	49	18.9%
	Tswana	16	6.2%
	Zulu	10	3.9%
	Other South African	17	6.6%
Education (schooling completed)	Primary	60	23.2%
	Secondary	115	44.4%
	Tertiary	67	25.9%
Reading	Very confident	131	50.6%
	Quite confident	102	39.4%
	Not confident	12	4.6%
Writing	Very confident	149	57.5%
	Quite confident	66	25.5%
	Not confident	19	7.3%
Use a computer	Every day	93	35.9%
	Once a week	10	3.8%
	Occasionally	37	14.3%
	No / None	108	41.7%
Have cell phone	Yes	233	90.0%
	No	10	3.9%
Access internet	Every day	80	30.9%
	Once a week	11	4.2%
	Occasionally	39	15.1%
	No	119	45.9%
Read newspaper	Every day	54	20.8%
	Weekly	56	21.6%
	Occasionally	109	42.1%
	No	24	9.1%
Have television	More than 2 televisions	37	14.3%
	2 televisions	77	29.7%
	1 television	129	49.8%
	No television	7	2.7%
Religion	Christian	205	79.2%
	Muslim	20	7.7%
	Hindu	5	1.9%
	Other, Believe in God	1	0.4%
Attend religious services	More than weekly	41	15.6%
	Weekly	84	31.9%
	Special occasions	90	34.2%

Not reported /missing: First language (n=4); Education (n=17); Reading confidence (n=14); Writing confidence (n=25); Computer use (n=11); Cellphone (n=16); Internet (n=10); Newspaper (n=16); Television (n=9); Religion (n=28); Attendance religious (n=25)



(Ch4) Figure 1 Proportion of respondents agreeing to the statements of beliefs



(Ch4) Figure 2 Relative risk of belief statement groups, adjusted and unadjusted

Fig. 2a Believing cancer is a punishment or curse (n= 220)
Fig. 2b Belief in alternative treatment methods for cancer (n= 176)
Fig. 2c Holding negative beliefs and outlook (n= 215)
Fig. 2d Holding positive beliefs and outlook (n= 185)
Multivariate adjusted for factors significant at p<0.10 in univariate: (2a) age category, black race, internet user, newspaper reader, confident reader and writer, English as first language. (2b) black race, government hospital, regular attendance at religious services. (2c) black race, secondary education, internet user, newspaper reader, confident reader and writer, English as first language. (2d) black race, secondary education, government hospital, regular attendance at religious services

Cancer as a punishment or curse

The relative risk of believing cancer to be a curse or punishment was uniformly higher in black compared to non-black women (RR: 6.85, 95%CI: 1.41-33.21), however confidence intervals were wide and the mean score for black women was less than 2. Figure 2a shows these relative risks both for the unadjusted and adjusted analysis. Religious belief with regular attendance (RR: 0.90, 95%CI: 0.21-3.93), attending the government hospital (RR: 5.01, 95%CI: 0.63-39.55), and secondary or higher education (RR: 0.38, 95%CI: 0.09-1.67) were not associated with the belief of cancer as a punishment in the univariate model and therefore were not included in the adjusted model. When adjusting for age and information access (by newspaper, internet and confidence in reading and writing), black race was no longer a statistically significant predictor of the belief of cancer as a punishment (aRR: 3.77, 95%CI: 1.00-14.27). Access to information was protective, for example internet users were 88% less likely to believe that cancer was a punishment or curse (aRR: 0.12, 95%CI: 0.02-0.99). Young patients (age ≤40) were significantly less likely to believe cancer to be a curse or punishment.

Alternative treatment methods

Beliefs in at least one statement of alternative treatment methods was present in 48.4% of the overall sample of patients and across the grouped statements of alternative treatments 21.2% indicated an average score of 6 and greater. Figure 2b illustrates that participants from the government hospital were twice as likely to believe in alternative treatments other than medicine and surgery (RR: 2.25, 95%CI: 1.18-4.30). Women who said they regularly read newspapers were less likely to agree with statements about alternative treatments (aRR: 0.51, 95%CI: 0.27-0.96). This effect was not further mitigated by access to the internet, nor changed by confidence in reading or writing. Although government hospital use was also associated with beliefs in alternative, faith-based and traditional medicines, the effect was not statistically significant in multivariate analysis (p-value=0.086; aRR: 1.95, 95%CI: 0.91-4.20). Black race and regular attendance at religious services were considered in the multivariate model but were no longer statistically significant for alternative treatments (aRR: 1.33, 95%CI: 0.74-2.39 and aRR: 1.70, 95%CI: 0.89-3.23, respectively). Age categories were not statistically significant predictors of beliefs in alternative treatments in the univariate analysis.

Negative statements of death and disfigurement

Black participants were far more likely to view their disease negatively on initial analysis, with belief that it is better to die with a breast than be less than a whole woman, they would rather die than lose a breast, or that people with cancer die when they go to hospital (RR: 11.57, 95%CI: 1.37-97.69, Figure 2c). These beliefs were considerably mitigated by education, information

access and confidence in reading and writing so that the effect of race was no longer statistically significant in the adjusted analysis (aRR: 3.55, 95%CI: 0.21 – 59.95). Reading a newspaper (RR: 0.11, 95%CI: 0.02-0.50; aRR: 0.29, 95%CI: 0.05-1.54) and internet use were protective against the negative beliefs of cancer. In particular internet use (aRR: 0.00, 95%CI: 0.00 – 0.00) was the most protective against the negative beliefs of cancer and remained statistically significant in multivariate analysis, irrespective of age and race.

Positive statements of cancer cure

In contrast, 90.3% agreed with positive statements about surviving and beating cancer. The relationship of positive beliefs alone to social and demographic characteristics is illustrated in Figure 2d. There was very little variance in different groups, displaying a universality of opinion. Whilst negative opinions were found more commonly in black participants and those attending the government hospital, positive expressions of cure and beating cancer were found equally in all women despite their different social, economic and religious characteristics. Race, secondary education, government hospital, and regular religious attendance were considered in the adjusted model; no characteristic was a statistically significant predictor of the grouped positive beliefs.

Discussion

Women diagnosed with breast cancer had a positive attitude towards breast cancer believing cure possible and support available. These beliefs were universally shared by women of all races, education and income. Further to this, whilst the expression of negative beliefs of dying in hospital and losing the breast were present, their effect was mitigated by education and information access in all racial and socioeconomic groups. Previous studies of attitudes to breast cancer in LMICs have shown high rates of negative beliefs [101–106]. These study findings provide some evidence to indicate that improving education levels and increasing patients access to (correct, trustworthy) information may assisting in moderating negative beliefs and attitudes of having breast cancer. This study also supports the assertion that race is not necessarily an important independent factor in patients' access or attitudes to care, but rather a proxy for socioeconomic or educational disparities [107].

Society's and patients' attitudes towards cancer are important. Surprisingly there is scarce literature addressing a woman's attitude of having the disease in Southern Africa. Most studies in LMICs have addressed attitudes towards screening, prevention and access in under-served populations, however, studies addressing concepts around causation and outcomes are underrepresented. It is important, however, to address this issue because not only do a woman's attitude towards her disease affect compliance to biomedical care [104,108,109], they may also

address her likelihood to attend early for investigation of symptoms, and encourage others in her community to attend. How we can change a woman's attitude towards treatments and outcomes is as important (if not more so) as addressing screening in countries where population screening is unlikely to be achieved in the next few years, because it could be an effective method of improving the proportion of women presenting with earlier stages of the disease.

Although a convenience sample, we believe that the demographic mix of patients here was representative of those attending for breast cancer care in our environment. Most of our patients were under 60 years and nearly one-fifth of cancers were in young women; the equivalent figure from the SEER database in the USA is <12% under the age of 45 and a median age of 61 at diagnosis [71]. The large proportion of patients with English as a first or second language and confidently literate was more indicative of the urban population surrounding the hospitals. Whilst this may be different to more rural parts of the country, the high rate of cell phone usage and internet access has become more prevalent across all areas in the last five years, with 34% of South African adults owning a smartphone with access to the internet [110].

As Africa becomes more connected technologically, there has been a surge in medical communication capacity (characterised as eHealth and mHealth technology, along with social media awareness and advocacy) serving to bring some quality of information access to different populations. Nine of every 10 South African adults own a cell phone [110]. In this study, access to the internet was protective against the beliefs of an external malevolent force in cancer causation, and cancer as a punishment from God or from others.

Increasingly mHealth is being used as a platform for health information and education amongst young people in South Africa and has been useful in modifying health behaviour [90], and improving patient-motivated healthcare [89]. Improving the message of breast awareness in social media, and the layering of breast cancer education through multiple platforms from traditional print or advert based campaigns to TV and radio soap-operas [87] and celebrity survivors, helps to tailor education appealing to different generations and cross-sections of society [88]. Access to information mitigated against the negative statements of belief. Some of this effect was lost in the multivariate analysis however, recognizing the complex interplay of differing socioeconomic factors that contribute to these beliefs [35, 104, 107, 111].

Interestingly although there was a small number of non-Christian believers amongst the participants, adherents to all religions were equally believing of cancer as a punishment from their god. These findings confirm recent anthropological work in this environment, that women with breast cancer possess a commonality of beliefs regarding 'god', social support, and biomedical faith/scepticism independent of culture or race [112]. This commonality was also

seen in positive and negative attitudes to their disease. Whilst over 90% of patients agreed with the positive statements of survival and support, some women (less than 10%) expressed the opposed negative views of dying and a loss of womanhood. In the multivariate analysis, both these positive and negative attitudes were held in all groups with little demographic differentiation between them. Whether this is confined to those sampled or a reflection of more positive attitudes held generally in the popular media in South Africa about the outcomes about cancer [88,113], the scarcity of negative opinions contradicts the notion that women, even when presenting late, are passive recipients of their disease and subsequent treatment.

Nearly half of all patients agreed with at least one statement that cancer could be cured with non-biomedical management. These beliefs were not well mitigated by literacy nor access to information but were also unaffected by race. Although other studies in Africa document a preferential engagement of traditional African healers above or alongside medical care, here when comparing different racial groups, there is a shared willingness to explore non-biomedical treatment equally in all groups. What is not clear from this study is whether the methods of cure considered are similar or differ according to other individual characteristics. The authors frequently experience patients considering choices of traditional African healers, 'western' vitamin remedies and 'eastern' traditional medicine according to each patient's own experiences and beliefs.

There are some limitations to this study. The beliefs and attitudes described cannot be generalised easily and in addition, willingness to participate in empirical research may serve as bias, in that these women may also be more willing to accept the scientific model of disease as part of their beliefs. Studies of any disease rely on participants who have been diagnosed, and therefore have reached some level of diagnostic medical care. It remains impossible to identify or know the attitudes of patients with breast cancer who never sought care before death. The absence of population-based screening means that few cancers are discovered without express help-seeking behaviour. However, many of the patients presented with advanced and very locally-advanced breast cancer, and therefore represents a good cross-section of the disease process, biased more towards locally-advanced patients, if at all, rather than early-stage disease.

The study was carried out anonymously and was not linked to patient's medical records due to local limitations of record keeping and follow-up, therefore it is not possible to compare beliefs in this group and link it to stage. The study sites were both breast (surgical) oncology clinics however, with patients attending with the aim of surgical curative intent with neo- or adjuvant chemotherapy and radiation, with approximately 50% presenting in stage 1 or 2 and less than 10% with metastatic disease [99].

In conclusion, within this diverse population of South African breast cancer patients most beliefs and attitudes towards cancer were relatively homogeneous, with little independent racial or socioeconomic variations. Strong mitigations of negative beliefs in patients, both towards their disease and the cause as a punishment, were achieved through access to information, and confidence in literacy. However, access to information also increased the likelihood that patients would have beliefs of non-biomedical methods of cancer care, and this should be considered when encouraging patients to access information about breast cancer, particularly through new media. Further understanding of patients' attitudes and beliefs remain important in providing treatment and support in breast cancer care.

Chapter 5: Delay to diagnosis and breast cancer stage in an urban South African breast clinic.

Reference: Rayne S, Schnippel K, Kruger D, Benn C, Firnhaber C Delay to diagnosis and breast cancer stage in an urban South African breast clinic South African Medical Journal *In press*

At the time of this thesis submission, Paper 3 was accepted for publication in South African Medical Journal. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university with combined references for clarity. See Appendix A3 for a PDF version of the submitted article.

Introduction

Breast cancer is the most common cancer in women in most low- and middle-income countries (LMIC), including South Africa where it is the most common cancer histologically diagnosed in women, giving a lifetime risk of one in 26 [70], and occurring as cause of death in at least 0.9% of all mortality in 2015 [12]. Despite having a good overall prognosis in comparison to other cancers with an 84-89% survival rate at five years reported in high-income countries, in LMICs these rates are substantially lower and a majority of women diagnosed with breast cancer will succumb to the disease. Mortality rates at five years of 47% in South Africa and 86.4% in Mali have been reported [114]. This high diagnosis-to-mortality ratio could be attributable to the late stage at presentation, as reported in most literature from LMICs, and this, in turn, would subsequently affect prognosis irrespective of the care available.

In South Africa, the Department of Health has recently launched a National Breast Cancer Policy[115], outlining standards to which healthcare providers should adhere when providing care. Many of the standards and publicity around the policy has focused on cancer care provision through better therapeutic modalities, such as geographical access to chemotherapy and novel monoclonal antibody therapies [116]. However, in addition to ensuring breast cancer care provision at tertiary services, ensuring access to early diagnosis and recognition of disease are equally, if not of increased importance. Where resources are limited, many expensive modalities of care may be avoided with prompt presentation and early diagnosis.

Whilst small studies from different parts of the world suggest that patient-related delay to care is common [101,104,106,117,118], the characteristics of delay, and its relationship to stage of breast cancer presentation is still poorly documented, especially in southern Africa. Older studies have cited fear of mastectomy and adherence to traditional healing as causes of delay [47,106,119], however more recent studies and systematic reviews show links between extremes of age (the youngest and oldest patients being most affected), marital status, education and

income as being of most importance [120]. South Africa is a middle-income country where open-access tertiary hospitals can provide care but where deep-rooted inequities may prevent access to all of the population. This study was designed to define the relationship between socio-economic characteristics of patients seeking care at a tertiary specialist clinic and describe where patient-related delays occur and how this relates to stage at presentation, which will ultimately have an implication on treatment requirements and survival.

Methods

This study was conducted in one of the few specialist breast care clinics in South Africa, where an open-access system allows all patients to attend for breast examination and investigation. The format of this clinic and spectrum of disease has been previously described [121], and the clinic currently diagnoses and manages more than 300 new diagnoses of breast cancer per year.

Over a 14-month period from January 2016, all patients who received a new breast cancer diagnosis were approached during their post-result counselling by a clinician to participate in the study. After written consent was obtained, they were asked, or completed themselves, a previously-piloted questionnaire regarding their demographics, socio-economic situation, education, and self-described ability to access care [122]. Participants were asked to quantify how long it took them to acknowledge or disclose a breast symptom once noticed, from that point how long to visit any health facility, and from that point how long until attend the open-access breast care clinic for diagnosis. Each of two research assistants involved in participant recruitment were fluent in at least two languages, and assistance was sought from other staff members to allow the participant to complete the questionnaire in a language most comfortable for them, through immediate verbal translation. The results of the questionnaire were linked via study number to the patient's clinical stage at presentation, as documented by the diagnosing breast specialist surgeon. Ethical approval was received from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The data were collected using REDCap (hosted by the University of the Witwatersrand) to enter and manage the data [123] and all statistical analyses were done in Stata v13.1 (College Station, Texas). Patients' characteristics were described using frequencies and proportions, and age was categorised as under 45 years or 45 years and older. Marital status was categorised as either married or unmarried, the latter of which included participants who were single, divorced or widowed. Education was categorised according to the highest level of formal schooling obtained: completed primary schooling, completed secondary schooling or matriculation from school with or without qualifications above that.

Participants who indicated at least some difficulty with transportation or taking time from work were compared with those that did not. Fear regarding missing an appointment or required attendance at the hospital due to work, money or transport were indicated on a four-category Likert scale (from strongly agree to strongly disagree) and those who expressed some fear (agree or strongly agree) were compared to those who did not express any fear. Time to presentation was comprised of time taken to acknowledge symptom(s) (T-Ack), time to seek healthcare services (T-HS) and time taken to attend a breast care clinic (T-BCC). To facilitate responses, participants were offered categories of less than 1 week, 1 week - 1 month, 1-6 months, 6-12 months, or greater than 1 year. To facilitate summation and analysis of the total delay numerically, these were then converted into total days of delay which was created by taking the minimum time for each response, e.g. if <1 week = 1 day, 1 week- 1m = 8 days, 1m-6m = 31 days, 6m-1y= 182 days and >1yr = 366 days.

Clinical stage at presentation was described using the "TNM" classification (8th Edition) [124] and stage was determined. For further determination of patients by clinical stage, it was then categorised into early (stage 1 to stage 2a) and locally advanced (stage 2b to stage 3c). For determination of delay by stage, patients with stage 0 were excluded because of the relationship with screening, rather than clinically detected disease in this group. Stage 4 was also excluded because these patients commonly follow a route to medical oncological care that may bypass a surgical clinic. Two-sided differences of proportions were compared using Pearson chi^2 test. Categorized delay was compared using ordinal logit. A p-value ≤0.05 was considered statistically significant.

Results

Over 14 months from January 2016 to February 2017, 352 patients received a new diagnosis of breast cancer. A total of 252 patients with newly-diagnosed stage 1-3 breast cancer completed the questionnaire, giving a response rate of 71.6%. Median age was 55 years (IQR 44-65), with 59 under 45 years (26.5%). Stage was recorded in 232 patients (92.1%) with stage at presentation as Stage 1, 36 (15.5%); Stage 2, 66 (28.5%); Stage 3, 130 (56.0%). Nearly one third of all patients presented with T4 cancer (either T4d inflammatory (6.1%) or involving skin above or muscle below (24.3%)). When categorised, it was found that only 32.3% of patients presented with early-stage breast cancer.

Key demographics, presented according to early or advanced stage at diagnosis, are presented in Table 1. There were very few relationships between any patient-reported fears or socio-economic characteristics and the stage of disease, however self-reported transport difficulties (p=0.011) and having a cell phone contract (p=0.035) were significantly associated with locally-advanced

disease at presentation. Total delay to present at the breast clinic was statistically associated with locally advanced stage at presentation (p=0.021).

(Ch5) Table 1 Patient characteristics by stage, row proportions and p-value [a]

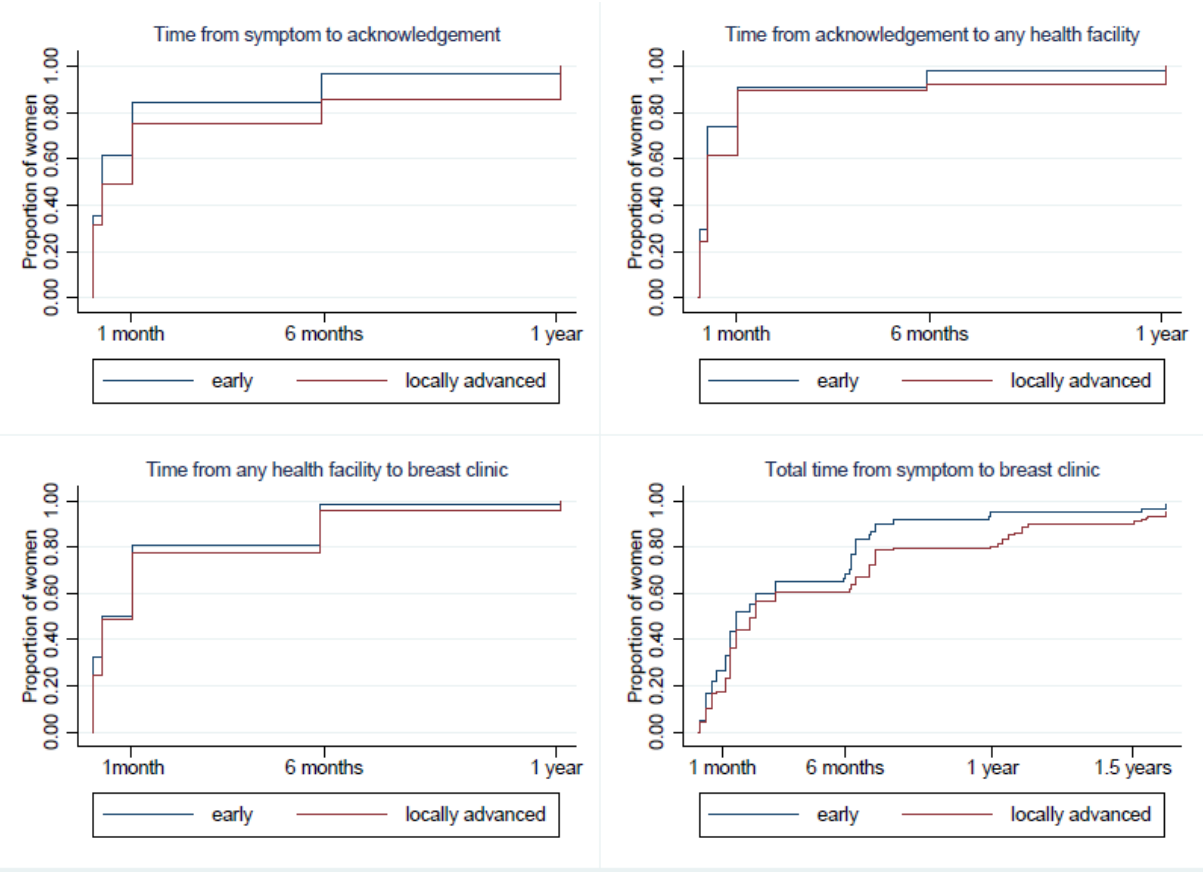
Description	Stage at presentation		
	Early (1-2a)	Locally advanced (2b-3c)	p-value*
All participants	75 (32.3%)	157 (67.7%)	
Age (n=223)			
< 45 years	14 (23.7%)	45 (76.3%)	0.072
45 years+	60 (36.6%)	104 (63.4%)	
Marital status (n=222)			
Married or in relationship	38 (34.6%)	72 (65.5%)	0.601
Not in relationship	35 (31.3%)	77 (68.8%)	
Education (n=218)			
Only primary school	21 (30.4%)	48 (69.6%)	0.516
Secondary school or above	52 (34.9%)	97 (65.1%)	
Family history			
Breast cancer in close family	6 (28.6%)	15 (71.4%)	0.733
No breast cancer in family	67 (32.2%)	141 (67.8%)	
Dependants (n=199)			
No dependants	17 (32.7%)	35 (67.3%)	0.936
1 to 3 dependants	22 (34.9%)	41 (65.1%)	
More than 3	27 (32.1%)	57 (67.9%)	
Cell phone (n=205)			
Contract (billed)	6 (17.7%)	28 (82.4%)	**0.035**
Airtime top-up	62 (36.3%)	109 (63.7%)	
Internet use (n=219)			
None	51 (35.9%)	91 (64.1%)	0.133
Occasionally or daily	20 (26.0%)	57 (74.0%)	
Employment status (n=221)			
Unemployed, piece work, student or retired	55 (34.8%)	103 (65.2%)	0.262
Employed, job	17 (27.0%)	46 (73.0%)	
Transport to breast clinic (n=219)			
Not difficult	63 (37.3%)	106 (62.7%)	**0.011**
Burdensome	9 (18.0%)	41 (82.0%)	
Travel to breast clinic (n=218)			
< 30 minutes	12 (30.8%)	27 (69.2%)	0.790
30 minutes to 1 hour	26 (35.1%)	73 (69.5%)	
1 to 4 hours	26 (35.1%)	48 (64.9%)	
Fears about missing appointments			
Due to work (n=143)	10 (33.3%)	20 (66.7%)	0.732
Due to transport (n=213)	16 (25.4%)	47 (74.6%)	0.133
Due to money (n=213)	25 (27.5%)	66 (72.5%)	0.185
Due to family obligations (n=207)	19 (40.4%)	28 (59.6%)	0.179
Total delay to presentation at breast clinic (n=206)			
< 1 month	16 (43.2%)	21 (56.8%)	**0.021**
1 to 6 months	23 (30.3%)	53 (69.7%)	
6 to 12 months	18 (42.9%)	24 (57.1%)	
> 1 year	3 (11.1%)	24 (88.9%)	
Delay to acknowledgement (n=206)			
< 1 week	23 (34.3%)	44 (65.7%)	0.296
< 1 month	17 (40.5%)	25 (59.5%)	
1 to 6 months	15 (29.4%)	36 (70,6%)	
> 6 months	10 (22.2%0	35 (77.8%)	
Delay to any health facility (n=206)			

< 1 week	19 (35.9%)	34 (64.2%)	0.361
< 1 month	29 (36.4%)	53 (64.6%)	
1 to 6 months	11 (22.0%)	39 (78.0%)	
> 6 months	6 (28.6%)	15 (71.4%)	
Delay to specialist breast clinic (n=206)			
< 1 week	34 (34.0%)	66 (66.0%)	0.257
< 1 month	21 (35.0%)	39 (65.0%)	
1 to 6 months	12 (32.4%)	25 (67.6%)	
> 6 months	2 (11.1%)	16 (88.9%)	

*p-values calculated using Pearson chi² difference of proportions. Statistically significant values of p<0.05 are bolded.

Self-reported median delay (IQR) to presentation at a breast unit was 2 months (1 to 7 months) after noticing a symptom. Total delay differed by whether the patient was diagnosed with early stage (1.5 months, IQR: <1 month to 6 months) compared to 2.5 months for participants diagnosed as locally advanced stage (IQR: 1 to 7 months). When the data on this delay was separated out and analysed, most of the delay occurred during the period between a woman acknowledging a problem and attending a health service and this delay had a median (IQR) of 1 week (1 day to 1 month) in early stage and 1 month (1 day to 3 months) in locally advanced breast cancer. The least delay was between attending a health service and presenting at the specialist breast care clinic: median (IQR) of 1 week (1 day to 1 month) in early stage versus 1 month (1 week to 1 month) in locally advanced disease with 75.0% of all study participants attending within 1 month (early stage 79.7%; locally advanced 72.1%).

The relationship of each part of the delay to stage of disease is indicated in Figure 1, with total delay for comparison. This shows that, whilst there is a person-by-person variation in timeline to care, patients with early stage disease tend to attend each part of their pathway more timeously. The most notable difference between patients with early and locally advanced disease was in time to acknowledging a symptom (T-Ack), where time to healthcare services (T-HS) and time to specialist care (T-BCC) were similar (Figure 1A, 1B and 1C, respectively).



(Ch5) Figure 1 Delay to presentation in early and locally advanced patients

A: Time to acknowledging a symptom (T-Ack), B: time to healthcare services (T-HS), C: Time to specialist care (T-BCC), D: Total time to presentation (T-Tot)

Similar to the analysis by stage, there were few patient characteristics associated with increased total delay (full results shown in Supplementary Tables S1 & S2); only travel time to hospital was found to be statistically significant ($p<0.001$). When delay was separated into its three constituents, lack of internet access was associated with delay to acknowledging a breast symptom ($p=0.051$). Having someone in the family with breast cancer was also associated with delay more than 6 months in acknowledging breast symptoms ($p=0.028$). Fear of missing work due to appointments was associated to delay to accessing any healthcare services ($p=0.04$). This delay in accessing healthcare services was also significantly more likely in patients with a low education (up to Grade 7) ($p=0.008$).

Discussion

This study was designed to evaluate the pre-diagnostic timeline of patients newly diagnosed with breast cancer in this urban specialist breast clinic. We aimed to determine the relationship between delay to definitive breast cancer diagnosis, stage of disease at presentation and the socio-economic characteristics which have previously been described as risk factors for delay to

care in other resource-limited settings. We expected to reproduce the findings that delay was related to stage, and that both delay and stage would be related to some of the common risk factors for inequitable access to care seen in our environment, namely low income, low education, insecure job circumstances and poor access to transport and money. The significant relationship of a cell phone contract (as opposed to top-up, indicating a more financially secure population) with locally-advanced disease was an unexpected finding that requires more investigation.

In this study a heterogenous group of newly-diagnosed participants was identified with few characteristics that defined them as at risk of presenting with locally-advanced disease. However, it is worth pointing out some of the characteristics that do make breast cancer a particular problem in our environment. More than a quarter of the newly diagnosed patients were patients under 45 years. This has been a consistent finding in breast cancer studies in SA [12, 125] and may be a result of bias due to a younger overall population in SA, a younger population in this urban sample, or absence in this SA sample of the more biologically indolent cancers detected by screening older women in high-income settings. This is a younger cohort of women at risk of the disease than may be expected by healthcare practitioners, who may not consider a breast cancer diagnosis possible or likely. Studies of provider-associated delays cite a lack of knowledge of breast cancer symptoms amongst providers with inappropriate reassurance [118,125,126] which could delay onward referral, specifically in younger patients.

Two thirds of participants presented with a locally-advanced breast cancer (Stage 2a - 3c) with disease in both the breast and axilla with a high-risk of systemic micro-metastatic disease. Almost all of these patients would require multi-modality therapy, with chemotherapy, surgery and radiation all indicated [128]. This highlights the fact that late presentation in breast cancer is not only a crisis for the patient, but also for the healthcare system. The earlier the cancer is diagnosed, the less likely that expensive and heavily under-resourced therapies such as radiation would be required. One quarter of all participants presented with a tumour that was ulcerating or fixed to the skin and surrounding tissues, however there was no relationship between this finding and any self-reported delay.

Many studies in sub-Saharan Africa have described significant delays to presentation [50,101,118,120,125,128–130]. In this study, the average time to presentation was two months from time of noticing any symptoms, which is a shorter time than in many other African studies, where delay can be measured in years, but comparable to study groups from urban populations in other upper-middle income countries worldwide. In Malaysia, 56% of patients presented over three months [105], in Brazil 70% were over three months [132], and in Mexico 73.7% were over three months [133]. The only outlier to this group was in Thailand [32], where only 17% of patients presented after three months. However, this study of tertiary facilities in northern

Thailand showed that 88% of all patients had a first consultation with a doctor, and for 89% of all patients this was within a hospital, thereby lessening the patient-related access issues of multiple visits, which can slow the progress of a patient through many tiers of the healthcare service towards tertiary or definitive care [121]. In our study, the least delay in both early and locally-advanced patients was seen between attending any healthcare services and attending the specialist clinic, with over 75% seen within one month, which confirms the improved accessibility of open-access care.

The limitations to this study should be acknowledged. Many patients with breast cancer may not present until the very latest stages, where palliation is appropriate and up-referral for interventional therapy is decided against. Lack of a comprehensive screening program also means that most breast cancer is detected after a clinical symptom, which will predispose toward a later stage. There may be women, even in the urban environs, who may never reach the specialist clinic despite open-access facilities. It is notoriously hard to characterise these women, but it can only be assumed that those women are more likely to have late stage disease (indeed end-stage disease) and have the longest time to presentation. This is an important source of selection bias in this current study, but one that is difficult to overcome. Additionally, some women may not recollect well their first acknowledgment of symptoms, or time taken to attend for care. This would be likely to affect all women equally however and would have less of an effect on the comparison of stage and time to presentation.

Whether these results from an urban tertiary centre are generalisable more widely in in South Africa, particularly in more rural areas is uncertain. South Africa is increasingly urbanising and the populations in urban centres are growing. These populations tend to be younger and may share many of the characteristics of this study population. In most of the main cities in South Africa there is access to tertiary breast cancer services, and therefore our findings can inform other clinicians as to the characteristics of their patients, and directions for future research around access to breast cancer care. It can also highlight to government the importance of a multi-modal method of improving cancer care, addressing education and awareness, but also opening up access to care to facilitate early diagnosis.

Conclusion

Despite an increase in breast cancer awareness in South Africa and the recent National Breast Cancer Policy, two thirds of patients presented with locally-advanced breast cancer. Whilst women with transport and work fears were more likely to present with locally-advanced disease, few socio-economic characteristics that could identify those at risk of delay to presentation. Most women delayed longer than recommended in both seeking any care and attending specialist breast care. Although time to acknowledge a symptom held the most delay, the reduction in time

to specialist care in these circumstances supports the availability of open-access care to facilitate access to care once symptoms are recognised.

(Ch 5) Supplemental Table S1 Patient characteristics by total delay to breast clinic, row proportions and p-value [a] (n=252)

Description	Total delay to breast clinic			
	<1 month	**1-6 months**	**>6 months**	**p-value**
All women	41 (20.8%)	82 (41.6%)	74 (37.6%)	
Age (n=186)				
< 45 years	11 (20.8%)	19 (35.9%)	23 (43.4%)	0.521
45 years+	30 (22.6%)	57 (42.9%)	46 (34.6%)	
Marital status (n=222)				
Married or in relationship	24 (25.8%)	38 (40.9%)	31 (33.3%	0.229
Not in relationship	17 (16.5%)	43 (41.8%)	43 (41.8%)	
Education (n=218)				
Only primary school	29 (21.2%)	53 (38.7%)	55 (40.2%)	0.524
Secondary school or above	11 (19.3%)	27 (47.4%)	19 (33.3%)	
Family history				
Breast cancer in close family	3 (16.7%)	5 (27.8%)	10 (55.6%)	0.284
No breast cancer in family	38 (21.7%)	73 (41.7%)	64 (36.6%)	
Dependants (n=199)				
No dependants	7 (14.6%)	24 (50.0%)	17 (35.4%)	0.304
1 to 3 dependants	15 (27.3%)	23 (41.8%)	17 (30.9%)	
More than 3	16 (21.6%)	26 (35.1%)	32 (43.2%)	
Cell phone (n=205)				
Contract (billed)	3 (11.1%)	13 (48.2%)	11 (40.7%)	0.326
Airtime top-up	38 (23.6%)	62 (38.5%)	61 (37.9%)	
Internet use (n=219)				
None	27 (21.8%)	53 (42.7%)	44 (35.5%)	0.728
Occasionally or daily	14 (19.2%)	29 (39.7%)	30 (41.1%)	
Employment status (n=221)				
Unemployed, piece work, student or retired	28 (20.4%)	55 (40.2%)	54 (39.4%)	0.626
Employed, job	13 (22.0%)	27 (45.7%)	19 (32.2%)	
Transport to hospital (n=219)				
Not difficult	35 (23.0%)	60 (39.5%)	57 (37.5%)	0.192
Burdensome	5 (11.9%)	22 (52.4%)	15 (35.7%)	
Travel to hospital (n=218)				
< 30 minutes	16 (45.7%)	6 (17.1%)	13 (37.1%)	**<0.001**
30 minutes to 1 hour	18 (18.6%)	46 (47.4%)	33 (34.0%)	
1 to 4 hours	7 (11.1%)	30 (47.6%)	26 (41.3%)	
Fears about missing appointments				
Due to work (n=135)	5 (17.8%)	11 (39.3%)	12 (42.9%)	0.663
Due to transport (n=192)	11 (19.3%)	24 (42.1%)	22 (38.6%)	0.967
Due to money (n=192)	16 (19.5%)	37 (45.1%)	29 (35.4%)	0.774
Due to family obligations (n=188)	10 (22.7%)	18 (40.9%)	16 (36.4%)	0.892

[a] p-values calculated using Pearson chi2 difference of proportions. Statistically significant values of p<0.05 are bolded.

(Ch 5) Supplemental Table S2 Patient characteristics by delay in acknowledging symptoms, row proportions and p-value [a] (n=252)

Description	Delay to acknowledging symptoms			
	<1 month	**1 to 6 months**	**6+ months**	**p-value**
All participants	118 (53.2%)	55 (24.8%)	49 (22.1%)	
Age (n=210)				
< 45 years	30 (50.9%)	14 (23.7%)	15 (25.4%)	0.849
45 years+	79 (52.3%)	39 (25.8%)	33 (21.9%)	
Marital status (n=221)				
Married or in relationship	60 (57.1%)	27 (25.7%)	18 (17.1%)	0.223
Not in relationship	57 (49.1%)	28 (24.1%)	31 (26.7%)	
Education (n=218)				
Only primary school	41 (60.3%)	14 (20.6%)	13 (19.1%)	0.344
Secondary school or above	74 (49.7%0	40 (26.9%)	35 (23.5%)	
Family history (n=217)				
Breast cancer in close family	10 (43.5%)	3 (13.0%)	10 (43.5%)	**0.028**
No breast cancer in family	106 (54.6%)	50 (25.8%)	38 (19.6%)	
Dependants (n=201)				
No dependants	24 (46.2%)	17 (32.7%)	11 (21.2%)	0.222
1 to 3 dependants	39 (60.0%)	16 (24.6%)	10 (15.4%)	
More than 3	48 (57.1%)	15 (17.9%)	21 (25.0%)	
Cell phone (n=205)				
Contract (billed)	14 (43.8%)	9 (28.1%)	9 (28.1%)	0.441
Airtime top-up	96 (55.5%)	42 (24.3%)	35 (20.2%)	
Internet use (n=219)				
None	82 (58.6%)	28 (20.0%)	30 (21.4%)	0.051
Occasionally or daily	35 (44.3%)	27 (34.2%)	17 (21.5%)	
Employment status (n=220)				
Unemployed, piece work, student or retired	83 (54.3%)	36 (23.5%)	34 (22.2%)	0.725
Employed, job	35 (52.2%)	19 (28.4%)	13 (19.4%)	
Transport to breast clinic (n=219)				
Not difficult	86 (50.3%)	46 (26.9%)	39 (22.8%)	0.161
Burdensome	31 (66.0%)	9 (19.2%)	7 (14.9%)	
Travel to breast clinic (n=218)				
< 30 minutes	23 (57.5%)	6 (15.0%)	11 (27.5%)	0.343
30 minutes to 1 hour	52 (50.0%)	32 (30.8%)	20 (19.2%)	
1 to 4 hours	42 (56.0%)	17 (22.7%)	16 (21.3%)	
Fears about missing appointments				
Due to work (n=149)	15 (46.9%)	8 (25.0%)	9 (28.1%)	0.497
Due to transport (n=214)	37 (58.7%)	13 (20.6%)	13 (20.6%)	0.528
Due to money (n=213)	46 (49.5%)	27 (29.0%)	20 (21.5%)	0.526
Due to family obligations (n=207)	27 (58.7%)	11 (23.9%)	8 (17.4%)	0.693

[a] p-values calculated using Pearson chi2 difference of proportions. Statistically significant values of $p<0.05$ are bolded.

Chapter 6: The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa.

Reference: Rayne S, Schnippel K, Grover S, Kruger D, Benn C, Firnhaber C The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa. Submitted to South African Journal of Surgery *In press*

At the time of this thesis submission, Paper 4 was published in South African Journal of Surgery. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university with combined references for clarity. See Appendix A4 for a PDF version of the submitted article.

Background

Breast cancer is the most common cancer to affect women in South Africa. Whilst the lifetime risk is lower than in high-income countries [12], outcomes are worse with reduced survival. This poor ratio of diagnosis to survival is often linked to difficulty in accessing care and poor availability of treatment options after diagnosis [10,132–134]. Screening and early diagnosis are limited and patients commonly present with advanced stage of disease limiting their outcomes despite treatment. Commonly cited or implied reasons for late diagnosis are often related in the literature to delay to care, both patient related delay, and provider (or system) delays. A delay of more than three months to presentation has been associated with more advanced breast cancer at diagnosis and decreased survival [16] however most studies from low- and middle-income countries (LMICs) indicate that the average delay exceeds this time. In countries of similar upper-middle income economic background to South Africa, delay to care (both patient- and provider-related) of more than three months ranges from 56% in Malaysia to 70% in Brazil [105,131].

In South Africa, few studies have examined the management of breast cancer in the government health system beyond pathological studies. Little has been described regarding patient-related delays, or indeed the complex path women take both psychologically and physically to access care. Patient-related delays commonly cited in other parts of Africa include socioeconomic and educational barriers, and indigent beliefs regarding cancer causes, symptoms and management. These beliefs may also include elements of 'cancer fatalism' where events are destined to happen with the individual relatively powerless to influence them [136]. Previous studies in South Africa have found that most patients self-refer to tertiary care, often due to delays in the system [121] and that farther geographical distance to hospital could be linked to late stage at presentation [99]. An older study from 2010 aimed to assess breast knowledge in South Africa and indicated

that poor knowledge was a main factor for delay, with less than 50% of respondents aware that changes in the breast may herald cancer [137]. The same study found that 44.9% of women felt they should not spend money on their health and 38.7% were not encouraged by families to seek healthcare. More than three-quarters of patients reported that they would wait less than one week to tell someone once they suspected they might have cancer [137]. The most recent qualitative study, amongst breast cancer patients, found low cancer awareness, and frequent monitoring of symptoms until a change in symptom or disclosure to a family member precipitates healthcare review [138].

In the absence of studies focusing on patient's own beliefs and the complex interplay between these views and their pathway to care, this study was designed to explore the relationship of attitudes and beliefs held regarding breast cancer and its management to the stage at presentation, and delay to diagnosis.

Methods

Women attending a South African government tertiary referral centre for breast cancer diagnosis and surgical management were approached to participate in a survey regarding their beliefs and fears surrounding breast cancer. The centre is an open access clinic for all patients with breast problems and routinely sees 4000 new patients each year and diagnoses 300-350 new breast cancers. The spectrum of breast problems and investigations in this urban centre in a limited resource setting has been previously described [121].

Consecutive women were included if they had a new diagnosis of a biopsy-proven breast cancer and accepted the invitation to participate during their post-diagnosis counselling by a clinician, with the survey administered within this period. Written consent was obtained, and the survey was administered by two trained research assistants, fluent in at least two languages. The survey was written in English and the assistants trained in the tool to minimise change in meaning during verbal translation. The questionnaire was completed in REDCap (hosted by the University of the Witwatersrand) [123] and linked to the participant's clinical findings at presentation. Ethical approval was received from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M111121).

The questionnaire comprised of multiple sections. The first established demographics, socio-economic situation, education, and self-described ability to access care. In the second section women were asked to quantify, from recollection, the length of time taken to attend the breast clinic, with the timeline separated into three categories: time taken to notice and acknowledge a breast symptom, time taken from then to access any healthcare services, and finally time taken from then to attend the open-access breast clinic. The final section comprised of 44 statements

describing a fear or belief grounded in their breast cancer diagnosis or understanding of treatment and prognosis. These were expressed on a four-point Likert scale from strongly disagree to strongly agree. Many of these statements have been previously piloted and described [122, 139] and were augmented to include, around cancer, fatalism and health beliefs [140, 141] from similar studies. Internal consistency measurements for each subscale (fears; beliefs; fatalism and risk factors) found a Cronbach's alpha co-efficient of 0.82, 0.73, 0.71 and 0.81 respectively. Scales are considered acceptable with an alpha ranging from 0.70-0.95 [141].

Data analysis

Patients characteristics were described, using frequencies and proportions, and categorised to facilitate analysis. Marital status categorised as partnered or unpartnered (which included women who were not in a relationship or widowed) and age was categorised as less than 45 years, 45- 64 years or 65 years and older. Less than 45 years was defined as "young" breast cancer. Education was categorised according to the highest level of formal schooling obtained: grade 9 (approx. 14 years of age) and above grade 9. Those who had achieved matriculation from secondary school and above were also differentiated from those that had no completion certification of secondary education.

Responses from the subscales for fears and beliefs were grouped according to those who expressed some fear or belief (agree or strongly agree) and compared to those who did not. Time to presentation was comprised of time taken to acknowledge symptom (T-Ack), time to seek healthcare services (T-HS) and time taken to attend breast care clinic (T-BCC). Each was categorised as < 1w, 1 week to 1 month, 1 month- 6 months, >6 months- 1 year and greater than 1 year. A total time to presentation (T-Tot) was calculated as the sum of the three individual time periods, and grouped as either 6 months or less, and greater than 6 months.

Clinical stage at presentation was determined from the clinical "TNM" staging system (AJCC, 8th edition) [124] of the examining physician. This was then categorised as early (between stage 1 and stage 2a) and late staged (stage 2b to stage 4). Stage 4 disease was included but may have been relatively underrepresented as these patients often may access medical oncological care without first attending a breast surgical clinic. For determination of delay by stage, patients with Stage 0 were excluded because of the relationship with screening, rather than clinically detected disease in this group. Two-sided differences of proportions were compared using Pearson chi^2 test. A p-value <0.05 was considered statistically significant. Poisson's regression methods of calculating odds ratio with 95% confidence intervals to compare early stage (up to Stage 2a) with advanced breast cancer (Stage2b and beyond) were used to identify factors associated with presentation with advanced stage.

Results

During the study period of 14 months, 233 participants completed the survey (response rate of 65.5% of all newly diagnosed breast cancers).

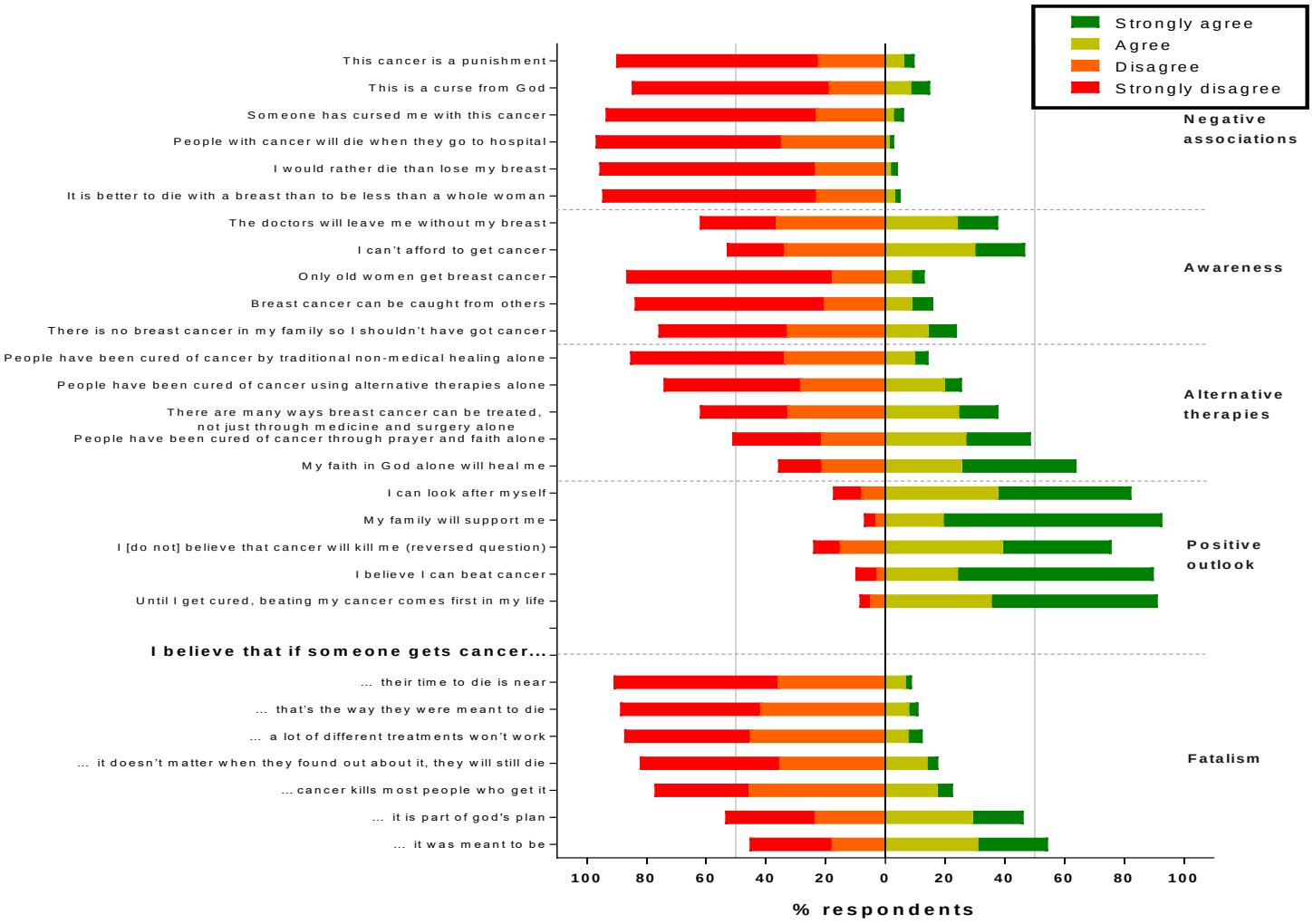
Demographic and clinical characteristics

The median (IQR) age was 56 years (46-65), with 23.6% under 45 years old. Most patients had a partner, had some dependants and had received a formal education beyond grade 9. The most common stage at presentation was Stage 3 (50.4%) or Stage 4 (2.6%), including 30.5% of all cancers presenting as T4 (skin involvement (T4b) (23.5%), inflammatory (T4d) 6.2%). Only 5% presented with metastatic disease at presentation after investigations. These, and further characteristics are summarised in Table 1.

(Ch6) Table 1 Demographic and clinical characteristics of patients presenting for care (n =252)

Description	**Total (n=233)**	
	n	%
Age (n=230)		
<45 years	48	20.9
45-64 years	121	73.5
≥65 years	61	26.5
Median years (IQR)	56	(46-65)
Relationship status (n=223)		
Partnered	112	50.2
Not partnered	111	49.8
Family History (n=225)		
Breast cancer in close relative	20	8.9
Formal education achieved beyond Grade 9 (n=219)		
No education beyond Grade 9	69	31.5
Matriculated from school (n=219)		
Yes	76	34.7
Dependants (n=200)		
No dependants	51	25.5
1-3 dependants	65	32.5
More than 3	84	42.0
Have cell phone (n=219)		
Yes- contract	34	15.5
Yes- top up	172	78.5
Do you access the internet? (n=220)		
No	139	63.2
Yes- occasionally	46	20.9
Yes -every day	35	15.9

Confident reader (n=221)		
Yes	211	95.5
Employed, job (n=222)		
Yes	70	31.5
Religion beliefs (n=223		
Yes- Christian	193	86.6
Yes- Muslim	13	5.8
Yes- Traditional African	4	1.8
Yes- other	13	5.8
Attend religious meetings at least once a week (n=196)		
Yes	123	62.8
Breast cancer in close relative or friend (n=100)		
Alive and cancer-free	22	22.0
Alive (with cancer)	12	12.0
Died from cancer	60	60.0
Stage at presentation (n=231)		
1	33	14.3
2a	36	15.6
2b	27	11.7
3a	56	24.2
3b	68	29.4
3c	5	2.2
4	6	2.6
Tumour T4 on presentation (n=226)		
Yes	73	32.3
Total delay to presentation		
< 1 month	38	21.0
1 month- 6 months	78	43.1
>6 months- 1 year	38	21.0
> 1 year	27	14.9



(Ch6) Figure 1 Participants beliefs, by percentage of responses.

Fears and beliefs

Figure 1 shows the statements with the percentages of respondents' answers. In general, the responses showed a positive outlook with high agreement to statements such as 'my family will support me (92.8% agree/strongly agree) and I believe I can beat cancer (90.0% agree/strongly agree). Equally emphatic was disagreement to both ideas of malevolent external origin (someone has cursed me with this cancer, 93.7% disagree/strongly disagree; this cancer is a punishment 90.2% disagree/strongly disagree) and resistance to biomedical therapies (cure with traditional healing 85.5% disagree/strongly disagree; cure with alternative therapy 75.3% disagree/strongly disagree; people die when they go to hospital 97.0% disagree/strongly disagree). Most questions regarding fatalistic beliefs were disagreed with, and only "…it is part of god's plan" and "…it was meant to be" were agreed with by more than one quarter of participants (46.4% and 54.5% respectively).

Overall, there were few beliefs that were strong predictors for presentation with late stage or delay to presentation. On univariate analysis, young women were 20% more likely to present with an advanced breast cancer (IRR 1.20 95%CI 1.01-1.42). Whilst limited education was not related to advanced disease, being a confident reader was protective against late presentation (IRR 0.77 95%CI 0.61-0.96). Patients who presented with an advanced cancer were more likely to believe that cancer could be caught from others (IRR1.28 95%CI 1.06-1.54), that they "could not afford to get cancer" (IRR1.24 95%CI 1.03-1.50), and to state that they "would rather die than lose a breast" (IRR 1.29 95%CI 1.01-1.66) or that if "someone gets cancer that was the way they were meant to die" (IRR 1.29 95%CI 1.06-1.58). Women with locally-advanced cancer were also 20% more likely to believe that cancer can be cured by methods other than medicine and surgery (IRR1.19 95%CI 1.00-1.42), however no other belief statements in alternative therapies showed significance here.

Self-reported transport difficulties also predicted late presentation in the univariate model (IRR1.26 95%CI 1.07-1.49), and when the model was adjusted for each of the beliefs with a significant relationship, the likelihood of late presentation was strengthened in women with transport difficulties if they believed that they "would rather die than lose a breast" (aIRR1.28 95%CI 1.09-1.52), believed cancer could be caught from another person (aIRR1.27 95%CI 1.06-1.52), believed that cancer can be cured by methods other than medicine and surgery, or traditional non-medical methods alone (aIRR1.38 95%CI 1.17-1.63 and aIRR1.32 95%CI 1.11-1.57 respectively) and believed that cancer "will eventually kill me" (aIRR1.34 95%CI 1.12-1.59) or if "someone gets cancer that was the way they were meant to die" (aIRR1.34 95%CI 1.14-1.58).

In considering delay to presentation, no socio-economic factors or beliefs increased the risk of delay more than six months including travel more than one hour, transport difficulties, lack of employment, or age. Only agreement with the statement “My family will support me” was associated with a total time to presentation within six months (IRR 1.26 95%CI 1.02-1.59). Agreement with the statement 'I am afraid of cancer' was not statistically significantly associated with delayed presentation or locally advanced.

Good social support and interaction with the world (via cellphone usage and internet) were not associated with an earlier stage at presentation or decreased delay. In considering religion, women who attended a religious meeting more than once a week were no more likely to present with late disease, although regular attendance predicted beliefs that God alone could heal disease (RR1.43 95%CI 1.07-1.91). Regular attendance at church was found in older women, with less education, and less access to the internet ($p<0.001$, $p=0.05$, $p=0.02$).

Discussion

South Africa is an upper-middle-income country with a relatively secure infrastructure, and Johannesburg is a relatively affluent city with relatively good access to local hospitals and specialised breast care. Within this setting however, more than three quarters of patients presented to an open-access breast clinic with advanced breast cancer and more than half of these with a T4 tumour. This study was designed to determine the relationship between beliefs and fears and an advanced presentation or delay to presentation in breast cancer.

Our study found that the predictors of late stage disease were socio-economic as well as related to attitudes of disease. We found that transport difficulties most consistently predicted an increased stage at presentation, (and confidence in reading was protective of this) whilst there were no identified factors which increased the likelihood of patient-related delay to care. A recent study using the pilot questionnaire in this same population [139] found that demographic and socio-economic factors (which often overlap in South Africa due to the legacy of Apartheid-era inequity) predicted for some beliefs, particularly regarding alternative treatment regimens and negative statements about death and disfigurement. However, this more comprehensive study has found that most of these beliefs were unrelated to stage of disease at presentation, as well as unrelated to delay to care. Therefore, although socio-economics may predict beliefs, beliefs alone did not consistently predict stage of disease. Furthermore, while fears and beliefs may impact on time to present to a breast specialist clinic, the linear relationship that is conceived of in literature between fear and misconception leading to a reticence to present and therefore delay to care with an advanced stage of cancer could not be traced here.

The implication of these finding is that the continual message of breast education and awareness, whilst an important strategy for advocacy may be failing to fully enable women to reach the care appropriate for them. This study found that late presentation was more consistently related to issues of navigation to the hospital through transport problems, money worries and through literacy. There was a relatively high level of appropriate agreement and disagreement to the belief questions, indicating that in this group of women of whom over one-third had T4 tumours, their breast "awareness" and education were satisfactory. Therefore, in addition to advocating breast education, a more holistic recognition that empowering women through raising the effective education levels of all women in the community could raise not only their awareness of disease but improve their ability to access care. Until this is achieved, women are still likely to present with late stage disease. This assertion is supported by the finding that confidence in reading rather than years of education was more predictive of earlier presentation.

Identifying that transport difficulties were related to both late presentation and delay to presentation (risks of which were independent of each other) would also indicate that further work also needs to be done in improving women's navigation to appropriate care from the community, through easing their transport and work difficulties. This study will provide useful information for government and local advocacy groups as to the best use of resources in reducing the breast cancer burden by decreasing late presentation.

Overall this study found that women presenting for breast cancer diagnosis had a relatively appropriate understanding of breast cancer within the biomedical model, as judged by their responses. Few patients had negative beliefs about the origin of their cancer, or surgical treatment. The area of heterogeneity that was most noted was around beliefs in alternative methods of cure, whilst only less than one quarter of patients believed in alternative or traditional methods of cure (24.5% and 14.2% agreed/strongly agreed respectively), nearly half stated they believed prayer and faith or God alone could cure them (48.2% and 64.1% agreed/strongly agreed). None of these beliefs predicted delay to presentation or stage at presentation and represent an interesting duality of belief between what is stated, and what is carried out by the patient. The degree of cancer fatalism in this population also differed from those in other African studies. Akhigbe et al [140] found high levels of fatalism amongst a Nigerian health professional population with agreement to each question ranging from 45%- 82%, and from a series reported in Ghanaian women [143], they too has higher levels of fatalism compared to our South African group. These beliefs are in sharp contrast to those described 15 years ago in South Africa where nursing staff reported "with breast cancer who wanted a mastectomy would die because their husbands refused to let them be "disfigured" [143] or the "…patient sought help first from a

traditional healer as a way of dealing with the cause of the disease…" [69] but supported by more recent studies in a similar group of South African women [136].

This study did not find a simple association between attitudes and beliefs around breast cancer and either stage at presentation or delay to presentation. The participants were a heterogeneous group, reporting prompt presentation or delayed presentation equally with early or late stage disease. On reviewing the literature regarding similar studies from other low- and middle-income countries, we did not find the standard associations of low education, poor employment and lack of awareness that other studies have found, even those carried out in urban settings in tertiary referral centres such as in Nigeria [144] Ghana [129,145] and Rwanda [147]. In these circumstances, using the health belief model to understand why and when patients access breast care may not necessarily be applicable, as persuading a woman of the significance of her problem does not necessarily equip her with the tools to seek care. It may be that recognising the disparity in socio-economic capital and addressing this inequity through increasing women's education levels, literacy and empowerment on a governmental level, together with facilitating physical access to care, will reduce late stage disease more than high-profile media campaigns.

There are limitations to this study. The small sample size and single study site limit the suitability of the findings to similar breast centres. However, as the management of breast cancer becomes more specialised, more tertiary centres are being identified in Africa [148], and these findings may help guide further work in understanding and assisting the women accessing care. The reflective retrospective nature of some of the questions, designed to give voice to patients concerns, may illicit bias responses despite separating the clinicians from those administering the survey. Allowing the participants voices to be better heard through qualitative studies would also enable better understanding of the nuances of beliefs around cancer. Whilst some work has been done in South Africa [112, 138], more is required. In addition, the beliefs reported here are only of those who attended for care. There is a cohort of women with breast cancer who never reach a referral centre, either due to complete inability to access the system through socio-economic or other constraints, or present so late in the disease process that referral for tertiary care is inappropriate. Only 5% of the women in this study had Stage 4 disease, which may not reflect the true burden of metastatic disease in our environment.

Conclusion

This study examined the beliefs of women with a new breast cancer diagnosis and found that most held positive and appropriate beliefs regarding breast cancer and treatment options. There were low levels of fatalism in the group, which contrasts with other studies from Africa and with older studies in South Africa. The relationship of stage of disease and delay to presentation was more associated with structural barriers such as transport difficulties, than with the investigated

beliefs, or demographic characteristics. Although education and awareness are the most common strategies for advocacy in South Africa, developing different models to improve access to care, such as facilitating transport, may be beneficial to the population served.

Chapter 7: Unravelling the South African breast cancer story: the relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting.

Reference: Rayne S, Schnippel K, Grover S, Fearnhead K, Kruger D, Benn C, Firnhaber C Unravelling the South African breast cancer story: the relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting. Submitted to Journal of Surgical Research *Under review*

At the time of this thesis submission, Paper 5 was under revision after review by Journal of Surgical Research. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university with combined references for clarity. See Appendix A5 for a PDF version of the submitted article.

Introduction

Breast cancer is the most common cancer to affect women in most countries and is a disproportionately large cause of death for women in low- and middle-income countries (LMICs) [3]. In developing national cancer control policies and understanding the epidemiology of breast cancer in LMICs, emphasis is placed on awareness and access to care [133,148]. A strong association between education and socio-economic factors, and stage at presentation is cited to support this [149,150]. Oncologically, there is also a strong association of stage at presentation with outcomes such as treatment modalities required, recurrence rates and ultimately survival.

The discovery of the oestrogen receptor (ER) on some breast cancer cells in the 1960s first allowed the individualization of breast cancer therapy [152]. In the last ten years, an increase in breast cancer translational research has led to a far greater understanding of the molecular biology of breast cancer. The heterogeneity of tumour subtypes is inherently related to response to treatment, sensitivity of modalities, and outcomes. In most specialist breast units in high income countries it is routine to carry out immunohistochemistry to determine ER, progesterone receptor (PR), human epidermal growth factor receptor 2 /neu (HER2) and Ki67% at least and considering these allows clinicians to translate this information into patient-centred clinical decision-making such as first modality of treatment, and to provide insight into prognosis. Further to this, more sensitive genomic tests are increasingly more routinely available to further sub-type and characterize tumours [153].There have been studies of these intrinsic molecular subtypes in LMICs, describing the incidence of adverse biology and linking this to clinical outcomes [150,153–155].

In parallel with this fresh understanding of the spectrum of breast cancer seen in LMICs, runs the continued focus on the reduction of advanced-stage disease through awareness and access to care. However, few studies in an African population have integrated the patient-centred association of socio-economic factors and access to care, with the more recent insights into tumour biology and its impact on progression of disease, as has been the case more globally [153,156]. Therefore, there remain two relatively discrete areas of investigation regarding breast cancer characteristics in Africa: one ascribing presentation at advanced stage to delay in diagnosis, traditional beliefs at conflict with treatment modalities, and low education, and the other describing adverse tumour biology and patient characteristics (such as young age or HIV status), which may also result in advanced stage presentation.

The purpose of this study is to examine the stage of disease at presentation in an urban South African population, and assess the relative contributions of patient characteristics, delay in treatment and tumour biology. We aim to tease out the most important contributing factors to advanced disease and through this, help inform policy regarding the provision of breast cancer care in LMICs.

Material and methods

In an urban South African open-access breast care clinic from January 2016 to February 2017, all patients with a new diagnosis of breast cancer were consented and invited to participate in a questionnaire regarding their demographics, socio-economic situation and access to care. These responses, together with their clinical examination at diagnosis, were then linked to their diagnostic histological specimen.

Of the 356 patients with a new cancer diagnosis over the study period, 252 patients responded to the questionnaire giving a response rate of 70.8%. Patients who did not respond to the survey were excluded from further parts of the study and their histopathological results were not considered. The reasons for refusal were not recorded. Of those that responded, 19 were then excluded due to inadequate immunohistochemistry results for this study, resulting in 231 participants included in this study population.

The questionnaire was completed in REDCap (hosted by the University of the Witwatersrand) [123] and linked to the participant's clinical findings at presentation, and pathological specimen. The questionnaire included questions around participant's demographics, socio-economic situation, education, and self-described ability to access care. To determine patient-associated delay, participants were asked to quantify on a categorical scale how long it took them to acknowledge or disclose a breast symptom once noticed (T-Ack), from that time, how long for them to visit any health services (T-HS) and from that point, how long until attend this breast care

clinic for diagnosis (T-BCC). Ethical approval was received from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M111121).

Setting

The open-access walk-in breast care clinic is situated in a tertiary surgical referral centre in a major metropolis in South Africa. It is a government-funded hospital and accepts patients from any area of the country. The spectrum of breast disease seen in this clinic has been previously described, with more than 4000 new patients and 300-350 new cancers diagnosed each year [121].

More than 93% of the diagnostic biopsies were processed in one laboratory (National Health Laboratory Systems, South Africa) for sub-type, grade and immunohistochemistry. Hematoxylin and eosin (H&E) stained sections of all core biopsy specimens received in the laboratory were interpreted morphologically by the receiving pathologist, and then subject to immunohistochemistry. Immunohistochemical analysis was performed using fully automated protocols on a Dako Autostainer Classic (Agilent technologies, via Diagnostech South Africa). Sections of 3 μm thickness were cut from paraffin blocks and subjected to staining protocols with the following antibodies: ER, PR, HER2 and Ki67.

Upon review by the pathologist, ER and PR were reported in a semiquantitative fashion, based on analysis of the proportion of positive cells (<1%, 1-10%, 10-33%, 33-66% and 66-100%) and staining intensity (low-, moderate- or strong-intensity); HER2 was reported as negative (scores 0 or 1+), positive (3+), or equivocal (2+), based on ASCO/CAP scoring protocols [158]. Cases that were HER2 equivocal on immunohistochemistry were subjected to reflex Fluorescence In-Situ Hybridization (FISH) for amplification of the HER2 receptor on chromosome 17, using the PathVysion 17q11.2-q12 (ERBB2) & CEP 17 assay. Cases with more than 6 copies of ERBB2 per cell and/or a dual-probe HER2/CEP17 ratio ≥2.0 were reported as positive; those and HER2/CEP17 ratio <2.0 and with between 4 and 6 copies of ERBB2 per cell were reported as equivocal and those with a HER2/CEP17 ratio <2.0 with an average HER2 copy number of less than 4 per cell were reported as negative. Internal quality assurance for breast marker immunohistochemistry is ensured by positive controls placed on each antibody-stained slide, and negative controls used in each staining run. The laboratory has been participating in the Breast Immunohistochemistry Markers module of a Royal College of Pathologists of Australia external quality assurance (EQA) program for the past decade and achieves satisfactory results herein.

Data categorization

Patient characteristics were described using frequencies and proportions and categorized to facilitate analysis. Age was categorized as age less than 45 years or age 45 years and older. Self-reported race was then grouped into black and non-black categories, (non-black including women who indicated white, indian (asian), and coloured (a South African statistical group denoting a specific mixed-race group)). Marital status was categorized as partnered or unpartnered, the latter of which included women who were either not in a relationship or widowed. Each of the three categories of patient-associated delay (T-Ack, T-HS and T-BCC) was recorded as < 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year and greater than 1 year then a total delay (T-Tot) was calculated. This was then grouped as either 6 months or less, and greater than 6 months.

Stage at presentation was determined using the TNM staging system [17] from the clinical examination of the physician, together with the mammogram and ultrasound of the breast, axilla and liver. Further investigations of metastatic disease, including computed tomography (CT) of the chest and abdomen, bone scan and magnetic resonance imaging (MRI), were carried out if clinically indicated. Stage was then categorized as early stage (between stage 1 and stage 2a) and advanced stage (stage 2b to stage 4).

ER and PR receptors were considered positive if nuclear staining of 1% or more cells was positive. HER2 was considered positive if over-expressed as "3+". A "2+" finding was equivocal and FISH requested. This was either "positive", "negative" or "true equivocal". Where FISH was not carried out or a "true equivocal" result was found, these patients were excluded from further analysis in this variable, or any grouping leading from this. Participants were categorized into molecular subtype-like groups according the 2011 St Gallen Consensus [158] as

- Luminal A: ER and/or PR+, HER2 Negative, Low Ki67 ≤14%;
- Luminal B (HER2-): ER and/or PR+, HER2 Negative, High Ki67 >14%;
- Luminal B (HER2+): ER and/or PR +, HER2 positive;
- HER2 positive: ER and PR Negative, HER2 positive; and
- Triple Negative: ER and PR Negative, HER2 Negative.

Tumours with any Luminal subtype but equivocal HER2 with High Ki67 were typed as Luminal B. All Luminal B sub-types were then grouped as "Luminal B". In addition to these groupings, for further analysis, all tumours which HER2 over-expressed (whether Luminal B or HER2 subtype), and all tumours with high Ki67 (>14%) were categorized and compared to those that did not.

Statistical analysis

Patient characteristics and tumour biology were compared between early and advanced stage using Fisher's exact test of proportions, a p-value <0.05 was considered statistically significant. Modified Poisson regression with robust error estimation [72] was applied to the data to estimate the relative risk of late stage presentation by demographic characteristics, and total time to presentation, and molecular subtypes. Incidence risk ratios (IRR) and a 95% confidence interval (CI) are presented. Factors that were associated with either an increased or decreased risk of advanced stage breast cancer presentation in univariate analysis (p-value<0.10) were included in multivariate analysis and adjusted IRR (aIRR) reported. All statistical analyses were done in Stata v13.1 (College Station, Texas).

Results

Patient characteristics by stage at presentation

During the study period of 13 months from January 2016, 231 participants with a new diagnosis of breast cancer were enrolled in this study. The median age was 56 years (IQR 46-55). The key demographic characteristics are presented in Table 1, grouped according to early or advanced stage at presentation.

Stage at presentation was recorded as follows: Stage 1, 33 (14.3%); Stage 2, 63 (27.3%); Stage 3, 129 (55.8%), and Stage 4, 6 (2.6%). More than two-third of patients with stage recorded presented with advanced stage breast cancer. Primary tumour (T) stage of T4 was present in 32.3% of all patients (n= 73) with 6.2% (n=14) presenting as inflammatory cancer (T4d). There were very few relationships between any patient characteristics and stage at presentation, however when grouped according to stage and ethnicity, there was a significant association between advanced stage disease and black ethnicity (p= 0.014). There was a significant relationship between delay to presentation of more than six months and advanced stage disease (p=0.025).

Tumour biology

Clinico-pathological characteristics, also grouped by early or advanced stage at presentation are presented in Table 2. Table 2 shows most tumours were invasive carcinoma of no special type (i.e. ductal carcinoma) (92.7%, n=214), with only 4.3% (n=10) lobular carcinoma. The most common molecular sub-type was a Luminal B (57.9%) with relatively few Luminal A breast cancers. The adverse findings of triple negative or HER2 positive subtype together accounted for 33.3% of all cancers. These tumours with adverse tumour biology (either triple negative or HER2 positive subtype) were 50% more likely in black participants than non-black (IRR: 1.55, 95%CI: 1.02-2.35).

(Ch7) Table 1 Demographic and clinical characteristics of patients diagnosed by stage at presentation (n =231)

Description	Total	Stage at presentation		P-value
		Early stage (1-2a)	Advanced stage (2b-3c)	p-value*
Stage at presentation (231)	231	69 (29.9%)	162 (70.1%)	
Age (n=217)				
<45 years	47 (21.6%)	9 (4.1%)	38 (17.5%)	
45-64 years	114 (52.5%)	39 (18.0%)	75 (34.5%)	p=0.12
≥65 years	56 (25.8%)	20 (9.2)	36 (16.6%)	
Median (IQR)	56 (46-65)			
Ethnicity (n=222)				
Black African	127 (57.2%)	30 (13.5%)	97 (43.7%)	
White	64 (28.8%)	22 (9.9%)	42 (18.9%)	p=0.06
Coloured	20 (9.0%)	10 (4.5%)	10 (4.5%)	**p=0.018**†
Indian	9 (4.1%)	4 (1.8%)	5 (2.3%)	
Other	2 (0.9%)	1 (0.5%)	1 (0.5%)	
Family History (n=223)				
Breast cancer in close relative (mother, sister, daughter)	20 (9.0%)	7 (3.1%)	13 (5.8%)	p= 0.62
Co-morbidities (n=231)				
Diabetes	27 (11.7%)	12 (5.2%)	15 (6.5%)	p=0.12
Hypertension	108 (46.8%)	36 (15.6%)	72 (31.2%	p=0.32
Known HIV positive†	21 (9.3%)	5 (2.2%)	16 (7.1%)	p=0.62
Tumour T4 on presentation (n=225)				
Yes	72 (32.0%)	0	72 (32.0%)	**p<0.001**
No	153 (68.0%)	69 (30.7%)	84 (37.3%)	
Total delay to presentation				
< 1 month	38 (21.2%)	16 (8.9%)	22 (12.3%)	
1 month- 6 months	76 (42.5%)	20 (11.2%)	56 (31.3%)	**p=0.02**
>6 months- 1 year	38 (21.2%)	15 (8.4%)	23 (12.9%)	
> 1 year	27 (15.1%)	3 (1.7%)	24 (13.4%)	

*p-values estimated using Fisher's exact test of proportions; † black ethnicity compared to all other races;

(Ch7) Table 2 Tumour biological characteristics by stage at presentation

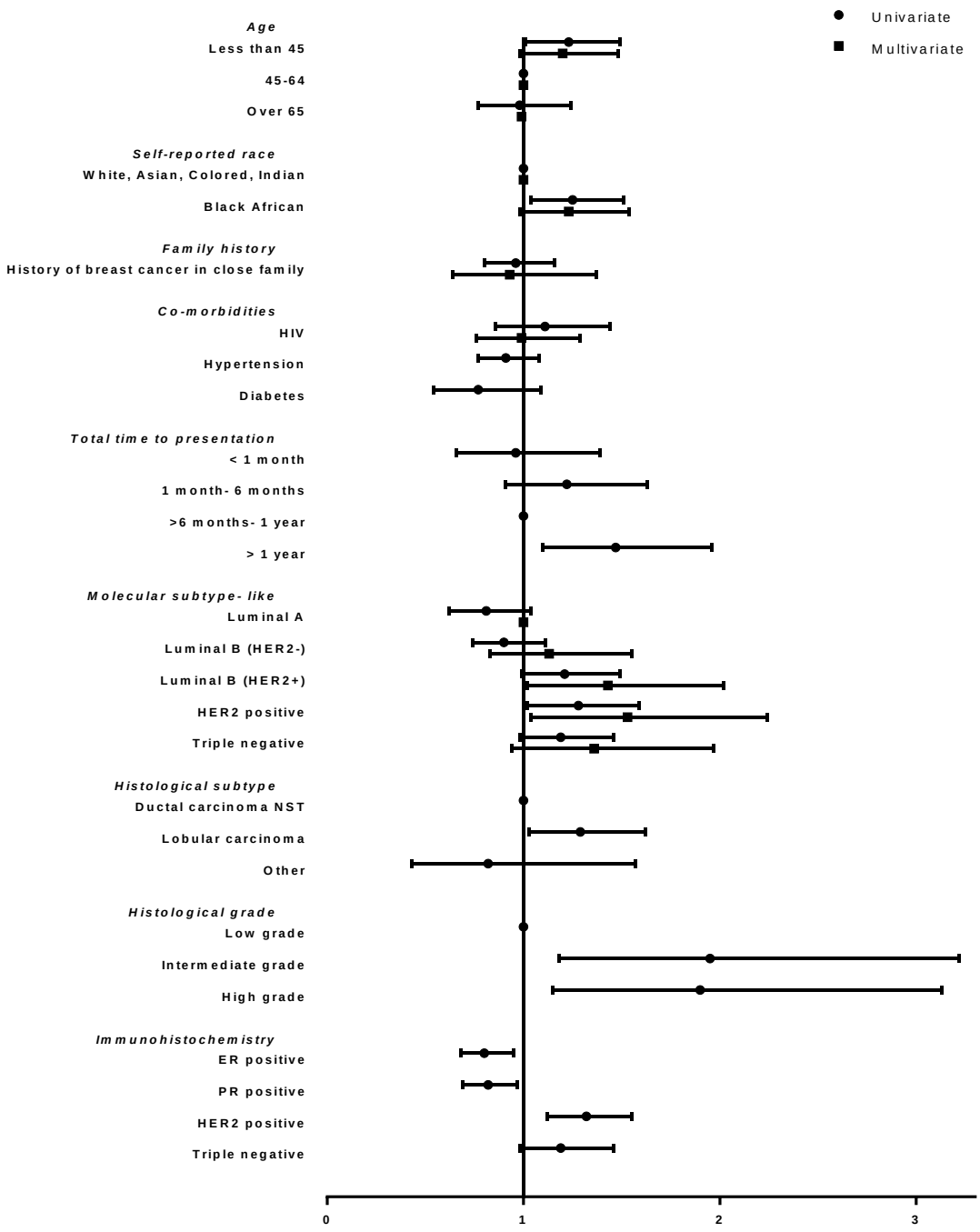
Description	Total	Stage at presentation		P-value
		Early stage (1-2a)	Advanced stage (2b-3c)	
Stage at presentation (n=231)	231	69 (29.9%)	162 (70.1%)	
Molecular Subtype (n=223)				
Luminal A	48 (21.6%)	20 (9.0%)	28 (12.6%)	
Luminal B	128 (57.6%)	40 (18.0%)	88 (39.6%)	
Luminal B (HER2-)	*102 (45.8%)*			p=0.09
Luminal B (HER2+)	*27 (12.1%)*			
HER2 positive	15 (6.7%)	2 (0.9%)	13 (5.7%)	
Triple negative	31 (14.0%)	6 (2.7%)	25 (11.3%)	
Tumour biology				
Tumour type (n=231)				
Invasive carcinoma NST (Ductal carcinoma)	214 (92.6%)	65 (28.1%)	149 (64.5%)	
Lobular carcinoma	10 (4.3%)	1 (0.4%)	9 (3.9%)	p=0.36
Other	7 (3.0%)	3 (1.3%)	4 (1.7%)	
Tumour grade (n=225)				
High grade	115 (51.1%)	31 (13.8%)	84 (37.3%)	
Intermediate grade	84 (37.3%)	21 (9.3%)	63 (28.0%)	**p=0.002**
Low grade	26 (11.6%)	16 (7.1%)	10 (4.4%)	
Immunohistochemistry				
ER positive (n=228)	177 (77.6%)	60 (26.3%)	117 (51.3%)	**p=0.03**
PR positive (n=228)	136 (59.7%)	49 (21.5%)	87 (38.2%)	**p=0.03**
HER2 positive (n=217)	42 (19.4%)	6 (2.8%)	36 (16.6%)	**p=0.01**
Fluorescence in situ hybridization (n=23)				
Positive	8 (34.8%)			
Triple negative (n=222)	31 (14.0%)	6 (2.7%)	25 (11.3%)	p=0.21

Factors associated with advanced stage at presentation: Univariate and Multivariate analysis

Figure 1 shows the relative risk of advanced stage disease at presentation, both for the univariate and multivariate analysis. On univariate analysis of demographic and socio-economic characteristics, participants less than 45 years and black participants were more likely to present with advanced-stage disease (IRR: 1.23, 95%CI: 1.01-1.49 and IRR: 1.25, 95%CI: 1.04-1.51 respectively). Whilst most tumours were ductal carcinoma, patients with lobular carcinoma were significantly more likely to present with advanced-stage disease (IRR: 1.29, 95%CI: 1.03-1.62). Most tumours were high grade, with high and intermediate grades nearly two times more common in advanced disease (IRR: 1.90, 95%CI: 1.15-3.13 and IRR: 1.95, 95%CI: 1.18-3.22 respectively). ER and PR positive tumours were more common in early stage breast cancer (IRR: 0.80, 95%CI: 0.68-0.95 and IRR: 0.82, 95%CI: 0.69-0.97). When other adverse factors were considered alone, both high Ki67 proliferation index and HER2 over-expression increased the risk of advanced disease (IRR: 1.30, 95%CI: 1.02-1.66 and IRR: 1.32, 95%CI: 1.12-1.55 respectively).

On multivariate analysis all socioeconomic characteristics were considerably mitigated by tumour biology so that the effect of age and race were no longer statistically significant in the multivariate analysis (aIRR: 1.12, 95%CI: 0.91-1.37 and aIRR: 1.17, 95%CI: 0.94-1.48 respectively). Participants with tumours of both HER2 and triple negative subtypes were associated with advanced disease, a finding which strengthened in multivariate analysis. HER2 positive patients were 50% more likely to present with advanced disease (aIRR: 1.49, 95%CI: 1.09-2.03). As a category, Luminal B cancers were not associated with advanced disease, however when separated into HER2 positive and HER2 negative, Luminal B (HER2+) cancers were predictive of advanced disease, almost equivalent to those of the HER2 sub-type (aIRR: 1.46, 95%CI: 1.10-1.95). Luminal B (HER2-) cancers behaved similarly to Luminal A cancers (aIRR: 1.09, 95%CI: 0.82-1.45).

When black and non-black participants were considered separately in adjusted analysis of advanced stage, non-black participants presenting with advanced stage disease were more likely to be young and have a HER2 positive subtype (aIRR: 1.85, 95%CI: 1.15-2.97 and aIRR: 3.10, 95%CI: 1.35-7.12). They were also far more likely to present after a delay of twelve months or more (aIRR: 3.45, 95%CI: 1.78-6.69). Conversely, black participants alone were a more heterogenous group, with no factors predicting advanced disease, with the exception of lobular carcinoma biology (aIRR: 1.58, 95%CI: 1.03-2.46).



(Ch7) Figure 1 Relative risk of advanced stage breast cancer at presentation, univariate and multivariate

Discussion

In South Africa, breast cancer is the most common cause of cancer in women [12], and here we found that advanced stage disease is the most common presentation. This study was designed to describe the variation in breast cancer subtypes in a heterogenous South African population and

determine the relationship between a patient's demographic and clinical characteristics at presentation and the molecular subtype of breast cancer they present with.

Despite living within the urban environment of Johannesburg, close to Africa's richest square mile [160], 70% of participants in this study presented with advanced stage disease, with nearly one third of participants having a T4 primary tumour. There was a relationship between young age, and between black race and advanced stage at presentation here. These relationships have been previously noted in other studies of women both in high-income settings [161–163] and from LMICs [125], however here we found that this relationship was mitigated by the presence of adverse tumour biology, which was found to influence stage at presentation more than any singular demographic.

Nearly 40% of patients were delayed for more than six months from time of initially noticing a symptom to specialist unit presentation, however there was no time frame where early disease was more common than advanced stage. In patients reporting less than one month to presentation, locally-advanced cancer was still more common, indicating that delay alone does not explain the propensity for locally-advanced disease. Without a screening program, patients are reliant on intermittent patient- or clinician-led breast examination and the presence of tumours greater than 2-5 cm or advanced nodal disease before detection may be a product of this. Similarly, without screening, smaller impalpable cancers are not represented and therefore there is a 'stage-migration' effect to an over-representation of advanced cancer.

In this current study, black participants were more than twice as likely to have a triple negative breast cancer. The strong association between triple negative cancers and mutations in the *BRCA1* gene in European and USA populations [164,165] are not well-studied in a South African population. In one recent study in a similar geographical population of breast cancer patients [166], 7/30 women with a triple negative breast cancer who underwent mutation screening without family history determination had a *BRCA1/2* genetic mutation. The significant relationship in the present study between a family history and triple negative cancers, together with the association between triple negative cancers and advanced stage at presentation here further highlights the need for more studies regarding genetic mutations in black South African women.

Most patients in this study presented with Luminal B type breast cancers. This was an unexpected finding which has not been described in other studies of breast cancer characteristics in Africa where (as in the rest of the world) Luminal A tumours are more described [155, 167, 168], however this overrepresentation of Luminal B tumours has been described globally in young women [155,169]. Our categorization of Luminal B included Ki67, as recommended in the St

Gallen consensus [159, 170] however in many studies in LMICs, Luminal B has rather been taken to be the absence of PR or presence of grade 3 or HER2 positive tumours [168]. We would hypothesize that the addition of the Ki67 marker has identified more patients into this Luminal B group, allowing a more accurate representation of the cancer population. Where LMICs studies discuss tumour biology but use only HER2 or grade to differentiate Luminal A from B, inaccurate assumptions of achievable survival outcomes and treatment provisions may occur. This study showed that within the Luminal B category, the presence or absence of HER2 overexpression was more sensitive to the likelihood of advanced presentation, with Luminal B (HER2+) tumours having clinical presentation even more akin to HER2 positive subtype than other Luminal cancers, but with an ameliorated impact on advanced presentation as seen in Figure 1.

In addition to Luminal B (HER2+) cancers, other adverse biological features such as grade and receptors increased the likelihood of advanced stage at presentation. In this study when grouped according to race, black participants were also more likely to have a tumour with adverse biological subtypes. This relationship can further be seen in the mitigation of race on multivariate analysis as a cause for late presentation. It may be that in retrospective studies in LMICs of young black women, the commonly described presentation with advanced breast cancer [10] is a composite finding of unrecognized/untested adverse tumour biology, potentiated by socioeconomic circumstances or in a young urban population. This is not to discount the importance of delay and patient/provider factors in stage at presentation, but rather adds the information that there is a subset of women for whom their biologically adverse tumour determines their stage at presentation more than any preventable delay.

The finding of adverse tumour biology in our patient population may enable us to guide governmental policy regarding breast cancer care. Most of the literature surrounding breast cancer control in LMICs is based around the dysfunctional pre-diagnosis health and welfare system, with an emphasis on education, awareness and access to services [8, 101, 133, 171]. In this study, based on international guidelines such as NCCN [172] 95% of tumours were probable candidates for neo/adjuvant chemotherapy based on stage and tumour biology, and at least 70% of patients would be suitable for radiation consideration. Even in the early breast cancer population seen here, more than 70% of participants had biological subtypes where chemotherapy would have been recommended.

These findings of a difference in the proportions of tumour biology when accurately calculated also raise the question of whether some of the disparity of outcomes in LMICs is due to an absence of screening-detected Luminal A indolent tumours within the total breast cancer incidence, rather than overall inherently more adverse tumour biology. This may occur in a similar fashion to the lack of early stage cancers seen in this study at all timeframes of presentation. It should be noted

that the incidence of breast cancer in South Africa is 1 in 33, far below that of countries where screening is carried out. Without national incidence figures per stage in South Africa it is hard to determine a per-capita advanced-cancer incidence, or adverse-biology incidence but it may be that there is actually an under-representation of early, indolent cancers, commonly seen (and sometimes described as over-diagnosed) in screening-detected populations due to lack of screening in South Africa.

Therefore, when considering provision of care to improve cancer-related outcomes, it is imperative that the discussion should be focused on adequacy of appropriate and comprehensive stage-based treatments rather than just early-detection as a method of reducing the societal burden of disease in LMICs. Studies of biology and stage specific populations can be used to guide treatment provision planning and costing in cancer care policies, such as South Africa's newly-conceived national breast cancer policy.

Conclusions

This study found that urban South African breast cancer patients had a high rate of advanced stage at presentation, and that there was a relationship between stage and adverse tumour biology, both in all HER2 positive cancers and in molecular subtypes. Despite being one of the most commonly studied cancer in South Africa [173] (and perhaps any LMIC population), the reasons for advanced stage in breast cancer are still not well understood. Because of the lack of reliable histopathological tumour characterization in many laboratories or even countries on the continent, studies may still mischaracterize tumour biological characteristics and under-represent adverse features. The need for more oncological specialty skills are well-described; however, access to accurate pathology and genetic counselling may be an essential part of providing well-timed comprehensive cancer care, to reduce the burden of breast cancer disease and mortality.

Chapter 8: Discussion

Breast cancer and other conditions of the breast are well researched in high-resource areas of the world but remain inadequately understood in LMICs. Much of the literature is characterised by generalisations of the patient populations, attitudes to disease, and screening and access to quality care at the point of need. In this thesis, the aim was to investigate attitudes and understanding of breast cancer diagnosis and care, within the specific context of diagnosed patients of an urban specialised breast cancer clinic in South Africa. Within this context, the objectives were to first define the relationship of their demographic and socio-economic characteristics with their attitudes, fears and beliefs held regarding breast cancer and its treatment; then determine the relationship of socio-economic and psychosocial characteristics with a patient's stage at presentation, and delay to presentation; and finally investigate and understand the heterogeneity of breast cancer molecular biology in this population, and assess its independent contribution to late-stage disease.

Objective One: ***To describe the relationship between patient socioeconomic characteristics with their fears and beliefs concerning breast cancer in an economic cross-section of South African survivors.***

Prior to the pilot study carried out as part of this project, there was very little evidence in South Africa examining the fears and beliefs of oncology patients. No study examined the treatment-related or hospital bound experiences related to breast cancer, nor beliefs of patients affected by cancer. The research finding presented here, that fears about treatment modalities were greater than fears surrounding socio-economic barriers, was original and supported the hypothesis of a more complex interplay of barriers to care than previously described. In additional support to this were the findings of unique combinations of concerns such as those between young women with cosmetic concerns, those with dependants associated with a fear of dying and those with job insecurities concerned that breast cancer would cause them to lose their jobs. In this study, education levels moderated concern over having cancer or dying, highlighting education in general, and health education particularly surrounding symptoms and disease management, as important.

Regarding the beliefs concerning breast cancer of this population who were undergoing or had undergone treatment, most patients held positive, and medically realistic, attitudes towards the disease. These were universal amongst the disparate demographic and socio-economic groups sampled. The few women who did hold negative beliefs of loss of womanhood and loss of life were a socio-economically and racially diverse group with little demographic distinctions. As found with fears surrounding cancer, race was not a strong independent factor but rather a proxy for socio-economic and educational inequities in this South African urban population. As with fears,

negative beliefs were mitigated in the multi-variate analysis by education, access to information and literacy. These initial findings were confirmed in the (second study) sample of newly-diagnosed women in the public sector, where there were also few negative associations and predominantly positive and biomedically appropriate beliefs. There was also little agreement with statements suggesting fatalistic beliefs.

These new findings are relatively novel within the breast cancer literature in LMICs, and contradicts the most common findings of high levels of passivity and fatalism [103, 141, 144, 174], but have been found in one other African study [143]. These results added to a body of evidence proposing a more complex relationship between fears and beliefs held by individuals, and population-based cancer statistics.

A significant limitation of the first study population was the presence of two very differing populations, those accessing the public sector and those accessing the private sector for healthcare. In this initial work, the populations differed significantly in race, education, access to information, employment, job insecurities and transport insecurities. Socio-economic factors were strong confounders of race, and on multi-variate analysis the absence of these relationships supported the assertion that education and socio-economic factors were the more important drivers of fear. This supported the second study population being drawn exclusively from the public sector in South Africa, where 84% of all South Africans access care without medical insurance [175].

In addition to a redefining of the study sample, the pilot questionnaire developed for the initial study population was analysed and refined. The importance of fatalism in the literature led to the inclusion of cancer fatalism modified from Powe's fatalism index [140, 141] and a modification of the summative scores from ten-point to four-point better facilitated analysis. Measurements of Cronbach's alpha for each subscale of the questionnaire found acceptable levels of internal consistency, thus validating it for use and analysis in this population. It has subsequently been used in other African projects [176].

Objective Two: To determine the relationship between stage of breast cancer at presentation with structural delays affecting the patient, including work, transport and healthcare access.

After the observation of the universality of many of the health beliefs and fears initially studied, it was important to ground these findings in the clinical presentation of breast cancer. Thus, this objective was designed to determine the relationship of delay with stage at presentation.

Whilst stage at presentation is described in previous studies and systematic reviews for South African populations [10, 125], previous studies had not examined the relationship between the

pathway to diagnosis and stage at presentation. Increasing pressure on the South Africa National Department of Health to develop a national cancer policy, and more particularly a breast cancer policy, resulted in this analysis being viewed as a method of documenting where gaps in access to breast care might occur or be avoided.

It has been previously noted that within the public sector, health systems mismanagement and poor or variable service delivery mechanisms prevent optimal timing and access to breast disease management and cancer treatment [138]. From our findings, more than two thirds of patients to this open-access clinic presented with locally-advanced stage disease and nearly one-third with a T4 lesion, the latter of which by its nature would have been extremely apparent to the individual patients themselves. Therefore, it is difficult to attribute delay at this stage on lack of awareness of what this symptom, often of a fungating malodourous mass, might mean.

Total delay to presentation was found to be associated with locally-advanced stage, but this delay was not associated with socio-economic factors such as education, dependants or access to information. Nor was it associated with fears concerning missed appointments due to work, money or transport. This is contrary to other studies which have found relationships between socio-economic factors and delay, and these new findings indicate a non-linear path between disadvantaged patient characteristics, total delay to presentation and stage. There were, however, relationships that indicated some association between patient characteristics and sub-groups of delay, such as delay in acknowledging a symptom in patients with a lack of internet access, or job insecurities associated with delay to accessing healthcare.

What is important to note is that these patients were all within the public sector of South African healthcare, which serves 84% of the population but most commonly not used by the most affluent in society who have private health insurance [175, 177]. Whilst the median total delay seen here was two-months, a two-month delay to access would represent extended rather than acceptable delay in a higher-income population or country.

Another important limitation of this study was the underlying facilitation of access provided by the open-access specialist clinic. The open-access nature of the study site meant that the study finding that least delay was between accessing any healthcare services and the specialist breast clinic was unsurprising. There was a median of one week (IQR: 1 day to 1 month) inferring that the specialist clinic may have often been first point of healthcare access. It is difficult to determine from this study alone what difference open-access makes to expediting care, and a further study comparing these findings to delay in an appointment-based clinic or non-specialist clinic would be necessary to support the assertion that open-access clinics reduce delay to care.

This study's first objective found that access to information and improved education in general were important in moderating fears and beliefs surrounding breast cancer. We also reported that treatment-specific education was necessary to moderate fears about breast cancer care. In addition to this, from the second objective, education requirements could be expanded to include further community education and awareness of the availability of the open access facilities, to ensure that delay from symptom acknowledgement to healthcare access is minimised.

Objective Three: To determine the relationship between stage of breast cancer at presentation with psychosocial factors affecting the patient, including their fears concerning breast cancer and beliefs held surrounding its presentation, causes and consequences.

Determining the importance of beliefs around breast cancer with regard to stage of disease allowed re-evaluation of the relationship of socio-economic factors with beliefs and their relationship to stage at presentation. Whilst level of education was unrelated to advanced presentation of itself, some of the factors that were previously found to be associated with lack of education could be found in this study to be related to advanced disease. These included literacy in general, but also biomedically incorrect beliefs such as cancer could be caught or was the "way they were meant to die". In the same way poor socio-economic circumstances in general did not increase the likelihood of advanced cancer, but if women had transport difficulties, and *also* showed evidence of lack of trust in the biomedical model (agreed with "would rather die than lose a breast' or cancer "will eventually kill me") or if they believed in non-medical methods of cure, they were 20-40% more likely to have advanced stage disease.

These findings begin to build a more complex picture of individual decision-making, where threat to life is weighed up against immediate socio-economic problems and viewed through a lens of belief in the hospital's or biomedical healthcare service's ability to cure disease. Within this paradigm, advanced stage at presentation itself should be questioned as outcome variable alone. Instead, progression of disease to an advanced stage, including fungating of the tumour through the skin, might be seen as an impetus for care rather than a consequence of delay, weighting the patient's deliberation in favour of biomedical (hospital) diagnosis and care even with its economic, transport and work burdens.

Objective Four: To assess the relative contributions to advanced stage at presentation of patient factors with tumour biology.

This thesis and the papers that have arisen from it can be seen as a linear path in the candidate's determination to understand the influencing delay in presentation and their impact on cancer stage in women with a diagnosis of breast cancer in South Africa. The initial study was conceived

to engage with patients as participants in understanding their experience of breast cancer. Following from this, was developing an independently reliable questionnaire which would allow understanding of the subjective experience of the participant to their objective stage at presentation.

However, it was important to recognise that developing over the last two decades in tandem with our understanding of patients with breast cancer, has been an understanding of the disease itself. With this is the recognition that the biological characteristics of breast cancer are as important, if not more so in prognosis, than the clinical stage. This has been recently fully acknowledged by the AJCC in their 8th edition of cancer staging [1] and in various expert consensus statements [1, 128, 178–180]. Therefore, the final analysis of this study population aimed to determine the place of tumour biology in influencing stage at presentation.

Tumour biology is the only variable in this study, and in breast cancer understanding in general (with the exception of age or race), in which no attempt can be made to alter or influence it. Therefore, understanding its contribution to advanced stage is more important for setting all the other modifiable factors in context, and determining whether substantial changes to socio-economic or psychosocial factors would influence stage, or indeed prognosis, in the light of unfavourable biology.

This study found that some forms of adverse biology were associated with advanced stage at presentation. This included high or intermediate grade tumours, ER or PR negativity, and HER2 over-expression. Importantly, all socio-economic factors were mitigated by tumour biology, and when considered in the multi-variate analysis which controlled for these factors, the relationship between adverse tumour biology and delay was strengthened. In addition, in the Luminal B cancers, when separated into those with or without HER2 overexpression, those with HER2 overexpression also behaved similarly to HER2 positive cancers, increasing the risk of advanced disease. Black participants were found to be a heterogeneous group with only one factor (lobular sub-type, often difficult to detect on imaging) predicting advanced disease. On the initial analysis here, there was a relationship between young age, and between black race and advanced stage at presentation. This was consistent with other studies of women both in high-income settings [161–163] and from LMICs [125], however crucially to the understanding of this aetiology of this relationship, we found that race, and young age were considerably mitigated by the presence of adverse tumour biology, which was found to influence stage at presentation more than any singular demographic.

Considering previous analyses of these study patients under the first two objectives which found that race alone was not a predictor of beliefs or delay and most commonly a proxy for inequity in

the country, these findings confirm the lack of evidence for singular racial differences in breast cancer characteristics in South Africa and highlight the complex interplay of disease biology with individual patient and provider factors in our environment.

This final analysis also found important considerations which have not been previously examined in low-income settings or discussed as causative factors for late-presentation in comparison to high-income populations. These are the comparison of a non-screened population to high-income screened populations, and the absence of receptor-marker consistency in sub-type categorisation for unbiased comparison between studies from LMICs.

In high-income screened populations, there has been a debate in the last decade regarding the effect of screening. Whilst it is accepted that more breast cancer is detected at an earlier stage, there has been failure to demonstrate a reciprocal fall in late-stage disease [181–185]. The presence in this study of late-stage disease, with a paucity of the Luminal A cancers most commonly seen in screened populations, may be an artefact of symptomatic rather than screening (over)diagnosed disease. In a systematic review of 12 multicentre studies from Europe and the USA (Blows), Luminal A cancers were found in 71% of patients (Luminal B 6%, HER2 6% and Triple Negative 9%). At presentation only 39% of Luminal A cancers had a tumour greater than 2cm (Luminal B 53% HER2 57% and Triple Negative 54%), and 42% were node-positive (Luminal B 56%, HER2 58% and Triple Negative 40%). In this current study, only 21.6% of patients had this favourable sub-type, and this sub-type accounted for only 18.2% of all advanced disease. Further to this, a study of the molecular sub-types of screening and symptomatic women in Sweden [186] found a significantly increased number of Luminal A tumours in screening-detected women and concluded that:

> "screening-detected breast cancer is characterized by more favourable tumour biology and is diagnosed at an earlier stage than symptomatic disease. Despite analysis with modern molecular pathology techniques according to validated protocols, stage migration was the most important confounder explaining the beneficial effect of mode of detection on survival." [186]

This would support a hypothesis that some of the propensity of advanced disease seen in this current population may be secondary to a paucity of screening-detected favourable-subtype indolent disease more commonly occurring with increased age. Also supportive of this would be the comparison of cancer incidence to life expectancy: there is a smaller incidence of breast cancer documented by the National Cancer Registry of South Africa (2012) of 1 in 26 women [12], with a life expectancy in of 62.9 years [187], as compared to

the USA where the SEER data indicates 1 in 7 women are affected [71] but with a life expectancy of 79.3 years.

The second new consideration in the finding of increased late stage disease is the importance of immunohistochemical accuracy in the determination of sub-type. In this study there were clear distinction in the rates of advanced disease between HER2 positive and negative disease, and within the Luminal B group, a movement of Luminal B HER2+ tumours towards Luminal A behaviours, and Luminal B HER2+ tumours towards findings associated with the HER2 positive subtype. A review of the literature concerning this in LMICs shows that the differentiation between Luminal A and Luminal B tumours can encompass PR status, grade, HER2 status or Ki67 (recommended by St Gallen [159], as in the current study) [154, 155, 168, 188]. The differentiation of these will affect the proportion of patients separated into Luminal A, Luminal B and HER2 positive groups, and therefore affect expectation of biological indolence, treatment success and ultimately prognosis.

It is important here, however, to restate that these propositions should not replace the understanding of individual or health system related factors in advanced disease but, in light of the full biopsychosocial findings of this study, continues to inform the understanding of the interactions between patient, health system and pathological feature that will impact on the individual's experience of their disease.

Chapter 9: Conclusions

This thesis and the manuscripts arising from this study report on the determinants of advanced stage at presentation of breast cancer in an urban South African specialist clinic. It was designed as a clinical observational study rooted in participation of the patients in understanding their experience of breast cancer, both psychosocially and within the health-system they relied on. As clinicians, the concept of a problem patient, quick to run to the traditional healer and slow to enter the biomedical world, was one perpetuated in the literature but not seen so commonly in clinical practice.

Through a two-part study, first comparing the attitudes of patients accessing public and private healthcare spaces, then comparing the clinical and personal features of patients within the public healthcare system, four objectives were met. This study found that the determinants of advanced stage at presentation are complex and individualistic. This study has highlighted how the many intersections in an individual's experience may impact on their stage at presentation. Race may affect stage, but through the socio-economic inequities currently present in South Africa, or an increased risk of adverse tumour biology. Poor access to information alone, or through education or literacy, will affect beliefs which subsequently affect delay. Delay to presentation does increase the risk of advanced stage at presentation, but not through a linear path of poor socio-economic circumstances alone.

Therefore, this study has not answered a binary question of why patients present with advanced-stage breast cancer. Rather it has shown that providing biomedical access for patients with breast disease in South Africa should be designed as a multi-faceted approach to safe-guard individual patients from failing to: accurately acknowledge a breast problem; recognise the appropriateness of expedient biomedical care; and be cognisant of local facilities to allow for that. In the same way, a healthcare system, and more specifically the South African National Breast Cancer policy, should be designed in such a way as to anticipate with social support the transport, financial and familial burdens associated with accessing care, and make medical provision to provide cancer stage and sub-type appropriate treatment for their patients.

This study has highlighted deficiencies in the approach to managing and reducing advanced stage breast cancer at many levels and has provided evidence for strategies required for improving care. These have been discussed through the chapters of this thesis but can be summarised here as:

1. **Community interventions and advocacy:** Ensuring the education of patients not just to be aware of breast care symptoms and the urgency of biomedical care, but also to understand cancer management and dispel uncertainties or fears about that biomedical

care. Using new technologies of mHealth and other internet or cellphone-based technologies can be considered, with the evidence that cellphone usage is high, thereby flattening the hierarchy of multiple tiers of healthcare and allowing direct access to appropriate specialist care which may prevent or at least mitigate delay.

2. **Population upliftment:** In addition to community intervention and advocacy around breast disease, there is a further need for community upliftment to enable patients to fully access appropriate diagnostic care. This study found that beliefs, fears and delay could be related to issues of literacy, job security and transport burdens, and together indicate a difficulty in navigating the health system. Further to this the relatively high level of appropriate agreement and disagreement to the questionnaire questions indicated adequate breast awareness. Therefore, more holistic measures of ensuring improvement in literacy, job security and social support would appear crucial in minimising delay and advanced disease at presentation, through all domains measured in this study accept tumour biology. Unfortunately, this last intersection between one thesis and health systems improvement is beyond the scope of this study or discussion, but documentation and advocacy of this is critical in the recognition of change required to improve care in South Africa.
3. **Improved access to health care and social support services:** Using an open-access model of care to deter delay in diagnosis, but also to combine services at one point-of-care that may improve patients' experience of holistic support and decrease the fears found in this study. This could be improved by social-work advice for accessing grants and governmental financial support; legal advice around labour law and job security; psychological support for patient and family; onsite childcare to allow longer or more frequent appointments; and stage-appropriate treatment provided within recommended time-frames.
4. **Improved oncological services:** In addition to diagnostic facilities and stage-appropriate treatments, this study found that accurate consistent molecular pathology was important in understanding and predicting disease. The small increase in adverse tumour biology also invites further population studies through genetic counselling and assessment, and the better integration of genetic testing at the interface of clinical care [166]. These are issues poorly resourced in the South African, or indeed the LMIC setting [189].
5. **More nuanced understanding of heterogeneous populations in LMICs:** This study, encompassing women from different self-reported races, nationalities and economic and educational brackets, found a heterogenous population that was not easily characterised along socio-economic or demographic lines alone. More studies, both descriptive and

qualitative are required to better characterise decision-making from symptom-recognition to treatment acceptance. This would include multi-centre studies within countries to allow rural/urban, differing sub-cultures or distinct populations groups to be included to properly represent the whole population, and prevent inherent selection bias causing country-sized generalisations.

The studies and research papers presented in this thesis have met the objectives and aim of the overall thesis. The first objective described the relationship of breast cancer patients to fears and beliefs about their disease and found a heterogeneity of attitudes not bound to patient characteristics. The second and third objectives described few direct associations between of stage of breast cancer at presentation and structural or psychosocial factors, but a more complex picture of individual decision-making, where decisions regarding biomedical treatment are weighed against socio-economic burdens and belief in the biomedical model. The final objective then discussed the relationship of advanced disease to the tumour biology of the breast cancer and found that the two were closely linked, but unrelated to most socio-economic or demographic characteristics.

Finally, the thesis has described and examined the experience of patients with breast cancer in an urban South African setting, examined the relevance of socio-economic and belief-based factors in causing advanced disease, and from this, recommended small-scale, community and governmental strategies for breast cancer care improvement, informed by future research.

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Appendix A1: Paper 1 (Journal of Global Oncology)

original report

Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa

abstract

Purpose Breast cancer is the most common cause of cancer in women in South Africa, and often patients present late. There is little understanding of the psychosocial stresses affecting women with breast cancer in Africa.

Methods A questionnaire was distributed to 263 patients with breast cancer at two sites (one government and one private facility) in Johannesburg. Self-reported levels of fear were recorded on summative scales and their relationship to demographic variables assessed through univariable and multivariable modified Poisson regression.

Results Fears related to treatments and prognosis, particularly radiation, loss of hair, and loss of breast, were far stronger than those related to socioeconomic barriers. Relative risk (RR) of most fears was higher in women younger than age 40 years, including treatment affordability (RR, 1.80; 95% CI, 1.26 to 2.56), hair loss (RR, 1.48; 95% CI, 1.12 to 2.95), and surgery (RR, 1.31; 95% CI, 1.02 to 1.68). Difficulty taking time off work predicted fear of job loss (RR, 2.59; 95% CI, 1.59 to 4.21) and missing appointments because of transport (RR, 2.46; 95% CI, 1.52 to 3.96) or family commitments (RR, 2.46; 95% CI, 1.52 to 3.96). Women with dependents and black women were more afraid of dying (RR, 1.73; 95% CI, 1.03 to 2.90; and RR, 1.79; 95% CI, 1.33 to 2.24, respectively); however, socioeconomic status in this sample was a strong confounder of race and explained most of the racial differences in levels of fear.

Conclusion The most significant fears around breast cancer were related to treatment modalities and adverse effects rather than transport, financial, or work concerns. Young age and job insecurity were predictive of increased fears. Education about treatments has a key role to play in improving access to breast cancer care in South Africa.

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INTRODUCTION

Breast cancer is the most common form of cancer to affect women in South Africa and in 2013 was responsible for 20.8% of female cancers and more than 10% of the entire cancer burden.[1] The National Cancer Registry (most recent report, 2009) reports an age-adjusted incidence of 27.6 per 100,000, equating to a lifetime risk of 1 in 33 women.[1]

In developed countries, advances in the management of breast cancer over the last 50 years, including screening and early detection programs, have led to an increase in survival rates. Early-stage breast cancer has a survival of > 95%;[2] however, late-stage disease continues to be responsible for most cancer deaths, through metastatic progression.

Optimal treatment of breast cancer and increased survival rely not just on early detection but on early and continued presentation at a center capable of treating the disease. Thus, health care disparities will affect a patient's outcome.[3] In trying to understand these disparities and their effect on outcome, studies often look to socioeconomic factors, including education, health insurance status, work, and transportation.[4,5] These factors may provide physical barriers in accessing adequate health care. Physical barriers can also become a source of psychosocial stress for the patient, causing fears that can also affect timely presentation, treatment, and patient choices about their breast cancer care.[6] In addition to physical barriers to access of care and fears

related to sociodemographic factors, further stress can be associated with knowledge (or lack of knowledge) of treatment modalities and their associations and adverse effects.

Understanding the fears associated with breast cancer in South Africa is important in improving care and enabling and encouraging all women to access treatment earlier. By interviewing women accessing services in both government and private facilities in Johannesburg, we sought to determine the fears experienced by all women with a diagnosis of breast cancer, allowing identification of important universal areas for education and improved care provision.

METHODS

This dual-center study included patients with and without medical aid in Johannesburg, South Africa. Medical aid is the system of health insurance in South Africa bought by the end-user that allows access to private facilities. Patients without medical aid or with poor coverage are seen in government-funded facilities at low or no cost. The government clinic is based within a provincial government tertiary hospital and manages approximately 350 new breast cancer diagnoses each year. Only 6% of these patients have medical insurance (unpublished local data). The private facility sees private- or medical insurance–funded patients and manages approximately 400 new breast cancer cases per year.

From November 2011 to May 2013, patients undergoing treatment of breast cancer in each center were recruited to complete a questionnaire. The questionnaire was distributed to consenting patients attending for diagnosis, operation, or follow-up over a 21-month period. Each patient was offered the choice to complete the questionnaire alone or with the aid of an assistant, who could translate into the patient's preferred language. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The first part of the questionnaire included sections on demographics, socioeconomic status, educational background, work, transport, and religious affiliations. The second part of the questionnaire used a summative scale of 0 (no fear) through 5 (fear under control) to 10 (very fearful) to determine the patients' feelings of fear and concern at diagnosis about issues related to their care, social circumstances, or prognosis.

Patient characteristics were described using frequencies and proportions. Age was categorized as age 40 years and younger or age 41 years and older. Having dependents was compared with not having dependents. Social status was categorized as being married or unmarried, the latter of which included women who were single, divorced, or widowed. Women who were employed by others or considered themselves self-employed were compared with women who were unemployed or retired. Education was grouped according to highest level of formal schooling completed: primary, secondary, or tertiary. Reported race was collapsed into black and nonblack categories, including women who indicated white, Indian (Asian), colored, and mixed races. Women who indicated that they sometimes or always had difficulty with transport or taking time off from work were compared with women who indicated they seldom or never had those difficulties. Two-sided differences of proportions were compared using Pearson's χ^2 test. A P value $< .05$ was considered statistically significant.

Patients who did not have a confirmed diagnosis of cancer were excluded from the analysis of fears (n = 4). Responses were categorized as fearful (score > 5) or not fearful. Modified Poisson regression with robust error estimation[7] was applied to the data to estimate the relative risk (RR) of being fearful according to patient characteristics; RRs and a 95% CIs are presented. Univariable and multivariable results adjusted for the patient characteristics described above are presented. All statistical analyses were done in Stata v13.1 (College Station, TX).

RESULTS

A convenience sample of 263 patients was included. Patient age ranged from 18 to 86 years, with a median of 52 years (interquartile range, 44 to 62), with 41 patients who were age 40 years or younger at diagnosis (16%). Table 1 lists patient characteristics grouped as either private hospital or government hospital and shows that government patients were more likely to be black ($P < .001$), single, and living with others. They were less likely to be employed when compared with private facility patients (52% *v* 73%; $P = .001$). Significantly more private facility patients had a tertiary education (53% *v* 13%, $P < .001$), and 36% of government patients attained primary education only compared with 6% from the private facility. Access to cell phones was extremely high in both groups (97% private facility, 95% government), but computer and internet usage was significantly higher in private patients (87% *v* 39%, $P < .001$).

Table 1 – Patient Characteristics

Description	Private Hospital (n = 93; 35%)	Government Hospital (n = 171; 65%)	Total (n = 263)	P
Age				
≤ 40 years	15 (16)	34 (21)	207 (81)	.388
≥ 41 years	77 (84)	130 (79)	49 (19)	
Race				
Black	7 (8)	78 (48)	85 (33)	< .001
Nonblack	85 (92)	85 (52)	170 (67)	
Marital status				
Married	50 (59)	70 (47)	120 (51)	.081
Not married	35 (41)	79 (53)	114 (49)	
Formal education				
Primary	5 (6)	56 (36)	61 (25)	< .001
Secondary	37 (41)	80 (51)	117 (48)	
Tertiary	48 (53)	20 (13)	68 (28)	
Dependents				
No dependents	18 (20)	23 (15)	41 (17)	.297
Any (≥ 1)	72 (80)	132 (85)	204 (83)	
Have cell phone				
Yes	98 (97)	147 (95)	265 (96)	.484
Use computer				
Yes	79 (87)	62 (39)	141 (56)	< .001
Employed, job				
Yes	67 (73)	83 (52)	150 (60)	.001
Time off for appointments difficult				
Yes	12 (13)	32 (24)	44 (20)	.039
Transport for appointments difficult				
Yes	8 (9)	58 (36)	66 (26)	< .001

Data presented as No. (%).

All Fears

Figure 1 illustrates how many patients with a confirmed cancer diagnosis (n = 259) were fearful (score > 5) for each domain included in the questionnaire. The overall pattern demonstrates that fears related to treatments and prognosis were far stronger than those related to socioeconomic barriers. The most common treatment-related fears were related to chemotherapy adverse effects (65.4%), followed by radiation and surgery (59.7% and 53.9%, respectively). Although some patients feared both surgery and breast loss, the differences between the women who feared surgery and those who feared breast loss was statistically significant ($P < .001$), as were women who feared surgery and women who feared radiation ($P < .001$), using the Pearson's χ^2 test. Concerns over ability to attend appointments for reasons including transport and work were the lowest.

Relative Risks of Different Fears

The RRs of fearfulness for women younger than age 40 years were uniformly higher than for older women (Fig 2). This was most pronounced in their worry over affording all appointments and treatments (RR, 1.80; 95% CI, 1.26 to 2.56). Young women also had an increased likelihood of treatment-related fears, significantly in fear of hair loss (RR, 1.48; 95% CI, 1.12 to 2.95) and fear of surgery (RR, 1.31; 95% CI, 1.02 to 1.68).

In women of all ages, difficulty with taking time off work (a relative measure of job insecurity) had increased likelihood of fear about job loss (RR, 2.59; 95% CI, 1.59 to 4.21), and women were more likely to fear missing appointments either because of transport (RR, 2.46; 95% CI, 1.52 to 3.96) or because of family commitments (RR,

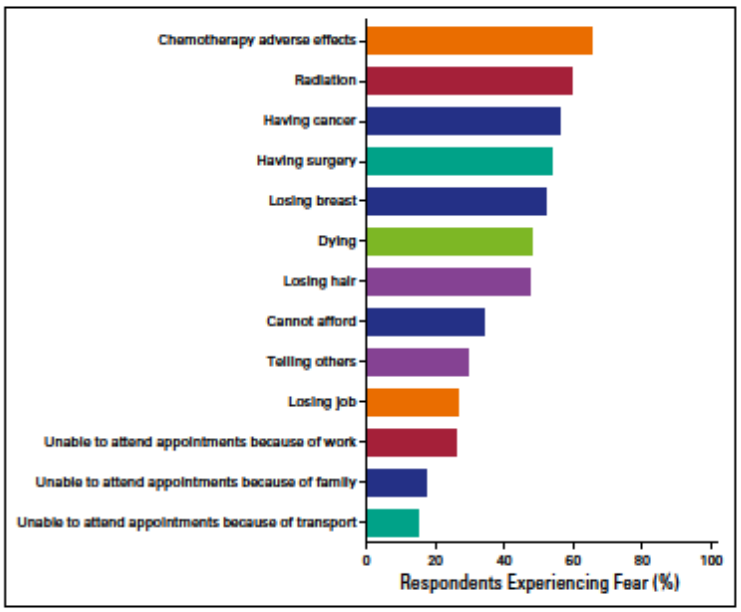


Fig 1 –
The percentage of women categorized as fearful (fear score > 5) in each described fear.

2.46; 95% CI, 1.52 to 3.96). They also feared the adverse effects of chemotherapy more (RR, 1.30; 95% CI, 1.07 to 1.58). A tertiary education was protective against fear of job loss (RR, 0.46; 95% CI, 0.24 to 0.92) and not attending appointments because of transport and family (RR, 0.20; 95% CI, 0.07 to 0.58; and RR, 0.33; 95% CI, 0.14 to 0.75, respectively).

The RR of fear of dying had a median of 5 and the widest spread of any of the fears, with an interquartile range of 1 to 9; 47.7% of participants indicated they were fearful of dying (a score > 5). Women with dependents were 1.73 times more likely to be afraid of dying (95% CI, 1.03 to 2.90), as were black women (RR, 1.79; 95% CI, 1.33 to 2.24). Figure 3 shows that black women experience much more fear toward the physical barriers to care: they were much more afraid of missing appointments because of transport problems (RR, 4.11; 95% CI, 1.42 to 8.12) or because of family commitments (RR, 2.56; 95% CI, 1.42 to 4.62) and worried they could not afford to get cancer (RR, 1.66; 95% CI, 1.17 to 2.37). These results are similar to those experienced by women in the public hospital (Fig 4).

In adjusted regression, where patient characteristics were held constant (Fig 5), black race remained a significant predictor of fear of dying (adjusted RR, 1.73; 95% CI, 1.13 to 2.64). Socioeconomic characteristics such as employment, use of the government hospital, and computer use were not statistically significant predictors of fear of dying. Although being young, black, in a government hospital, or with transport difficulties increased the fear of affordability of treatments, none remained significant in the multivariable adjusted model.

DISCUSSION

In women with a diagnosis of breast cancer, this study found that breast cancer treatment and its adverse effects, including the universal fears of cancer and dying, were associated with increased fear at diagnosis, but socioeconomic factors, including transport, work, and financial issues, were not. Affordability of cancer treatment was the only socioeconomic factor that was associated with an increased level of concern.

Studies have found that fear can be important in determining delay to treatment.[8-11] How patients are treated also seems to influence if they continue to attend for care, whether by their physicians[12,13] or because of adverse effects.[10,14,15] However, the relative contribution of these factors to fear

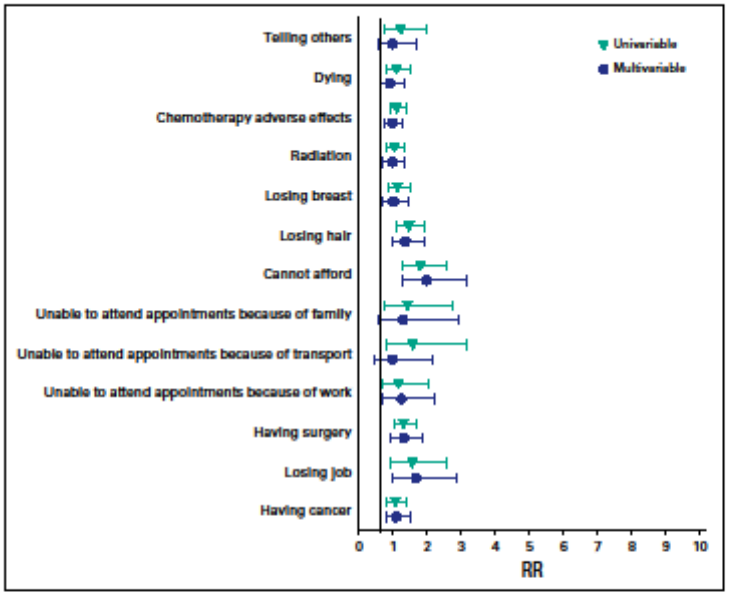


Fig 2 –
The relative risk (RR) of fears in women age 40 years or younger shown relative to those older than age 40 years.

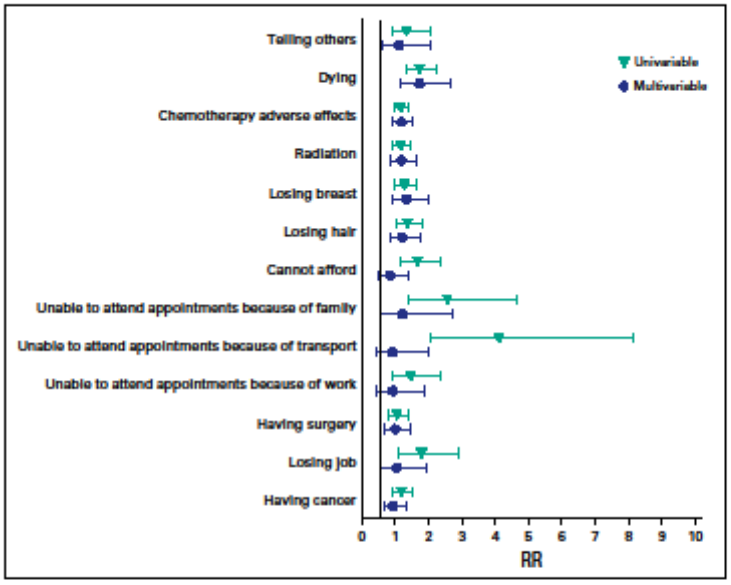
associated with a diagnosis has not been determined. The new findings from this study suggest that physical obstacles may represent less of a barrier to care than psychological fears associated with treatments in our urban South African setting.

Within this sample, different populations emerged, each with unique combinations of concerns. Like many other studies,[16,17] we found a significant relationship between younger age and higher cosmetic fears around hair loss, although not loss of the breast. This lack of fear around mastectomy may reflect the options of reconstruction and breast-conserving surgery. Younger women also face increased fears over affordability of treatment, having surgery, and job insecurities. These differences reflect the pressures these women face in maintaining income after a diagnosis. The loss of hair could also be concerning in this light, as it would publicize cancer therapy to employers and colleagues. Studies that have looked at the psychological needs of young women have found that younger patients viewed themselves as different from older patients, with problematic work and relationship issues, fertility decisions, and poor support when transitioning into survivorship.[18,19] Our findings are consistent with this and highlight the distinctive support needs of this young group.

In addition, this study highlighted other groups with less psychological resilience around breast cancer treatments, including those with job insecurities (increased fear of job loss) and those with dependents (fear of dying), whose additional supportive needs may be overlooked. The near-universal fear of cancer, with all its negative connotations, was present in increasing measure in those with dependents. In an economic center such as Johannesburg, members of the working population are often held responsible for household dependents in addition to supporting an extended family and homesteads in rural areas. It is possible that the demands of close caregiving to family, the economic demands of dependents near and far, and the unexpected nature of cancer can add significant psychological stress to such patients.

The highest-scoring fear was in relation to possible radiation treatment. This mirrors other studies that show women have a nonspecific fear of radiation[5,20] and possibly fear its relationship to causing cancer. These findings highlight the important role of education of the presymptomatic woman (essentially every woman) in how breast cancer is not just diagnosed but also treated. Education has been shown to reduce fears and improve attendance in diverse global populations,[21-28] including recent successes of HIV/AIDS community education in sub-Saharan Africa, where radio and television soap operas have

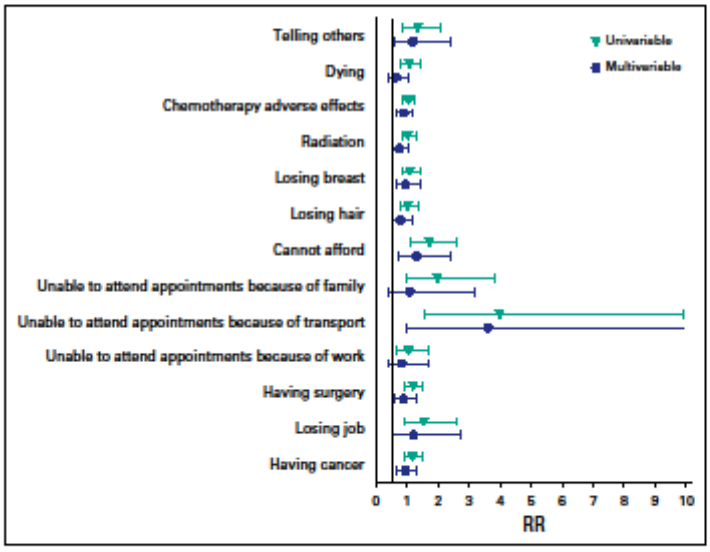
Fig 3 –
The relative risk (RR) of fears in women of black race shown relative to all other women in the study.



been used to highlight diseases such as HIV/AIDS with measurable effect.[24] The contribution of recent high-profile breast cancer survivors in South Africa can also be used as an opportunity to introduce public discussion of treatment options and successes in breast cancer care.[25]

The current study indicated an extremely high ownership of mobile phones in the population studied (89%). This, coupled with the increasing use of internet through smartphone connectivity, allows eHealth (using communication technology for health) and mHealth (using mobile

Fig 4 –
The relative risk (RR) of fears in women at public sector hospital shown relative to women at private sector hospital.



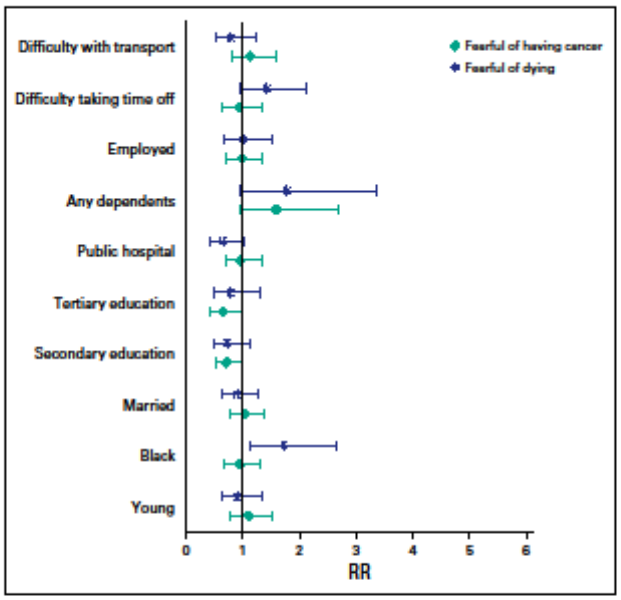


Fig 5 –
Multivariable analysis of influences on the fears of affordability of appointments and treatment and dying. RR, relative risk.

communication technology to deliver health care) strategies to be used for education. Already, young patients in South Africa access health information for themselves and family through smartphone internet access,[26] and this has been shown to modify health behavior, if not knowledge, in a South African patient population.[27] These forms of education can complement more traditional mass-education initiatives, which have been used in breast cancer awareness in low-income, low-awareness areas of the world[28,29] and in South Africa, with layering of messages of education through multimedia.[24] This new finding that breast cancer treatments are a source of fear and potential barrier to care means that introducing management options and expectations into the dialogue of breast cancer awareness and screening should be a practical application after this study for cancer care in South Africa.

The fear of dying in black women was moderated by attendance at a government hospital. This may be a reflection of good social support, closer ties to community, and in particular the presence of survivor-navigators in the government hospital, funded by a nongovernmental organization. Other studies have also found that having counsellors or navigators present reassures patients and helps them negotiate the complex medical system, and they are then likely to receive recommended standard treatment.[30] In addition, navigators are able to identify and resolve intrapersonal (defined as beliefs, knowledge, attitudes, and socioeconomic) barriers that affect patients.[31] Securing funding to maintain and increase the number of available navigators is a challenging undertaking in our resource-limited environment; however, the potential future outcome of improved patient care highlights the necessity.

Previous studies have shown strong relationships between disparities of access and response to breast cancer care for different races internationally and in South Africa.[14,32] Studies from Africa or of African migrants often rely on using cultural beliefs and fears to explain these barriers to care,[4-6,8,11,32,33] whereas in this study we found that although there were differences between races in their levels of fear, these were related to inherent socioeconomic disparities rather than cultural responses. Black women were more likely to fear hair or breast loss and more likely to experience concerns over socioeconomic obstacles. However, because of the legacy of previous economic/political policies in the country, there remains a significant association between race and socioeconomic status. These socioeconomic factors were strong confounders of race in this study and, on multivariable analysis, most of the race-fear relationships weakened, demonstrating

few inherent racial differences but inherent strong educational and economic drivers of fear. These data provide preliminary support for questioning the existence of culturally bound reasons for delay and failure in breast cancer treatment and point to more holistic concerns shared by women of all races in all countries.

In all countries, but particularly in post-apartheid South Africa, relying on factors such as race to predict fears, attitudes, and access is problematic. These data confirm the questioning of the influence race alone has on fears around breast cancer and receptiveness to treatment and, in fact, whether universal concerns over welfare and fear around treatment and death transcend race or culture. Health surveys among other seemingly homogeneous groups show great diversity of language, education, diet, and health behaviors,[34] and therefore assuming help-seeking behavior or barriers will be standardized in a racial group should be treated with caution.

For practical reasons, an opt-in invitation method was used in this study, and no information is available for those who declined to complete the questionnaire. Although translation was available, there may be a selection bias toward English-speaking patients of all races, and this may confound some of the variables, particularly around education and employment. Therefore, the extent to which this can be generalized to all patients with breast cancer is unknown. An additional consideration and scope for further work is that the study was purely quantitative in its approach. Examination of the full scope of fears and attitudes of patients through interviews would increase the range of our understanding of the patient's experience.

The study was cross-sectional in nature, and although women were asked to recall the fear experienced at diagnosis, in recollection some of these fears may have been moderated or increased for women who had already started treatment. In addition, a further limitation as with many studies of breast cancer in sub-Saharan Africa is that this sample is taken from patients attending an urban specialist center. Although they would have vital and valid responses for this study, particularly regarding access and barriers to care, it is impossible to target patients with breast cancer who fail or refuse to present to medical services at any point in their care. However, many of the patients in this study would be presenting in the later stages of the disease for final palliative care of fungating wounds or terminal disease symptoms. More studies are required to relate medical details, including staging at presentation, to psychosocial and socioeconomic characteristics.

In conclusion, studies on barriers to cancer care in underserved populations have often focused on the physical barriers that prevent patients from accessing care. Our results show that women are far less fearful of how they will negotiate life during treatment (including work, finances, and family commitments) than they are of the planned treatments. Young patients are particularly vulnerable to increased fear when approaching treatment of breast cancer, and this group should be targeted with specific support. For all women, the public message of breast awareness should include education about breast cancer treatment and emphasize the importance of treatment for survival.

DOI: 10.1200/JGO.2015.002691
Published online on jgo.ascopubs.org on June 22, 2016.

AUTHOR CONTRIBUTIONS

Conception and design: Sarah Rayne, Carol-Ann Benn
Collection and assembly of data: Sarah Rayne, Kathryn Schnippel, Kathryne Wright
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Sarah Rayne
Consulting or Advisory Role: AstraZeneca

Kathryn Schnippel
No relationship to disclose

Cynthia Fimhaber
Research Funding: Merck (Inst)

Kathryne Wright
No relationship to disclose

Deirdre Kruger
No relationship to disclose

Carol-Ann Benn
Employment: International SOS (I)
Consulting or Advisory Role: Netcare Hospital Group (Inst)
Travel, Accommodations, Expenses: Novartis

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Appendix A2: Paper 2 (Journal of Cancer Education)

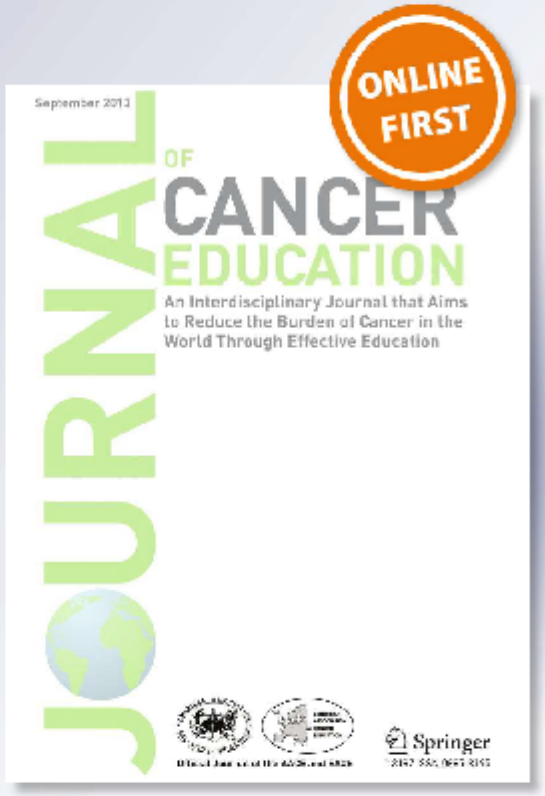
The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa

Sarah Rayne, Kathryn Schnippel, Carol Benn, Deirdre Kruger, Kathryne Wright & Cynthia Firnhaber

Journal of Cancer Education

ISSN 0885-8195

J Canc Educ
DOI 10.1007/s13187-017-1234-3



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J Canc Educ
DOI 10.1007/s13187-017-1234-3

The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa

Sarah Reyne[1] · Kathryn Schnippel[2,3] · Carol Benn[1] · Deirdre Kruger[1] · Kathryne Wright[1] · Cynthia Fitzhaber[2,3]

Abstract Breast cancer is the most common cancer affecting women in South Africa. There is little knowledge of beliefs to help identify key areas to improve support and education in this demographically and culturally diverse population. Women with a variety of demographic and socioeconomic characteristics screening care for breast cancer were asked their agreement to statements of knowledge and beliefs about breast cancer. Of the 259 participants, positive statements of medical cure (87.9%) and family support (90.5%) were most commonly believed. Beliefs in faith-based cure and alternative treatments were also present (79.5 and 24.9%, respectively). Negative beliefs were initially more likely in black patients (RR: 11.57, 95%CI: 1.37–97.69) as was belief of cancer as a punishment (RR: 6.85, 95%CI: 1.41–33.21). However, in multivariate analysis adjusting for age, education and access to information (by newspaper, Internet and confidence in reading and writing), there was no difference between racial groups or hospital attended. Reading a newspaper or accessing the Internet was the most protective against belief that cancer was a punishment or curse (Internet use: aRR: 0.12, 95%CI: 0.02–0.99), belief in alternative methods of cure (newspaper use: aRR: 0.51, 95%CI: 0.27–0.96) and the negative beliefs of death and disfigurement (Internet use: aRR: 0.00, 95%CI: 0.00–0.00). Positive expressions of cure and beating cancer were found equally in all women. Attitudes and beliefs about cancer showed little independent demographic or socioeconomic variance. Negative beliefs were mitigated by access to information and confidence in literacy.

Keywords Breast cancer · Knowledge and attitudes · Disparities · Surgery · Oncology · mHealth

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Published online: 24 May 2017

Introduction/Background

In South Africa, breast cancer is the most common cancer to affect women. Breast cancer is responsible for 20.8% of all cancers and one of the two leading causes of cancer death, being preceded only by cervical cancer [1]. The most recent figures from the National Cancer Registry (2009) report that the lifetime risk for developing breast cancer in South Africa is 1 in 33 (age-adjusted incidence of 27.6 per 100,000) [1]. In a country and region where the HIV, tuberculosis and other communicable disease burden is extremely high and a maternal peri-natal mortality rate of 154 per 100,000 [2], cancer has often not been prioritised. However, recent successes concerning comprehensive roll-out of anti-retroviral treatment and better treatment of the complications of HIV/AIDS has

mount that non-communicable disease management has become more relevant for the long-term health of the population. In the last 30 years, advances in breast cancer management globally have led to a universal increase in detection and survival. Despite this, delayed presentation and late stage disease continue to be responsible for a significant disparity between international survival rates and those in South Africa and other low- and middle-income countries (LMICs).

There is a considerable lack of understanding and research as to the extent to which South African patients' psychosocial or socioeconomic influences affect their help-seeking behaviour in breast cancer care. Whilst some of these areas have been investigated in individual groups, such as in black African women [3], there has been no holistic analysis on how, or indeed if, beliefs concerning breast cancer and its care differ by race, culture, education or environment in sub-Saharan Africa. There can be a great diversity of culture beliefs and barriers amongst seemingly homogeneous groups [4], and reliance on specific demographic characteristics to predict attitudes in a diverse and changing country like South Africa may no longer be valid.

This study examines the attitudes and beliefs surrounding breast cancer held by women in the many diverse socioeconomic and racial groups in urban South Africa and aims to determine where there are important universal or specific areas for improved education and understanding.

Methods

This study included patients from two specialist breast care clinics in Johannesburg, South Africa. One is a government-funded hospital serving predominantly uninsured patients and managing approximately 350 new breast cancer diagnoses each year. In close geographical proximity is a private or medical insurance funded practice diagnosing and managing approximately 400 new breast cancer diagnoses per annum.

A convenience sample of patients was recruited from all patients undergoing management for breast cancer at either of the two study centres between November 2011 and August 2013. Recruitment was strictly voluntary, encouraged through posters and direct invitation to take part in the study. Consenting participants completed a questionnaire and assistance was provided by breast clinic staff for patients who required translation of the questionnaire into their preferred language or clarification during completion. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The study questionnaire was designed with multidisciplinary involvement from specialists involved in breast cancer care and included general questions and questions specific to our patient population. Demographic information included age, race and ethnic background, first language, marital status and dependents. Questions on socioeconomic status included educational background, employment, and work and transport logistics. Women were asked whether they affiliated with any religion and the frequency of attendance at religious services. Particular attention was paid to determining participant's interaction with the world around them, including confidence in reading and writing, access and use of newspapers, television, computer, cell phone, Internet and time spent outside the home. It should be noted that due to the availability of non-text content in traditional media and online, access to information was considered separate to literacy.

Finally women were asked to rate their agreement with 22 statements (Fig. 1) which embodied preconceptions pertaining to delays in health-seeking behaviour, based on those previously described in the literature for breast cancer [5–8] and HIV for Southern Africa [9, 10] and from their personal experience in our multidisciplinary team. A 10-point normative scale was used to quantify responses from strongly disagree to strongly agree.

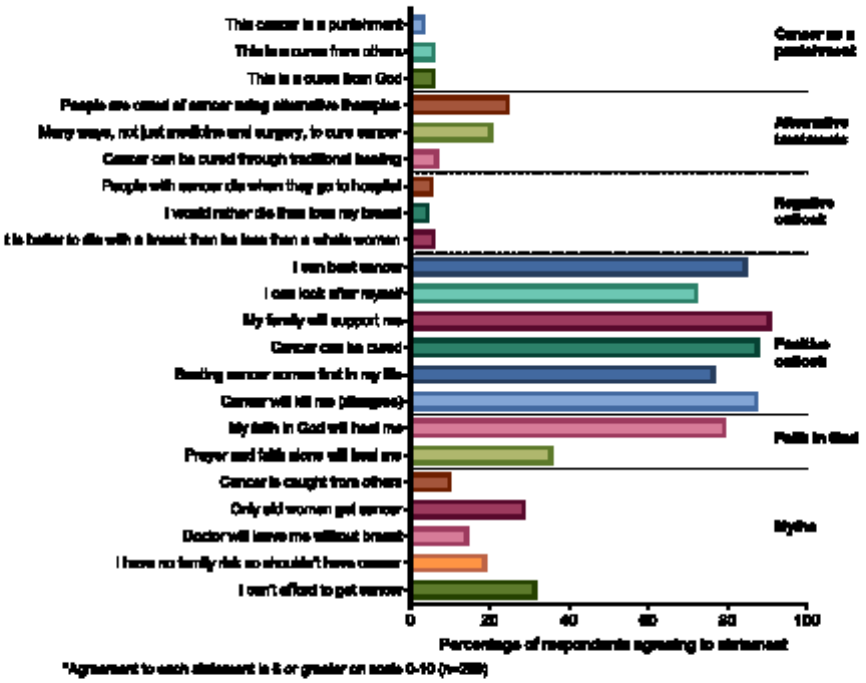
Analyses

Frequencies and proportions were used to describe patient characteristics, and social circumstances were categorised (categories found in Tables 1 and 2). Health services accessed were categorised as government or private depending on which facility they attended. Only 5% of patients in the government hospital have medical insurance (unpublished local data), and this is predominantly low-cost plans which exclude care in private facilities. No government patients are treated in the private facility.

Women who were employed by others or considered themselves self-employed (which may be formal or informal work in South Africa) were compared to women who were either unemployed or described themselves as retired. After the initial demographic description (Table 1), self-reported race was then collapsed into black and non-black categories, (non-black including women who indicated white, Indian (Asian), coloured (a South African statistical group denoting a mixed race) and mixed races).

Responses to statements of belief were categorised as agree (scoring 6 or greater out of 10) or not agree (scoring 5 or below). Two-sided differences of proportions were compared using Pearson's chi^2 test. A p value < 0.05 was considered statistically significant. Patient characteristics were also tested using a correlation matrix, and no strong correlations were observed. As a result, interaction terms were not included in the analysis.

In order to facilitate analysis, similar attitudes or belief statements were grouped together (Fig. 1), and an average score was calculated. Four groups were



*Agreement to each statement is 6 or greater on scale 0-10 (n=259)

Fig. 1 Proportion of respondents agreeing to the statements of beliefs. Agreement to each statement is six or greater on a scale of 0–10 (n = 259)

analysed further. Scores from beliefs related to cancer as a punishment and with external control—i.e. this is a curse from God, this is a curse from others and this is a punishment—were summed, and an average across the three statements was analysed for this 'punishment' group. The other three groups were negative outlook (e.g. 'I will die in hospital'), positive outlook (e.g. 'I will beat cancer') and belief in alternative treatments (i.e. acceptance of non-medical therapies and healing). Women who did not respond to all statements in a particular group were excluded from that group's analysis. Myths about cancer (regarded as factually incorrect) and questions regarding faith in God were not analysed further because of ambiguity in the interpretation of these questions or ability to group them homogeneously for analysis.

Modified Poisson regression with robust error estimation [7] was applied to the data to estimate the relative risk of agreeing with each of the grouped beliefs according to patient characteristics; relative risk ratios (RR) and 95% confidence intervals (CI) are presented. Using stepwise regression, any patient characteristic that was significant at the $p < 0.10$ level in univariate analysis was included in the multivariate model, and multivariate results adjusted (aRR) for the patient characteristics described above are presented. The choice of stepwise regression allowed for inclusion of women in the analysis who did not have complete information (all questions with a response). All statistical analyses were done in Stata v14 (College Station, Texas).

Table 1 Patient demographic characteristics (n = 259)

Characteristic	Description	Count	%
Age	<=40 years	47	18.1
	41 to 60	133	51.3
	61 years+	70	27.0
Hospital sector	Government	166	64.1
	Private	93	35.9
Race	Black	82	31.7
	Coloured	20	7.7
	Indian	25	9.7
	White	124	47.9
Employed, job	Yes	149	57.5
	No	83	32.1
	Pensioner (retired)	16	6.2

Not reported/missing: age (n = 7); race (n = 5); employment (n = 11)

Table 2 Social characteristics of study participants (n = 259)

Characteristic	Description	Count	%
First language	English	163	62.9
	Afrikaans	49	18.9
	Tswana	16	6.2
	Zulu	10	3.9
	Other South African	17	6.6
Education (schooling completed)	Primary	60	23.2
	Secondary	115	44.4
	Tertiary	67	25.9
Reading	Very confident	131	50.6
	Quite confident	102	39.4
	Not confident	12	4.6
Writing	Very confident	149	57.5
	Quite confident	66	25.5
	Not confident	19	7.3
Use a computer	Every day	93	35.9
	Once a week	10	3.8
	Occasionally	37	14.3
	No/none	108	41.7
Have cell phone	Yes	233	90.0
	No	10	3.9
Access Internet	Every day	80	30.9
	Once a week	11	4.2
	Occasionally	39	15.1
	No	119	45.9
Read newspaper	Every day	54	20.8
	Weekly	56	21.6
	Occasionally	109	42.1
	No	24	9.1
Have television	More than 2 televisions	37	14.3
	2 televisions	77	29.7
	1 television	129	49.8
	No television	7	2.7
Religion	Christian	203	78.2
	Muslim	20	7.7
	Hindu	5	1.9
	Other, believe in God	1	0.4
Attend religious services	More than weekly	41	15.6
	Weekly	84	31.9
	Special occasions	90	34.2

Not reported/missing: first language (n = 4); education (n = 17); reading confidence (n = 14); writing confidence (n = 25); computer use (n = 11); cellphone (n = 16); Internet (n = 10); newspaper (n = 16); television (n = 9); religion (n = 28); attendance religious (n = 25)

Results

Two hundred and fifty-nine patients consented to complete the questionnaire. The age range of participants was 20 to 86 years with a median of 52 years (IQR: 44–62). 49 participants were categorised as 'young' (≤40 years; 18.6%), and 70 participants were classified as 'older' (>60 years; 26.6%). Table 1 shows the demographic characteristics of the participants, and that approximately two-thirds of participants were from the government hospital (64.6%), most were formally or informally employed (57.0%) and most described themselves as either white (47.2%) or black (32.2%). A significantly higher percentage of government patients were black at 47.9% compared to black private patients at 7.6% ($p < 0.0001$).

The social characteristics of participants are summarised in Table 2. Overall, the predominant language spoken was English (62.7%) and was indicated as a first language in 24.4% of black and 75.8% of non-black participants ($p < 0.0001$). English was indicated as either a first or second language for 93.3%. Self-reported levels of competency in reading and writing were high at 89.5 and 83.2%, respectively. Cell phone usage was very high (89.7%), and more than half used a computer (56.0%). Forms of social and informational interaction regularly used by participants were television (94.0%), newspapers (43.0%) and Internet (35.0%). At the time of this study (2011–2013), most cell phones owned by members in this population would not have been smartphones with Internet or intensive data capability which can be seen in the difference between cell phone and Internet usage rates. Religious attendance was high with nearly half of all participants (47.5%) attending services at least once a week.

Beliefs

The frequency of patients expressing agreement or belief (a score of 6 and greater) for each statement included in the questionnaire is illustrated in Fig. 1. Positive statements of outlook in medical care and family support were the most commonly believed, followed by beliefs in alternative treatments, both complementary and faith-based. Least believed were statements regarding cancer as a punishment or curse either by God or others.

Cancer as a Punishment or Curse

The relative risk of believing cancer to be a curse or punishment was uniformly higher in black compared to non-black women (RR: 6.85, 95%CI: 1.41–33.21); however, confidence intervals were wide, and the mean score for black women was less than 2. Figure 2a shows these relative risks both for the unadjusted and adjusted analysis. Religious belief with regular attendance (RR: 0.90, 95%CI: 0.21–3.93), attending the government hospital (RR: 5.01, 95%CI: 0.63–39.55), and secondary or higher education (RR: 0.38, 95%CI:

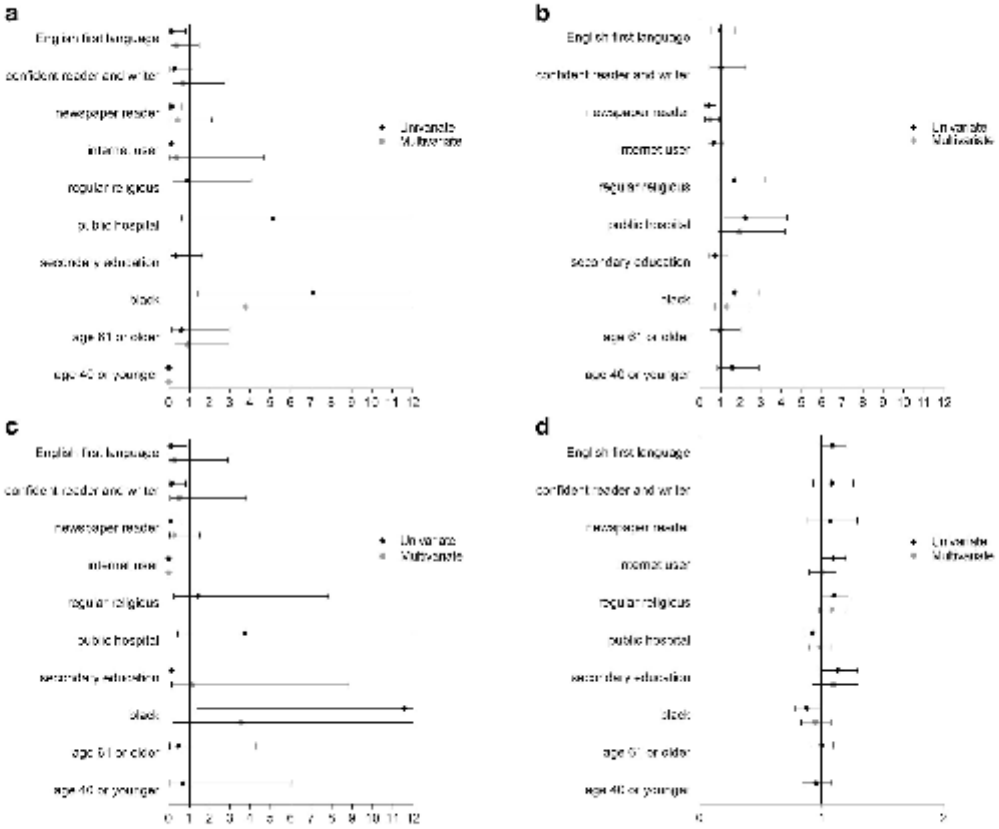


Fig. 2 Relative risk of belief statement groups, adjusted and unadjusted. (a) Believing cancer is a punishment or curse (*n* = 220). (b) Belief in alternative treatment methods for cancer (*n* = 176). (c) Holding negative beliefs and outlook (*n* = 215). (d) Holding positive beliefs and outlook (*n* = 185). Multivariate adjusted for factors significant at $p < 0.10$ in univariate. a Age category, black race, Internet user, newspaper reader, confident reader and writer, and English as first language. b Black race, government hospital, and regular attendance at religious services. a Black race, secondary education, Internet user, newspaper reader, confident reader and writer, and English as first language. d Black race, secondary education, government hospital, and regular attendance at religious services. Modified Poisson regression with robust error variance

0.09–1.67) were not associated with the belief of cancer as a punishment in the univariate model and therefore were not included in the adjusted model. When adjusting for age and information access (by newspaper, Internet and confidence in reading and writing), black race was no longer a statistically significant predictor of the belief of cancer as a punishment (aRR: 3.77, 95%CI: 1.00–14.27). Access to information was protective, for example Internet users were 88% less likely to believe that cancer was a punishment or curse (aRR: 0.12, 95%CI: 0.02–0.99). Young patients (age ≤ 40) were significantly less likely to believe cancer to be a curse or punishment.

Alternative Treatment Methods

Beliefs in at least one statement of alternative treatment methods was present in 49.4% of the overall sample of patients, and across the grouped statements of alternative treatments, 21.2% indicated an average score of 6 and greater. Figure 2b illustrates that participants from the government hospital were twice as likely to believe in alternative

treatments other than medicine and surgery (RR: 2.25, 95%CI: 1.18–4.30). Women who said they regularly read newspapers were less likely to agree with statements about alternative treatments (aRR: 0.51, 95%CI: 0.27–0.96). This effect was not further mitigated by access to the Internet, nor changed by confidence in reading or writing. Although government hospital use was also associated with beliefs in alternative, faith-based and traditional medicines, the effect was not statistically significant in multivariate analysis (p value = 0.086; aRR: 1.95, 95%CI: 0.91–4.20). Black race and regular attendance at religious services were considered in the multivariate model but were no longer statistically significant for alternative treatments (aRR: 1.33, 95%CI: 0.74–2.39 and aRR: 1.70, 95%CI: 0.89–3.23, respectively). Age categories were not statistically significant predictors of beliefs in alternative treatments in the univariate analysis.

Negative Statements of Death and Disfigurement

Black participants were far more likely to view their disease negatively on initial analysis, with belief that it is better to die with a breast than be less than a whole woman, they would rather die than lose a breast or that people with cancer die when they go to hospital (RR: 11.57, 95%CI: 1.37–97.69, Fig. 2c). These beliefs were considerably mitigated by education, information access and confidence in reading and writing so that the effect of race was no longer statistically significant in the adjusted analysis (aRR: 3.55, 95%CI: 0.21–59.95). Reading a newspaper (RR: 0.11, 95%CI: 0.02–0.50; aRR: 0.29, 95%CI: 0.05–1.54) and Internet use were protective against the negative beliefs of cancer. In particular, Internet use (aRR: 0.00, 95%CI: 0.00–0.00) was the most protective against the negative beliefs of cancer and remained statistically significant in multivariate analysis, irrespective of age and race.

Positive Statements of Cancer Cure

In contrast, 90.3% agreed with positive statements about surviving and beating cancer. The relationship of positive beliefs alone to social and demographic characteristics is illustrated in Fig. 2d. There was very little variance in different groups, displaying a universality of opinion. Whilst negative opinions were found more commonly in black participants and those attending the government hospital, positive expressions of cure and beating cancer were found equally in all women despite their different social, economic and religious characteristics. Race, secondary education, government hospital and regular religious attendance were considered in the adjusted model; no characteristic was a statistically significant predictor of the grouped positive beliefs.

Discussion

Women diagnosed with breast cancer had a positive attitude towards breast cancer believing cure possible and support available. These beliefs were universally shared by women of all races, education and income. Further to this, whilst the expression of negative beliefs of dying in hospital and losing the breast were present, their effect was mitigated by education and information access in all racial and socioeconomic groups. Previous studies of attitudes to breast cancer in LMICs have shown high rates of negative beliefs [11–16]. These study findings provide some evidence to indicate that improving education levels and increasing patients access to (correct, trustworthy) information may assist in moderating negative beliefs and attitudes of having breast cancer. This study also supports the assertion that race is not necessarily an important independent factor in patients' access or attitudes to care, but rather a proxy for socioeconomic or educational disparities [17].

Society's and patients' attitudes towards cancer are important. Surprisingly, there is scarce literature addressing a woman's attitude of having the disease in Southern Africa. Most studies in LMICs have addressed attitudes towards screening, prevention and access in under-served populations; however, studies addressing concepts around causation and outcomes are underrepresented. It is important, however, to address this issue, because not only do a woman's attitude towards her disease affect compliance to biomedical care [15, 18, 19], they may also address her likelihood to attend early for investigation of symptoms and encourage others in her community to attend. How we can change a woman's attitude towards treatments and outcomes is as important (if not more so) as addressing screening in countries where population screening is unlikely to be achieved in the next few years, because it could be an effective method of improving the proportion of women presenting with earlier stages of the disease.

Although a convenience sample, we believe that the demographic mix of patients here was representative of those attending for breast cancer care in our environment. Most of our patients were under 60 years, and nearly one-fifth of cancers were in young women; the equivalent figure from the SEER database in the USA is <12% under the age of 45 and a median age of 61 at diagnosis [20]. The large proportion of patients with English as a first or second language and confidently literate was more indicative of the urban population surrounding the hospitals. Whilst this may be different to more rural parts of the country, the high rate of cell phone usage and Internet access has become more prevalent across all areas in the last 5 years, with 34% of South African adults owning a smartphone with access to the Internet [21].

As Africa becomes more connected technologically, there has been a surge in medical communication capacity

(characterised as eHealth and mHealth technology, along with social media awareness and advocacy) serving to bring some quality of information access to different populations. Nine of every 10 South African adults own a cell phone [21]. In this study, access to the Internet was protective against the beliefs of an external malevolent force in cancer causation and cancer as a punishment from God or from others.

Increasingly, mHealth is being used as a platform for health information and education amongst young people in South Africa and has been useful in modifying health behaviour [22] and improving patient-motivated healthcare [23]. Improving the message of breast awareness in social media and the layering of breast cancer education through multiple platforms from traditional print or advert-based campaigns to TV and radio soap-operas [24] and celebrity survivors helps to tailor education appealing to different generations and cross-sections of society [25]. Access to information mitigated against the negative statements of belief. Some of this effect was lost in the multivariate analysis, however, recognising the complex interplay of differing socioeconomic factors that contribute to these beliefs [15, 17, 26, 27].

Interestingly, although there was a small number of non-Christian believers amongst the participants, adherents to all religions equally believed cancer as a punishment from their God. These findings confirm recent anthropological work in this environment, that women with breast cancer possess a commonality of beliefs regarding 'god', social support and biomedical faith/scepticism independent of culture or race [28]. This commonality was also seen in positive and negative attitudes to their disease. Whilst over 90% of patients agreed with the positive statements of survival and support, some women (less than 10%) expressed the opposed negative views of dying and a loss of womanhood. In the multivariate analysis, both these positive and negative attitudes were held in all groups with little demographic differentiation between them. Whether this is confined to those sampled or a reflection of more positive attitudes held generally in the popular media in South Africa about the outcomes about cancer [25, 29], the scarcity of negative opinions contradicts the notion that women, even when presenting late, are passive recipients of their disease and subsequent treatment.

Nearly half of all patients agreed with at least one statement that cancer could be cured with non-biomedical management. These beliefs were not well mitigated by literacy nor access to information but were also unaffected by race. Although other studies in Africa document a preferential engagement of traditional African healers above or alongside medical care, here, when comparing different racial groups, there is a shared willingness to explore non-biomedical treatment equally in all groups. What is not clear from this study is whether the methods of care considered are similar or differ according to other individual characteristics. The authors frequently experience patients considering choices of traditional African healers, 'western' vitamin remedies and 'eastern' traditional medicine according to each patient's own experiences and beliefs.

There are some limitations to this study. The beliefs and attitudes described cannot be generalised easily, and in addition, willingness to participate in empirical research may serve as bias, in that these women may also be more willing to accept the scientific model of disease as part of their beliefs. Studies of any disease rely on participants who have been diagnosed, and therefore have reached some level of diagnostic medical care. It remains impossible to identify or know the attitudes of patients with breast cancer who never sought care before death. The absence of population-based screening means that few cancers are discovered without express help-seeking behaviour. However, many of the patients presented with advanced and very locally advanced breast cancer, and therefore represents a good cross-section of the disease process, biased more towards locally advanced patients if at all, rather than early-stage disease.

The study was carried out anonymously and was not linked to patient's medical records due to local limitations of record keeping and follow-up; therefore, it is not possible to compare beliefs in this group and link it to stage. The study sites were both breast (surgical) oncology clinics, however, with patients attending with the aim of surgical curative intent with neo- or adjuvant chemotherapy and radiation, with approximately 50% presenting in stage 1 or 2 and less than 10% with metastatic disease [3].

In conclusion, within this diverse population of South African breast cancer patients, most beliefs and attitudes towards cancer were relatively homogeneous, with little independent racial or socioeconomic variations. Strong mitigations of negative beliefs in patients, both towards their disease and the cause as a punishment, were achieved through access to information and confidence in literacy. However, access to information also increased the likelihood that patients would have beliefs of non-biomedical methods of cancer care, and this should be considered when encouraging patients to access information about breast cancer, particularly through new media. Further understanding of patients' attitudes and beliefs remain important in providing treatment and support in breast cancer care.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Financial Support This study had no funding support.

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Springer

Appendix A3: Paper 3 (As accepted to South African Medical Journal)

South African Medical Journal

Delay to diagnosis and breast cancer stage in an urban South African breast clinic

--Manuscript Draft--

Manuscript Number:	SAMJ13283
Article Type:	Original Research
Section/Category:	Non-communicable Diseases
Keywords:	Breast cancer; Barriers to care; Disparities; Surgery; Oncology
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Manuscript Region of Origin:	SOUTH AFRICA
Abstract:	Background Breast cancer is the most common cancer in women in many low and middle-income countries, and often presents at advanced stage affecting prognosis irrespective of the care available. Although patient-related delay is commonly cited, the reasons for delay and relationship to stage is still poorly documented, especially in Africa. This study was designed to describe where patient- related socio-economic delays occur and how this relates to stage at presentation. Methods Consecutive women with a new breast cancer diagnosis were prospectively invited to participate in a questionnaire about their socio-economic characteristics and ability to access care. Clinical stage at presentation was documented. Results Over 14 months, 252 women completed the questionnaire (response rate of 71.6%). Median age was 55 years (IQR 44-65), with 26.5% under 45 years. Stage at presentation was Stage 1 15.5%; Stage 2 28.5%; Stage 3 56.0%. Almost a third of patients (30.4%) presented with T4 tumour (6.1% inflammatory). Total delay to present at the breast clinic was significantly associated with locally advanced stage at presentation (p=0.021). Average delay differed between early stage (1.5 months) and locally-advanced (2.5 months) and most delay occurred between acknowledging a breast symptom and seeking care. The least delay was between attending a health service and presenting at the open-access breast clinic with 75% presenting within 1 month. Reasons associated with delay were difficulties with transport, low education and fear of missing appointments due to work. Conclusion Most women delayed in seeking breast care. Facilitating direct access to specialist breast clinics could reduce delays in presentation and improve time to diagnosis and care.

Appendix A4: Paper 4 (South African Journal of Surgery)

The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa

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Background: The disparity in breast cancer survival in Africa is often linked to poor education and awareness leading to late diagnosis and subsequent reduced survival. This study was designed to explore the relationship of attitudes and beliefs held regarding breast cancer to the stage and delay to diagnosis in South Africa.
Aims: To provide an epidemiological analysis of the spectrum of disease and outcomes of primary amputation for diabetic foot sepsis in a regional rural hospital.
Methods: Women attending an open-access breast unit over 14 months with newly-diagnosed breast cancer answered a survey regarding their fears and beliefs of breast cancer care. Questions addressed demographic, socioeconomic and educational factors linked to delay, and documented time taken to care. Odds ratio with 95% confidence intervals were calculated to identify factors associated with advanced stage at presentation and delay greater than six months.
Results: Of the 233 participants the median (IQR) age was 56 years (46–65). The most common stage at presentation was Stage 3 (55%), with 30.5% presenting with T4 tumour at presentation.
Most women believed cancer could be beaten (90.0%), and their families would support them (92.8%). They disagreed that cancer was a curse (93.8%), punishment (90.5%) or that alternative therapies or traditional healing would cure their cancer (75.3% and 85.5% respectively). On univariate analysis, age under 45 years and transport difficulties predicted advanced stage at presentation. No socio-economic factors or beliefs increased the risk of delay to presentation.
Conclusion: Participants' beliefs about their new breast cancer were most commonly appropriate, and showed a low level of fatalism, in contrast to other studies in Africa. Whilst raising awareness may be important, efforts to increase awareness alone may not directly prevent the likelihood of late or advanced diagnosis in this population.
Keywords: Breast cancer; Barrier to care; Disparities; Surgery; Oncology

S Afr J Surg 2018;56(2) http://dx.doi.org/10.17159/2078-5151/2018/v56n2a2704

Background

Breast cancer is the most common cancer to affect women in South Africa. Whilst the lifetime risk is lower than in high-income countries,[1] outcomes are worse with reduced survival. This poor ratio of diagnosis to survival is often linked to difficulty in accessing care and poor availability of treatment options after diagnosis.[2-5] Screening and early diagnosis are limited and patients commonly present with advanced stage of disease limiting their outcomes despite treatment. Commonly cited or implied reasons for late diagnosis are often related in the literature to delay to care, both patient related delay, and provider (or system) delays. A delay of more than three months to presentation has been associated with more advanced breast cancer at diagnosis and decreased survival,[6] however most studies from low- and middle-income countries (LMICs) indicate that the average delay exceeds this time. In countries of similar upper-middle income economic background to South Africa, delay to care (both patient- and provider-related) of more than three months ranges from 56% in Malaysia to 70% in Brazil.[7,8]

In South Africa, few studies have examined the management

of breast cancer in the government health system beyond pathological studies. Little has been described regarding patient-related delays, or indeed the complex path women take both psychologically and physically to access care. Patient-related delays commonly cited in other parts of Africa include socioeconomic and educational barriers, and indigent beliefs regarding cancer causes, symptoms and management. These beliefs may also include elements of 'cancer fatalism' where events are destined to happen with the individual relatively powerless to influence them.[9] Previous studies in South Africa have found that most patients self-refer to tertiary care, often due to delays in the system[10] and that farther geographical distance to hospital could be linked to late stage at presentation.[11] An older study from 2010 aimed to assess breast knowledge in South Africa and indicated that poor knowledge was a main factor for delay, with less than 50% of respondents aware that changes in the breast may herald cancer.[12] The same study found that 44.9% of women felt they should not spend money on their health and 38.7% were not encouraged by families to seek healthcare. More than three-quarters of patients reported that they would wait less than one week to tell someone once they suspected they might have cancer.[12] The most recent qualitative study, amongst breast cancer patients, found low cancer awareness and frequent monitoring of symptoms until a change in symptom or disclosure to a family member precipitates healthcare review.[13]

In the absence of studies focusing on patients' own beliefs and the complex interplay between these views and their pathway to care, this study was designed to explore the relationship of attitudes and beliefs held regarding breast cancer and its management to the stage at presentation, and delay to diagnosis.

Methods

Women attending a South African government tertiary referral centre for breast cancer diagnosis and surgical management were approached to participate in a survey regarding their beliefs and fears surrounding breast cancer. The centre is an open access clinic for all patients with breast problems and routinely sees 4000 new patients each year and diagnoses 300–350 new breast cancers. The spectrum of breast problems and investigations in this urban centre in a limited resource setting has been previously described.[10]Consecutive women were included if they had a new diagnosis of a biopsy-proven breast cancer and accepted the invitation to participate during their post-diagnosis counselling by a clinician, with the survey administered within this period. Written consent was obtained, and the survey was administered by two trained research assistants, fluent in at least two languages. The survey was written in English and the assistants trained in the tool to minimise change in meaning during verbal translation. The questionnaire was completed in REDCap (hosted by the University of the Witwatersrand) and linked to the participant's clinical findings at presentation. Ethical approval was received from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M111121).

The questionnaire comprised of multiple sections. The first established demographics, socio-economic situation, education, and self-described ability to access care. In the second section women were asked to quantify, from recollection, the length of time taken to attend the breast clinic, with the timeline separated into three categories: time taken to notice and acknowledge a breast symptom, time taken from then to access any healthcare services, and finally time taken from then to attend the open-access breast clinic. The final section comprised of 44 statements describing a fear or belief grounded in their breast cancer diagnosis or understanding of treatment and prognosis. These were expressed on a four-point Likert scale from strongly disagree to strongly agree. Many of these statements have been previously piloted and described[15,16] and were augmented to include, around cancer, fatalism and health beliefs[17,18] from similar studies. Internal consistency measurements for each subscale (fears, beliefs, fatalism and risk factors) found a Cronbach's alpha co-efficient of 0.82, 0.73, 0.71 and 0.81 respectively. Scales are considered acceptable with an alpha ranging from 0.70–0.95.[19]

Data analysis

Patients' characteristics were described, using frequencies and proportions, and categorised to facilitate analysis. Marital status categorised as partnered or unpartnered (which included women who were not in a relationship or widowed) and age was categorised as less than 45 years, 45–64 years or 65 years and older. Less than 45 years was defined as "young" breast cancer. Education was categorised according to the highest level of formal schooling obtained: grade 9 (approx. 14 years of age) and above grade 9. Those who had achieved matriculation from secondary school and above were also differentiated from those who had no completion certification of secondary education.

Responses from the subscales for fears and beliefs were grouped according to those who expressed some fear or belief (agree or strongly agree) compared to those who did not. Time to presentation was comprised of time taken to acknowledge symptom (T-Ack), time to seek healthcare services (T-HS) and time taken to attend breast care clinic (T-BCC). Each was categorised as < 1w, 1 week to 1 month, 1 month to 6 months, > 6 months to 1 year and greater than 1 year. A total time to presentation (T-Tot) was calculated as the sum of the three individual time periods, and grouped as either 6 months or less, and greater than 6 months.

Clinical stage at presentation was determined from the clinical "TNM" staging system (AJCC, 8th edition)[20] of the examining physician. This was then categorised as early (between stage 1 and stage 2a) and late staged (stage 2b to stage 4). Stage 4 disease was included but may have been relatively underrepresented as these patients often may access medical oncological care without first attending a breast surgical clinic. For determination of delay by stage, patients with Stage 0 were excluded because of the relationship with screening, rather than clinically detected disease in this group. Two-sided differences of proportions were compared using Pearson chi^2 test. A p-value < 0.05 was considered statistically

Table 1 Demographic and clinical characteristics of patients presenting for care (n = 252)

Description	Total (n = 233)	
	n	%
Age (n = 230)		
< 45 years	48	20.9
45–64 years	121	73.5
> 65 years	61	26.5
Median years (IQR)	56	(46–65)
Relationship status (n = 223)		
Partnered	112	50.2
Not partnered	111	49.8
Family History (n = 225)		
Breast cancer in close relative	20	8.9
Formal education achieved beyond Grade 9 (n = 219)		
No education beyond Grade 9	69	31.5
Matriculated from school (n = 219)		
Yes	76	34.7
Dependants (n = 200)		
No dependants	51	25.5
1–3 dependants	65	32.5
More than 3	84	42.0
Have cell phone (n = 219)		
Yes – contract	34	15.5
Yes – top up	172	78.5
Do you access the internet? (n = 220)		
No	139	63.2
Yes – occasionally	46	20.9
Yes – every day	35	15.9
Confident reader (n = 221)		
Yes	211	95.5
Employed, job (n = 222)		
Yes	70	31.5
Religion beliefs (n = 223)		
Yes – Christian	193	86.6
Yes – Muslim	13	5.8
Yes – Traditional African	4	1.8
Yes – other	13	5.8
Attend religious meetings at least once a week (n = 196)		
Yes	123	62.8
Breast cancer in close relative or friend (n = 100)		
Alive and cancer-free	22	22.0
Alive (with cancer)	12	12.0
Died from cancer	60	60.0
Stage at presentation (n = 231)		
1	33	14.3
2a	36	15.6
2b	27	11.7
3a	56	24.2
3b	68	29.4
3c	5	2.2
4	6	2.6
Tumour T4 on presentation (n = 226)		
Yes	73	32.3
Total delay to presentation		
< 1 month	38	21.0
1 month – 6 months	78	43.1
> 6 months – 1 year	38	21.0
> 1 year	27	14.9

significant. Poisson's regression methods of calculating odds ratio with 95% confidence intervals to compare early stage (up to Stage 2a) with advanced breast cancer (Stage2b and beyond) were used to identify factors associated with presentation with advanced stage.

Results

During the study period of 14 months, 233 participants completed the survey (response rate of 65.5% of all newly diagnosed breast cancers).

Demographic and clinical characteristics:

The median (IQR) age was 56 years (46–65), with 23.6% under 45 years old. Most patients had a partner, had some dependants and had received a formal education beyond grade 9. The most common stage at presentation was Stage 3 (50.4%), with 30.5% of all cancers presenting as T4 (skin involvement (T4b) 23.5%, inflammatory (T4d) 6.2%). Only 5% presented with metastatic disease at presentation after investigations. These, and further characteristics are summarised in Table 1.

Fears and beliefs:

Figure 1 shows the statements with the percentages of respondents' answers. In general, the responses showed a positive outlook with high agreement to statements such as 'my family will support me (92.8% agree/strongly agree) and I believe I can beat cancer (90.0% agree/strongly agree). Equally emphatic was disagreement to both ideas of malevolent external origin (someone has cursed me with this cancer, 93.7% disagree/strongly disagree; this cancer is a punishment 90.2% disagree/strongly disagree) and resistance to biomedical therapies (cure with traditional healing 85.5% disagree/strongly disagree; cure with alternative therapy 75.3% disagree/strongly disagree; people die when they go to hospital 97.0% disagree/strongly disagree). Most questions regarding fatalistic beliefs were disagreed with, and only "…it is part of god's plan" and "…it was meant to be" were agreed with by more than one quarter of participants (46.4% and 54.5% respectively).

Overall, there were few beliefs that were strong predictors for presentation with late stage or delay to presentation. On

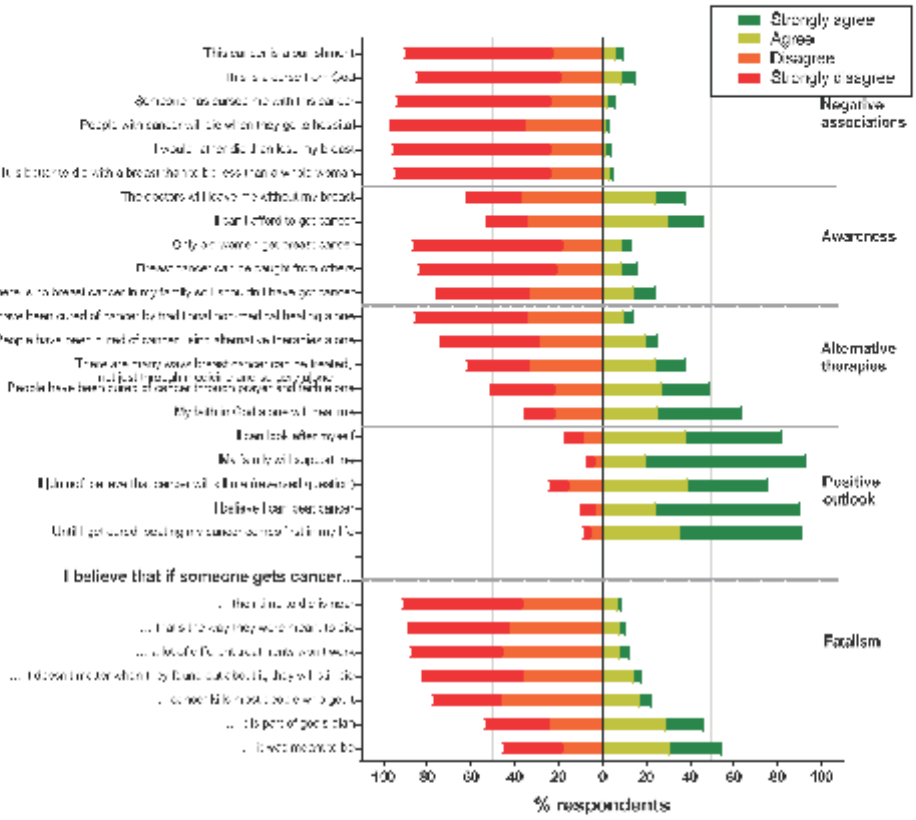

Figure 1. Participants beliefs, by percentage of responses.

univariate analysis, young women were 20% more likely to present with an advanced breast cancer (IRR 1.20 95%CI 1.01–1.42). Whilst limited education was not related to advanced disease, being a confident reader was protective against late presentation (IRR 0.77 95% CI 0.61–0.96). Patients who presented with an advanced cancer were more likely to believe that cancer could be caught from others (IRR1.28 95% CI 1.06 –1.54), that they "could not afford to get cancer" (IRR1.24 95% CI 1.03–1.50), and to state that they "would rather die than lose a breast" (IRR 1.29 95% CI 1.01–1.66) or that if "someone gets cancer that was the way they were meant to die" (IRR 1.29 95% CI 1.06–1.58). Women with locally-advanced cancer were also 20% more likely to believe that cancer can be cured by methods other than medicine and surgery (IRR1.19 95% CI 1.00–1.42), however no other belief statements in alternative therapies showed significance here.

Self-reported transport difficulties also predicted late presentation in the univariate model (IRR1.26 95% CI 1.07–1.49), and when the model was adjusted for each of the beliefs with a significant relationship, the likelihood of late presentation was strengthened in women with transport difficulties if they believed that they "would rather die than lose a breast" (aIRR1.28 95% CI 1.09–1.52), believed cancer could be caught from another person (aIRR1.27 95% CI 1.06–1.52), believed that cancer can be cured by methods other than medicine and surgery, or traditional non-medical methods alone (aIRR1.38 95% CI 1.17–1.63 and aIRR1.32 95% CI 1.11–1.57 respectively) and believed that cancer "will eventually kill me" (aIRR1.34 95% CI 1.12–1.59) or if "someone gets cancer that was the way they were meant to die" (aIRR1.34 95% CI 1.14–1.58).

In considering delay to presentation, no socio-economic factors or beliefs increased the risk of delay more than six months including travel more than one hour, transport difficulties, lack of employment, or age. Only agreement with the statement "My family will support me" was associated with a total time to presentation within six months (IRR 1.26 95% CI 1.02–1.59).

Agreement with the statement 'I am afraid of cancer' was not statistically significantly associated with delayed presentation or locally advanced.

Good social support and interaction with the world (via cell phone usage and internet) were not associated with an earlier stage at presentation or decreased delay. In considering religion, women who attended a religious meeting more than once a week were no more likely to present with late disease, although regular attendance predicted beliefs that God alone could heal disease (RR1.43 95% CI 1.07–1.91). Regular attendance at church was found in older women, with less education, and less access to the internet ($p < 0.001$, $p = 0.05$, $p = 0.02$).

Discussion

South Africa is an upper-middle-income country with a relatively secure infrastructure, and Johannesburg is a relatively affluent city with relatively good access to local hospitals and specialised breast care. Within this setting, however, more than three quarters of patients presented to an open-access breast clinic with advanced breast cancer and more than half of these with a T4 tumour. This study was designed to determine the relationship between beliefs and fears and an advanced presentation or delay to presentation in breast cancer.

Our study found that the predictors of late stage disease were socio-economic as well as related to attitudes of disease. We found that transport difficulties most consistently predicted an increased stage at presentation (and confidence in reading was protective of this), whilst there were no identified factors which increased the likelihood of patient-related delay to care. A recent study using the pilot questionnaire in this same population[16] found that demographic and socio-economic factors (which often overlap in South Africa due to the legacy of Apartheid-era inequity) predicted for some beliefs, particularly regarding alternative treatment regimens and negative statements about death and disfigurement. However, this more comprehensive study has found that most of these beliefs were unrelated to stage of disease at presentation, as well as unrelated to delay to care. Therefore, although socio-economics may predict beliefs, beliefs alone did not consistently predict stage of disease. Furthermore, while fears and beliefs may impact on time to present to a breast specialist clinic, the linear relationship that is conceived of in literature between fear and misconception leading to a reticence to present and therefore delay to care with an advanced stage of cancer could not be traced here.

The implication of these findings is that the continual message of breast education and awareness, whilst an important strategy for advocacy may be failing to fully enable women to reach the care appropriate for them. This study found that late presentation was more consistently related to issues of navigation to the hospital through transport problems, money worries and through literacy. There was a relatively high level of appropriate agreement and disagreement to the belief questions, indicating that in this group of women of whom over one-third had T4 tumours, their breast "awareness" and education were satisfactory. Therefore, in addition to advocating breast education, a more holistic recognition that empowering women through raising the effective education levels of all women in the community could raise not only their awareness of disease, but improve their ability to access care. Until this is achieved, women are still likely to present with late stage disease. This assertion is supported by the finding that confidence in reading rather than years of education was more predictive of earlier presentation.

Identifying that transport difficulties were related to both late presentation and delay to presentation (risks of which were independent of each other) would also indicate that further work also needs to be done in improving women's navigation to appropriate care from the community, through easing their transport and work difficulties. This study will provide useful information for government and local advocacy groups as to the best use of resources in reducing the breast cancer burden by decreasing late presentation.

Overall this study found that women presenting for breast cancer diagnosis had a relatively appropriate understanding of breast cancer. Few patients had negative beliefs about the origin of their cancer, or surgical treatment. The area of heterogeneity that was most noted was around beliefs in alternative methods of cure, whilst only less than one quarter of patients believed in alternative or traditional methods of cure (24.5% and 14.2% agreed/strongly agreed respectively), nearly half stated they believed prayer and faith or God alone could cure them (48.2% and 64.1% agreed/strongly agreed). None of these beliefs predicted delay to presentation or stage at presentation, and represent an interesting duality of belief between what is stated, and what is carried out by the patient. The degree of cancer fatalism in this population also differed from those in other African studies. Akhigbe et al.[18] found high levels of fatalism amongst a Nigerian health professional population with agreement to each question ranging from 45–82%, and from a series reported in Ghanaian women,[21] they too had higher levels of fatalism compared to our South African group. These beliefs are in sharp contrast to those described 15 years ago in South Africa where nursing staff reported "with breast cancer who wanted a mastectomy would die because their husbands refused to let them be "disfigured"[22] or the "…patient sought help first from a traditional healer as a way of dealing with the cause of the disease…"[23] but supported by more recent studies in a similar group of South African women.[12]This study did not find a simple association between attitudes and beliefs around breast cancer and either stage at presentation or delay to presentation. The participants were a heterogeneous group, reporting prompt presentation or delayed presentation equally with early or late stage disease. On reviewing the literature regarding similar studies from other low- and middle- income countries, we did not find the standard associations of low education, poor employment and lack of awareness that other studies have found, even those carried out in urban settings in tertiary referral centres such as in Nigeria,[24] Ghana,[25,26] and Rwanda.[27] In these circumstances, using the health belief model to understand why and when

patients access breast care may not necessarily be applicable, as persuading a woman of the significance of her problem does not necessarily equip her with the tools to seek care. It may be that recognising the disparity in socio-economic capital and addressing this inequity through increasing women's education levels, literacy and empowerment on a governmental level, together with facilitating physical access to care, will reduce late stage disease more than high-profile media campaigns.

There are limitations to this study. The small sample size and single study site limit the suitability of the findings to similar breast centres. However, as the management of breast cancer becomes more specialised, more tertiary centres are being identified in Africa,[28] and these findings may help guide further work in understanding and assisting the women accessing care. The reflective retrospective nature of some of the questions, designed to give voice to patients concerns, may illicit bias responses despite separating the clinicians from those administering the survey. Allowing the participants voices to be better heard through qualitative studies would also enable better understanding of the nuances of beliefs around cancer. Whilst some work has been done in South Africa,[13,29] more is required. In addition, the beliefs reported here are only of those who attended for care. There is a cohort of women with breast cancer who never reach a referral centre, either due to complete inability to access the system through socio-economic or other constraints, or present so late in the disease process that referral for tertiary care is inappropriate. Only 5% of the women in this study had Stage 4 disease, which may not reflect the true burden of metastatic disease in our environment.

Conclusion

This study examined the beliefs of women with a new breast cancer diagnosis and found that most held positive and appropriate beliefs regarding breast cancer and treatment options. There were low levels of fatalism in the group, which contrasts with other studies from Africa and with older studies in South Africa. The relationship of stage of disease and delay to presentation was more associated with structural barriers such as transport difficulties, than with the investigated beliefs, or demographic characteristics. Although education and awareness are the most common strategies for advocacy in South Africa, developing different models to improve access to care, such as facilitating transport, may be beneficial to the population served.

Financial support:

This study had no funding support.

Conflict of interest:

The authors declare no conflicts of interest.

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Appendix A4: Paper 5 (As submitted to Journal of Surgical Research)

JOURNAL OF SURGICAL RESEARCH • MARCH 2019 (235) 181–189

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Unraveling the South African Breast Cancer Story: The Relationship of Patients, Delay to Diagnosis, and Tumor Biology With Stage at Presentation in an Urban Setting

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ARTICLE INFO

Article history:
Received 20 April 2018
Received in revised form
13 July 2018
Accepted 25 September 2018
Available online 26 October 2018

Keywords:
Breast cancer
Barrier to care
Knowledge, attitudes, and beliefs
Disparities
Surgery
Oncology
Tumor biology

ABSTRACT

Background: Adverse outcomes from breast cancer disproportionately affect women in sub-Saharan Africa, with delay the most studied contribution to advanced stage at presentation. However, tumor molecular biology and its contribution to advanced stage are yet to be explored.

Materials and methods: Patients newly diagnosed with breast cancer in a South African tertiary breast center completed a questionnaire and file review concerning socioeconomics, delay to care, stage at presentation, and molecular characteristics. Logistic regression was done to determine the relative risk of advanced stage presentation.

Results: Advanced stage was present in 70.1% (n = 182) of the 231 participants, with 55.8% stage III (n = 129) and 22% (n = 72) having a T4 tumor. The median age was 56 y with 21.8% (n = 47) aged <45 y. Most common subtype was luminal B (57.7%, n = 128) followed by luminal A (27.6%, n = 48), triple negative (13.9%, n = 31), and HER2 positive (8.7%, n = 19). Lobular cancer (incidence risk ratio [IRR], 1.28; 95% confidence interval [CI], 1.03–1.60), high grade and intermediate grade tumors (IRR, 1.50; 95% CI, 1.15–3.13 and IRR, 1.95; 95% CI, 1.18–3.22, respectively), high Ki67 proliferation index (IRR, 1.30; 95% CI, 1.02–1.66), and HER2 overexpression (IRR, 1.36; 95% CI, 1.12–1.65) were more likely to present with advanced disease, as were luminal B (HER2+) cancers (adjusted IRR [aIRR], 1.46; 95% CI, 1.10–1.95). Although on univariate analysis Black and young participants were both more likely to have advanced

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https://doi.org/10.1016/j.jss.2018.09.067

stage (HR, 1.28; 95% CI, 1.01-1.63 and HR, 1.25; 95% CI, 1.04-1.51, respectively), in multivariate analysis controlling for tumor biology and delay, these were no longer significant (aHR, 1.12; 95% CI, 0.91-1.37 and aHR, 1.17; 95% CI, 0.94-1.46, respectively).

Conclusions: Tumor biology has a compelling role in the etiology of advanced-stage disease irrespective of socioeconomic factors. Accurate pathologic assessment is important in planning breast cancer care in Africa.

Introduction

Breast cancer is the most common cancer to affect women in most countries and is disproportionately a major cause of death for women in low- and middle-income countries (LMICs).[1] In developing national cancer control policies and understanding the epidemiology of breast cancer in LMICs, emphasis is placed on awareness and access to care.[2,3] A strong association between education and socioeconomic factors, and stage at presentation is cited to support this.[4,5] Oncologically, there is also a strong association of stage at presentation with outcomes such as treatment modalities required, recurrence rates, and ultimately survival.

The discovery of the estrogen receptor (ER) on some breast cancer cells in the 1960s first allowed the individualization of breast cancer therapy.[6] In the past 10 y, an increase in breast cancer translational research has led to a far greater understanding of the molecular biology of breast cancer. The heterogeneity of tumor subtypes is inherently related to response to treatment, sensitivity of modalities, and outcomes. In most specialist breast units in high-income countries it is routine to carry out immunohistochemistry to determine ER, progesterone receptor (PR), human epidermal growth factor receptor 2/neu (HER2), and Ki67% at least, and considering these allows clinicians to translate this information into patient-centered clinical decision-making such as first modality of treatment, and to provide insight into prognosis. Further to this, more sensitive genomic tests are increasingly more routinely available to further subtype and characterize tumors.[7] There have been studies of these intrinsic molecular subtypes in LMICs, describing the incidence of adverse biology and linking this to clinical outcomes.[8,9,10]

In parallel with this fresh understanding of the spectrum of breast cancer seen in LMICs runs the continued focus on the reduction in advanced-stage disease through awareness and access to care. However, few studies in an African population have integrated the patient-centered association of socioeconomic factors and access to care, with the more recent insights into tumor biology and its impact on the progression of disease, as has been the case more globally.[8,11] Therefore, two relatively discrete areas of investigation regarding breast cancer characteristics remain in Africa: one ascribing presentation at advanced stage to delay in diagnosis, traditional beliefs at conflict with treatment modalities, and low education, and the other describing adverse tumor biology and patient characteristics (such as young age or HIV status), which may also result in advanced stage presentation.

The purpose of this study was to examine the stage of disease at presentation in an urban South African population and assess the relative contributions of patient characteristics, delay in treatment, and tumor biology. We aim to tease out the most important contributing factors to advanced disease and through this help inform governmental policy regarding the provision of breast cancer care in LMICs.

Materials and methods

In an urban South African open-access breast care clinic from January 2016–February 2017, all patients with a new diagnosis of breast cancer were consented and invited to participate in a questionnaire regarding their demographics, socioeconomic situation, and access to care. These responses, together with their clinical examination at diagnosis, were then linked to their diagnostic histologic specimen.

Of the 256 patients with a new cancer diagnosis over the study period, 252 patients responded to the questionnaire giving a response rate of 70.8%. Patients who did not respond to the survey were excluded from further parts of the study and their histopathologic results were not considered. The reasons for refusal were not recorded. Of those that responded, 19 were then excluded because of inadequate immunohistochemistry results for this study, resulting in 231 participants included in this study population.

The questionnaire was completed in REDCap (hosted by the University of the Witwatersrand)[12] and linked to the participant's clinical findings at presentation and pathologic specimen. The questionnaire included questions around participant's demographics, socioeconomic situation, education, and self-described ability to access care. To determine patient-associated delay, participants were asked to quantify on a categorical scale how long it took them to acknowledge or discover a breast symptom once noticed (hereafter referred to as T-Ack), from that time, how long for them to visit any health services (hereafter referred to as T-HS), and from that point, how long until they attended this breast care clinic for diagnosis (hereafter referred to as T-BCC). Ethical approval was received from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M111121).

Setting

The South African Department of Health launched a national breast cancer policy in 2017[13] with accompanying costing and guidelines in development. It was designed to set standards and pathways to care for the development of regional breast cancer units, which would provide opportunistic screening, diagnostic services, and management of breast disease. Currently, there is no screening program in South Africa, and access to reliable high-quality breast cancer care is

geographically varied, with cancer centres concentrated in only the most developed metropolitan centres.

This study took place in an open-access walk-in breast care clinic situated in a tertiary surgical referral centre in a major metropolis in South Africa. It is a government-funded hospital and accepts patients from any area of the country. The spectrum of breast disease seen in this clinic has been previously described, with more than 4000 new patients and 300–350 new cancers diagnosed each year.[14]

More than 95% of the diagnostic biopsies were processed in one laboratory (National Health Laboratory Systems, South Africa) for subtype, grade, and immunohistochemistry. Hematoxylin and eosin–stained sections of all core biopsy specimens received in the laboratory were interpreted morphologically by the receiving pathologist, and then subject to immunohistochemistry. Immunohistochemical analysis was performed using fully automated protocols on a Dako Autostainer Classic (Agilent technologies, via Diagnostech South Africa). Sections of 3 μm thickness were cut from paraffin blocks and subjected to staining protocols with the following antibodies: ER, PR, HER2, and Ki67.

On review by the pathologist, ER and PR were reported in a semiquantitative fashion, based on the analysis of the proportion of positive cells (<1%, 1%-10%, 10%-33%, 33%-66%, and 66%-100%) and staining intensity (low, moderate, or strong intensity); HER2 was reported as negative (scores 0 or 1+), positive (3+), or equivocal (2+), based on American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) scoring protocols.[15] Cases that were HER2 equivocal on immunohistochemistry were subjected to reflex fluorescence in situ hybridization (FISH) for amplification of the HER2 receptor on chromosome 17, using the PathVysion 17q11.2-q12 (ERBB2) and CEP 17 assay. Cases with more than six copies of ERBB2 per cell, a dual-probe HER2/CEP17 ratio ≥2.0 were reported as positive or both, those with HER2/CEP17 ratio <2.0 and with between four and six copies of HER2 per cell were reported as equivocal, and those with a HER2/CEP17 ratio <2.0 with an average HER2 copy number of less than four per cell were reported as negative. Internal quality assurance for breast marker immunohistochemistry is ensured by positive controls placed on each antibody-stained slide, and negative controls used in each staining run. Samples were reviewed by a single pathologist or trainee working under direct supervision. Problem cases are routinely reviewed. The laboratory has been participating in the Breast Immunohistochemistry Markers module of a Royal College of Pathologists of Australia external quality assurance program for the past decade and achieves satisfactory results hereto.

Data categorization

Patient characteristics were described using frequencies and proportions, and categorized to facilitate analysis. Age was categorized as <45 or ≥45 y. Self-reported race was then grouped into Black and non-Black categories (non-Black including women who indicated White, Indian (Asian), and Colored [a South African statistical group denoting a specific mixed-race group]). Marital status was categorized as partnered or unpartnered, the latter of which included women who were either not in a relationship or widowed. Each of the three categories of patient-associated delay (T-Ack, T-HS, and T-ECC) was recorded as <1 wk, 1 wk-1 mo, 1-6 mo, 6 mo-1 y, and >1 y, and then a total delay (T-Tot) was calculated. This was then grouped as ≤6 and >6 mo.

Stage at presentation was determined using the "TNM" clinical staging system (American Joint Committee on Cancer Eighth Edition)[16] from the clinical examination of the physician, together with the mammogram and ultrasound of the breast, axilla, and liver. Further investigations of metastatic disease, including computed tomography of the chest and abdomen, bone scan, and magnetic resonance imaging, were carried out if clinically indicated. Stage was then categorized as early stage (between stages I and IIA) and advanced stage (stages IIB–IV).

ER and PR receptors were considered positive if nuclear staining of 1% or more cells was positive. HER2 was considered positive if overexpressed as "3+." A "2+" finding was equivocal and FISH requested. This was "positive," "negative," or "true equivocal." Patients for whom FISH was not carried out or a true equivocal result was found, they were excluded from further analysis in this variable or any grouping leading from this. Participants were categorized into molecular subtype-like groups according the 2011 St Gallen consensus[17] as follows:

- Luminal A: ER and/or PR+, HER2 negative, low Ki67 ≤14%.
- Luminal B (HER2−): ER and/or PR+, HER2 negative, high Ki67 >14%.
- Luminal B (HER2+): ER and/or PR+, HER2 positive.
- HER2 positive: ER and PR negative, HER2 positive.
- Triple negative: ER and PR negative, HER2 negative.

Tumors with any luminal subtype but equivocal HER2 with high Ki67 were typed as luminal B. All luminal B subtypes were then grouped as "luminal B." In addition to these groupings, for further analysis, all tumors which HER2 overexpressed (whether luminal B or HER2 subtype) and all tumors with high Ki67 (>14%) were categorized and compared with those that did not.

Statistical analysis

Patient characteristics and tumor biology were compared between early and advanced stage using Fisher's exact test of proportions, a P value <0.05 was considered statistically significant. Modified Poisson regression with robust error estimation[18] was applied to the data to estimate the relative risk of late stage presentation by demographic characteristics, total time to presentation, and molecular subtypes. Incidence risk ratios (IRRs) and a 95% confidence interval (CI) are presented. Factors that were associated with either an increased or a decreased risk of advanced stage breast cancer presentation in univariate analysis ($P < 0.10$) were included in multivariate analysis and adjusted IRR (aIRR) reported. All statistical analyses were done in Stata v13.1 (College Station, TX).

Results

Patient characteristics by stage at presentation

During the study period of 13 mo from January 2016, 251 participants with a new diagnosis of breast cancer were enrolled in this study. The median age was 56 y (interquartile range 46-65).

The key demographic characteristics are presented in Table 1, grouped according to early or advanced stage at presentation.

Stage at presentation was recorded as follows: stage I, 33 (16.5%); stage II, 63 (27.5%); stage III, 129 (55.8%); and stage IV, 6 (2.6%). More than two-thirds of patients with stage recorded presented with advanced stage breast cancer. Primary tumor (T) stage of T4 was present in 32.3% of all patients (n = 73) with 6.2% (n = 14) presenting as inflammatory cancer (T4d). There were very few relationships between any patient characteristics and stage at presentation; however, when grouped according to stage and ethnicity, there was a significant association between advanced-stage disease and Black ethnicity (P = 0.014). There was a significant relationship between delay in presentation of more than 6 mo and advanced-stage disease (P = 0.025).

Tumor biology

Clinicopathologic characteristics, also grouped by early or advanced stage at presentation, are presented in Table 2. Table 2 shows most tumors were invasive carcinoma of no special type (i.e., ductal carcinoma) (82.7%, n = 214), with only 4.3% (n = 10) lobular carcinoma. The most common molecular subtype was a luminal B (57.9%) with relatively few luminal A breast cancers. The adverse findings of triple negative or HER2 positive subtype together accounted for 33.3% of all cancers. These tumors with adverse tumor biology (either triple negative or HER2 positive subtype) were 50% more likely in Black participants than non-Black (RR, 1.55; 95% CI, 1.03-2.35).

Factors associated with advanced stage at presentation: univariate and multivariate analysis

Figure shows the relative risk of advanced-stage disease at presentation, both for the univariate and multivariate analysis. On univariate analysis of demographic and socioeconomic characteristics, participants aged <45 y and Black participants were more likely to present with advanced-stage disease (RR, 1.23; 95% CI, 1.01-1.49 and RR, 1.25; 95% CI, 1.04-

Table 1 – Demographic and clinical characteristics of patients diagnosed by stage at presentation (n = 231).

Description	Total	Stage at presentation		P value*
		Early stage (I-IIA)	Advanced stage (IIB-IIIC)	
Stage at presentation (231)	231	69 (29.9%)	162 (70.1%)	
Age (n = 217)				
<45 y	47 (21.6%)	9 (4.1%)	38 (17.5%)	0.12
45-64 y	114 (52.5%)	39 (18.0%)	75 (34.5%)	
≥65 y	56 (25.8%)	20 (9.2)	36 (16.6%)	
Median (IQR)	56 (46-65)			
Ethnicity (n = 222)				
Black African	127 (57.2%)	39 (18.5%)	87 (41.7%)	0.85
White	64 (28.8%)	22 (9.9%)	42 (18.9%)	0.013†
Colored	20 (9.0%)	10 (4.5%)	10 (4.5%)	
Indian	9 (4.1%)	4 (1.8%)	5 (2.3%)	
Other	2 (0.9%)	1 (0.5%)	1 (0.5%)	
Family history (n = 228)				0.62
Breast cancer in close relative (mother, sister, daughter)	20 (9.0%)	7 (3.1%)	13 (5.8%)	
Comorbidities (n = 231)				
Diabetes	37 (21.7%)	12 (5.2%)	15 (6.5%)	0.12
Hypertension	108 (46.8%)	36 (15.6%)	72 (31.2%)	0.32
Known HIV positive‡	21 (9.1%)	5 (2.2%)	16 (7.1%)	0.62
Tumor T4 on presentation (n = 225)				
Yes	72 (32.0%)	0	72 (32.0%)	<0.001
No	153 (68.0%)	69 (30.7%)	84 (37.3%)	
Total delay to presentation				
<3 mo	38 (21.2%)	16 (8.9%)	22 (12.3%)	0.03
3-6 mo	76 (42.5%)	20 (11.2%)	56 (31.3%)	
>6 mo-1 y	38 (21.2%)	15 (8.4%)	23 (12.9%)	
>1 y	27 (15.1%)	3 (1.7%)	24 (13.4%)	

Bolded values represents the significance of P value.
Abbreviations: IQR = interquartile range; HIV = human immunodeficiency virus.
*P values estimated using Fisher's exact test of proportions.
†Black ethnicity compared with all other races.

Table 2 – Tumor biological characteristics by stage at presentation

Description	Total	Stage at presentation		P value
		Early stage (I-IIA)	Advanced stage (IIB-IIIC)	
Stage at presentation (n = 281)	281	69 (29.9%)	162 (70.1%)	
Molecular subtype (n = 228)				
Luminal A	48 (21.6%)	20 (9.0%)	28 (12.6%)	0.69
Luminal B	128 (57.6%)	40 (18.0%)	88 (39.6%)	
Luminal B (HER2−)	102 (45.9%)			
Luminal B (HER2+)	27 (12.1%)			
HER2 positive	15 (6.7%)	2 (0.9%)	13 (5.7%)	
Triple negative	31 (14.0%)	6 (2.7%)	25 (11.3%)	
Tumor biology				
Tumor type (n = 233)				
Invasive carcinoma NST (ductal carcinoma)	234 (93.6%)	63 (25.1%)	149 (59.5%)	0.26
Lobular carcinoma	10 (4.3%)	1 (0.4%)	9 (3.9%)	
Other	7 (3.0%)	3 (1.3%)	4 (1.7%)	
Tumor grade (n = 225)				
High grade	113 (51.1%)	31 (13.8%)	84 (37.3%)	0.002
Intermediate grade	84 (37.3%)	21 (9.3%)	63 (28.0%)	
Low grade	28 (12.4%)	16 (7.1%)	12 (5.3%)	
Immunohistochemistry				
ER positive (n = 228)	177 (77.6%)	69 (26.3%)	117 (51.3%)	0.03
PR positive (n = 228)	196 (59.7%)	49 (21.5%)	87 (38.2%)	0.02
HER2 positive (n = 217)	42 (19.4%)	6 (2.8%)	36 (16.6%)	0.01
Fluorescence in situ hybridization (n = 23)				
Positive	3 (34.8%)			
Triple negative (n = 222)	31 (14.0%)	6 (2.7%)	25 (11.3%)	0.21

Abbreviations: ER = estrogen receptor; NST = no specific type; PR = progesterone receptor.

1.51, respectively). Although most tumors were ductal carcinoma, patients with lobular carcinoma were significantly more likely to present with advanced-stage disease (IRR, 1.29; 95% CI, 1.03–1.62). Most tumors were high grade, with high and intermediate grades nearly two times more common in advanced disease (IRR, 1.90; 95% CI, 1.15–3.13 and IRR, 1.95; 95% CI, 1.12–3.22, respectively). ER and PR positive tumors were more common in early stage breast cancer (IRR, 0.80; 95% CI, 0.63–0.95 and IRR, 0.82; 95% CI, 0.69–0.97). When other adverse factors were considered alone, both high Ki67 proliferation index and HER2 overexpression increased the risk of advanced disease (IRR, 1.30; 95% CI, 1.02–1.66 and IRR, 1.32; 95% CI, 1.13–1.55, respectively).

On multivariate analysis, all socioeconomic characteristics were considerably mitigated by tumor biology so that the effect of age and race was no longer statistically significant in the multivariate analysis (aIRR, 1.12; 95% CI, 0.91–1.37 and aIRR, 1.17; 95% CI, 0.94–1.46, respectively). Participants with tumors of both HER2 and triple negative subtypes were associated with advanced disease, a finding that strengthened in multivariate analysis. HER2 positive patients were 50% more likely to present with advanced disease (aIRR, 1.48; 95% CI, 1.08–2.03). As a category, luminal B cancers were not associated with advanced disease; however, when separated into HER2 positive and HER2 negative, luminal B (HER2+) cancers were predictive of advanced disease, almost equivalent to those of the HER2 subtype (aIRR, 1.45; 95% CI, 1.16–1.95). Luminal B (HER2−) cancers behaved similarly to luminal A cancers (aIRR, 1.08; 95% CI, 0.82–1.45).

When Black and non-Black participants were considered separately in adjusted analysis of advanced stage, non-Black participants presenting with advanced-stage disease were more likely to be young and have a HER2 positive subtype (aIRR, 1.85; 95% CI, 1.15–2.97 and aIRR, 3.10; 95% CI, 1.35–7.12). They were also far more likely to present after a delay of 12 mo or more (aIRR, 3.45; 95% CI, 1.78–6.69). Conversely, Black participants alone were a more heterogeneous group, with no factors predicting advanced disease, with the exception of lobular carcinoma biology (aIRR, 1.58; 95% CI, 1.03–2.46).

Discussion

In South Africa, breast cancer is the most common cause of cancer in women,[18] and here we found that advanced-stage disease is the most common presentation. This study was designed to describe the variation in breast cancer subtypes in a heterogeneous South African population, and determine the relationship between a patient's demographic and clinical characteristics at presentation and the molecular subtype of breast cancer they present with.

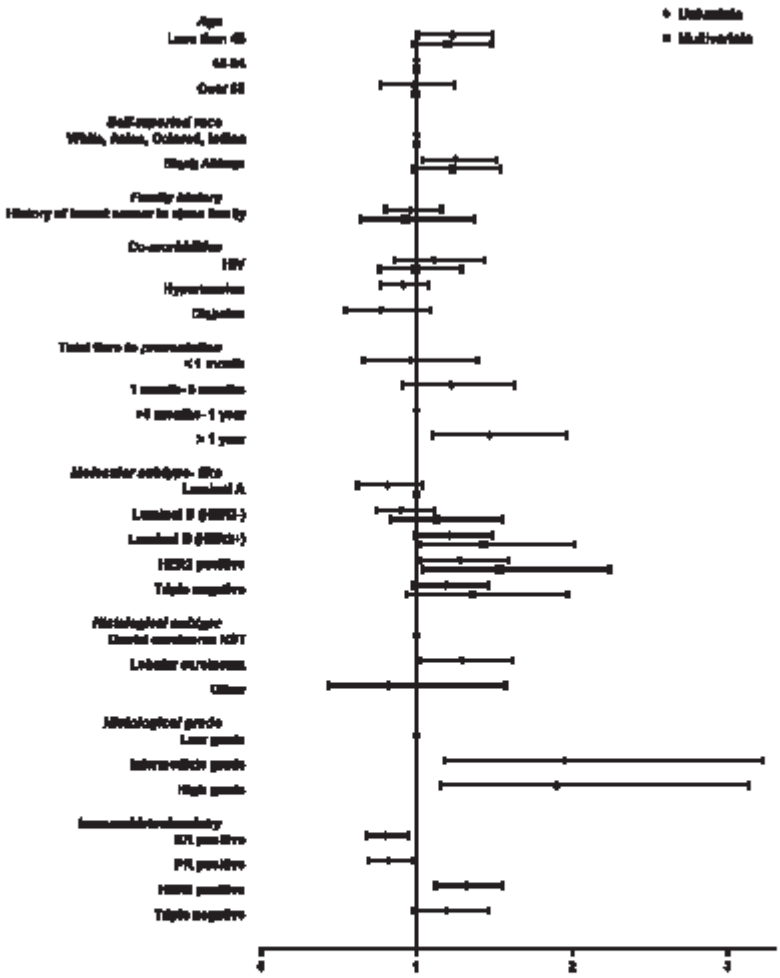

Fig — Relative risk of advanced stage breast cancer at presentation, univariate and multivariate.

Despite living within the urban environment of Johannesburg, close to Africa's richest square mile,[23] 70% of participants in this study presented with advanced-stage disease, with nearly one-third of participants having a T4 primary tumor. There was a relationship between young age and between Black race and advanced stage at presentation here. These relationships have been previously noted in other studies of women both in high-income settings[20–22] and from LMICs;[19] however, we found that this relationship was mitigated by the presence of adverse tumor biology, which was found to influence stage at presentation more than any singular demographic.

Nearly 60% of patients were delayed for more than 6 mo from time of initially noticing a symptom to specialist unit presentation; however, there was no time frame where early disease was more common than advanced stage. In patients reporting <1 mo to presentation, locally advanced cancer was still more common, indicating that delay alone does not explain the propensity for locally advanced disease. Without a screening program, patients are reliant on intermittent patient- or clinician-led breast examination and the presence of tumors >2–5 cm or advanced nodal disease before detection may be a product of this. Similarly, without screening, smaller impalpable cancers are not represented, and therefore there is a "stage-migration" effect to an over-representation of advanced cancer.

In this present study, black participants were more than twice as likely to have a triple negative breast cancer. The

strong association between triple negative cancers and mutations in the BRCA1 gene in European and USA populations[24,25] are not well-studied in a South African population, although testing in the government-funded hospitals is possible. In one recent study in a similar geographical population of breast cancer patients,[26] 7 of 30 women with a triple negative breast cancer who underwent mutation screening without family history determination had a BRCA1/2 genetic mutation. The significant relationship in the present study between a family history and triple negative cancers, together with the association between triple negative cancers and advanced stage at presentation here further highlights the need for more studies regarding genetic mutations in Black South African women.

Most patients in this study presented with luminal B-type breast cancers. This was an unexpected finding, which has not been described in other studies of breast cancer characteristics in Africa where (as in the rest of the world) luminal A tumors are more described;[8,27,28] however, this over-representation of luminal B tumors has been described globally in young women.[29,30] Our categorization of luminal B included Ki67, as recommended in the St Gallen consensus;[17,18] however, in many studies in LMICs, luminal B has rather been taken to be the absence of PR or the presence of grade 3 or HER2 positive tumors.[22] We would hypothesize that the addition of the Ki67 marker has identified more patients into the luminal B group, allowing a more accurate representation of the cancer population. Although the studies in LMICs discuss tumor biology but use only HER2 or grade to differentiate luminal A from B, inaccurate assumptions of achievable survival outcomes and treatment provisions may occur. This study showed that within the luminal B category, the presence or absence of HER2 overexpression was more sensitive to the likelihood of advanced presentation, with luminal B (HER2+) tumors having clinical presentation even more akin to HER2 positive subtype than other luminal cancers, but with an ameliorated impact on advanced presentation as seen in Figure.

In addition to luminal B (HER2+) cancers, other adverse biological features such as grade and receptors increased the likelihood of advanced stage at presentation. In this study when grouped according to race, Black participants were also more likely to have a tumor with adverse biological subtypes. This relationship can further be seen in the mitigation of race on multivariate analysis as a cause for late presentation. It may be that in retrospective studies of young Black women in LMICs, the commonly described presentation with advanced breast cancer[31] is a composite finding of unrecognized or untreated adverse tumor biology, potentiated by socioeconomic circumstances or in a young urban population. This is not to discount the importance of delay and patient or provider factors in stage at presentation, but rather adds the information that there is a subset of women for whom their biologically adverse tumor determines their stage at presentation more than any preventable delay.

This study was based in one specialist center in urban South Africa, and therefore its findings may not be representative of the full spectrum of disease in the country. However, breast cancer specialist centers are becoming more common in Africa,[32] and these data may be reflective of that which presents to a tertiary center. In addition, the findings of receptor status here are similar to a study using (in part) South African national cancer registry data.[27] Both these data and the national cancer registry data rely on a tissue diagnosis being made. There is a cohort of women with breast cancer who may never reach diagnosis, because of inability to access care at all, or extreme late disease at presentation resulting in palliation without tissue diagnosis. It is hard to determine how this cohort of women can be reached for further understanding of their disease, and efforts to characterize this population should form part of further studies.

The finding of adverse tumor biology in our patient population may enable us to guide governmental policy and spending regarding breast cancer care. Most of the literature surrounding breast cancer control in LMICs is based around the dysfunctional prediagnosis health and welfare system, with an emphasis on education, awareness, and access to services.[33–35] In this study, on the basis of the international guidelines such as National Comprehensive Cancer Network (NCCN)[17] 95% of women were probable candidates for neoadjuvant or adjuvant chemotherapy based on stage and tumor biology, and at least 70% of patients would be suitable for radiation consideration. Even in the early breast cancer population seen here, more than 70% of participants had biological subtypes where chemotherapy would have been recommended. Further to this, 19.4% of patients were diagnosed with HER2 positive tumors and therefore suitable for anti-HER2 therapies in addition to chemotherapy. Preliminary tumor biology findings from this study were shared with the National Department of Health during the development of the national breast cancer policy and its costing. These were used to help guide the estimation of provision of anti-HER2 therapy in this resource-limited environment, and the subsequent adoption of anti-HER2 therapy as a recommended therapy (subject to access) in the national breast cancer policy.[36]

These findings of a difference in the proportions of tumor biology when accurately calculated also raise the question of whether some of the disparity of outcomes in LMICs is because of an absence of screening-detected luminal A indolent tumors within the total breast cancer incidence, rather than overall inherently more adverse tumor biology. This may occur in a similar fashion to the lack of early stage cancers seen in this study at all timeframes of presentation. It should be noted that the incidence of breast cancer in South Africa is one in 33, far less than that of countries where screening is carried out. Without national incidence figures per stage in South Africa it is hard to determine a per-capita advanced-cancer incidence or adverse-biology incidence, but it may be that there is actually an under-representation of early, indolent cancers, commonly seen (and sometimes described as overdiagnosed) in screening-detected populations because of lack of screening in South Africa.

Therefore, when considering provision of care to improve cancer-related outcomes, it is imperative that the discussion should be focused on adequacy of appropriate and comprehensive stage-based treatments rather than just early detection as a method of reducing the societal burden of disease in LMICs. Studies of biology and stage-specific populations can be used to guide treatment provision planning and costing in cancer care policies, such as South Africa's newly conceived national breast cancer policy.[36]

Conclusions

This study found that urban South African breast cancer patients had a high rate of advanced stage at presentation, and that there was a relationship between stage and adverse tumor biology, both in all HER2 positive cancers and in molecular subtypes. Despite being one of the most commonly studied cancer in South Africa[22] (and perhaps any LMIC population), the reasons for advanced stage in breast cancer are still not well understood. Because of the lack of reliable histopathologic tumor characterization in many laboratories or even countries on the continent, studies may still misclassify tumor biological characteristics and underrepresent adverse features. The need for more oncological specialty skills is well described; however, access to accurate pathology and genetic counseling may be an essential part of providing well-timed comprehensive cancer care, to reduce the burden of breast cancer disease and mortality.

Acknowledgment

The authors would like to acknowledge the invaluable partnership of the participants and their families as well as the assistance of the clinic staff in enabling this research to be carried out. In addition, the authors would also like to thank Ronnie Van der Vlist and Dorcas Makhleis for their interest, input, and care.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: E.B. conceived and designed the study, collected and interpreted data, drafted and critically revised manuscript, and approved final version. K.S. and D.K. analyzed and interpreted data, critically revised manuscript, and approved final version. K.F. interpreted data, contributed to the manuscript, and approved final version. C.F., C.-A.R., and S.G. interpreted data, critically revised manuscript, and approved final version.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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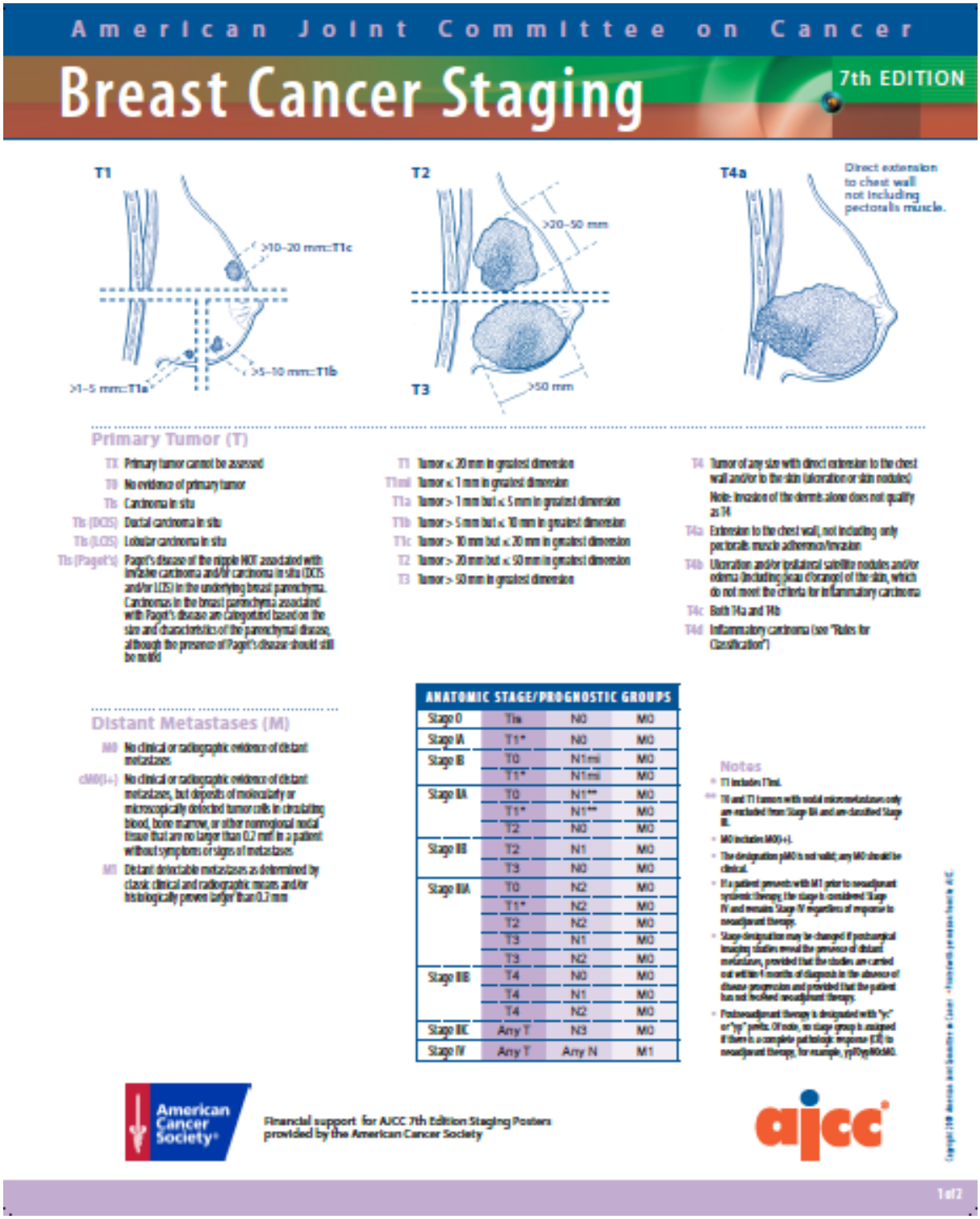
Appendix B: American Joint Committee on Cancer Breast Cancer Staging (7th Edition)



American Joint Committee on Cancer

Breast Cancer Staging

7th EDITION

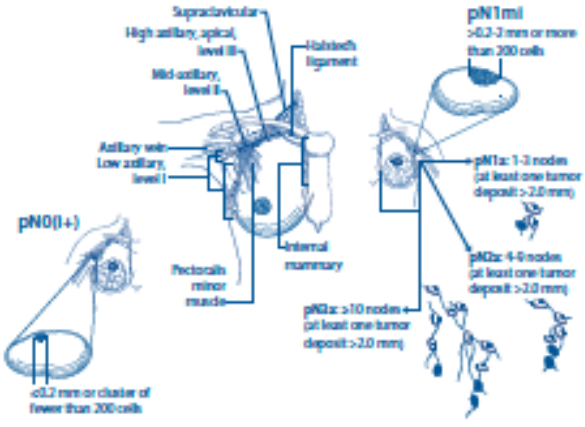
Regional Lymph Nodes (N)

CLINICAL

- NX Regional lymph nodes cannot be assessed (for example, previously removed)
- N0 No regional lymph node metastases
- N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
- N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- N3a Metastases in ipsilateral infraclavicular lymph node(s)
- N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- N3c Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN1a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, (for example, cN1). Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node* biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.



PATHOLOGIC (PN)*

- pNX Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
- pN0 No regional lymph node metastasis identified histologically

  Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
- pN0(i-) No regional lymph node metastasis histologically, negative IHC
- pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
- pN0(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)**
- pN0(mol+) Positive molecular findings (RT-PCR)**, but no regional lymph node metastasis detected by histology or IHC
- pN1 Micrometastases; or metastases in 1–3 axillary lymph nodes, and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
- pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
- pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
- pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
- pN2 Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- pN2a Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
- pN2b Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
- pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
- pN3b Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes, or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN3c Metastases in ipsilateral supraclavicular lymph nodes

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

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Appendix C: Context and additional methodology

Study design

Study overview

The main study was a prospective, descriptive study with two components:

- Questionnaire to be filled in by enrolled participants
- Prospective capture of patient clinical information of enrolled participants

An initial pilot study of the questionnaire only, was carried out using patients from both government and private centres and analysis of this work was be included in the first part of this doctorate (paper one and two). The results were used to amend the questionnaire for the main study (papers three to five).

Study site and context

Breast cancer is the most common form of cancer to affect women in South Africa, however access to accurate data concerning cancer is difficult to obtain and out of date. Cancer statistics depend on the National Cancer Registry (NCR) which has been operating for 30 years intermittently but is currently not up to date. The National Cancer Registry (most recent report, 2009 at the time of study design, 2014 at time of submission in 2019) relies on pathology and hospital reporting and is not population-based. Cancer incidence thus is reported to be largely under-reported because of a lack of nationwide cancer surveillance networks [115].

This study was conducted at the Helen Joseph Breast Care Clinic (HJBCC) and Netcare Breast Care Centre (NBCC) in Johannesburg, South Africa and included patients with and without medical aid. Medical aid is the system of health insurance in South Africa bought by the end-user which allows access private facilities. Patient without medical aid or with poor coverage are seen in government funded facilities at low- or no-cost.

The HJBCC is a government-funded hospital serving predominantly uninsured patients averages 3,000 new patients each year. Only 6% of these patients have medical insurance (unpublished local data). Approximately 7-10 patients are diagnosed with breast cancer each week, corresponding to between 340-370 new breast cancer diagnoses each year. In close geographical proximity is a private or medical insurance funded practice (Netcare Breast Care Centre) diagnosing and managing approximately 400 new breast cancer diagnoses per annum.

In these hospitals diagnosis is by the global gold standard of triple assessment (i.e. clinical breast examination, imaging by ultrasound or mammography or both, and biopsy) performed by a multi-disciplinary team. HJBCC receives patients from primary healthcare facilities, district hospitals,

and in some cases, as walk-in, or "self-referred" patients. This self-referred patient predominates in the NBCC.

Both hospitals include a multi-disciplinary breast cancer diagnostic team combining surgery, radiology, nurses and counsellors. At a separate but close geographical location, cancer services including medical and radiation oncologists, and pathologists. As part of the hospital team breast cancer advocates, representing survivors and other interested parties, are a part of the team and contribute to assistance with transportation, translation, and overall education for patients on the disease management process. Advocates also assist in raising awareness of survivorship issues such as prosthesis following surgery, psychosocial support, and access to grants and social welfare, which may not be routinely addressed by the medical team.

Study population and period

The pilot study consisted of all female patients of all ages who were diagnosed with breast cancer, and were currently undergoing active management at either centre. This is defined as current oncological management for a primary (non-recurrent) breast cancer including chemotherapy, radiation or surgical management.

Whilst patients choosing not to present with breast cancer could not be targeted in this study, primarily because a diagnosis of breast cancer can only be achieved after presentation, patients often present in the very latest stages of the disease for final palliative care of fungating wounds or terminal disease symptoms. These patients formed part of the late presentation group.

Exclusion

- Patients with recurrent (and therefore previously medically treated) breast cancer will be excluded because they have already experienced biomedical management which may have influenced their beliefs and fears.

- Patients completed current oncological management on long term hormonal blockade or patients undergoing close surveillance or follow-up for breast cancer. Whilst these women will have valid experiences and beliefs concerning breast cancer, they have also experienced biomedical management for at least 6 months and may have difficulty recalling or differentiating pre-treatment beliefs from those now held.

- Male patients with breast cancer. Whilst this is a valid group to study, the numbers are too small to analyse appropriately, whilst they may will a further variable and are therefore to be excluded from this study. Dr Sarah Rayne has previously studied this group of patients with regards to patient and disease characteristics and feelings about breast cancer [190].

- Patients not resident in South Africa due to additional variables for delay and treatment constraints.

In the main study, consecutive women were included if they had a new diagnosis of a biopsy-proven breast cancer and accepted the invitation to participate during their post-diagnosis counselling by a clinician, with the survey administered within this period.

The recruitment period of the pilot population was from November 2012 to May 2013 at both centres and a convenience sample of 160 patients were recruited. This was carried out on an as-and-when basis reliant on availability of research staff. The recruitment of the main study population took place from January 2016 to February 2017 and consecutively all patients with a new diagnosis of breast cancer were consented and invited to participate.

Study procedures

Questionnaire

A structured questionnaire was designed with multidisciplinary input and after critical review of the literature related to testing and using questionnaires in breast cancer. At the time of the design of the questionnaire (2011), there were no appropriate tools available or validated in a LMIC cancer population.

Analysis of the pilot data allowed internal validation of the questionnaire and alteration at that time prior to the main study. This questionnaire achieved internal consistency measurements for each subscale (fears; beliefs; fatalism and risk factors) found a Cronbach's alpha co-efficient of 0.82, 0.73, 0.71 and 0.81 respectively (p48). It has subsequently been used in a Botswanan population [191]

Therefore, a review of the literature led to a design that encompassed questions to determine the following:

- demographics including age, race and ethnical background, first language and marital status
- socioeconomic and educational background, work and transport difficulties, and religious affiliations
- time delay from first symptom through first disclosure, first healthcare presentation up to definitive care with opportunity to record difficulties in access (for instance "sent away from clinic")
- patients' feelings of fear concerning facets of breast cancer treatment previously cited in literature as important for decision-making.

- patient's agreement with statements which embodied preconceptions pertaining to delays in health-seeking behaviour,

For the pilot study a 11-point summative scale was used however analysis was difficult with such a wide scale and marked central tendency bias. This was condensed in the main study to a 'forced-choice' four-point scale. Participants were invited to leave out a question if they wanted to not answer. As an undecided mid-point is used more commonly in those with lower levels of education and encourages a social-desirability bias [192], because the sample size was small it was important to gather as many opinions as possible. To remove bias of positive or negative answers, some of the questions were reversed.

Administration

Normally a participant's clinical consultation disclosing a cancer diagnosis was followed by post-diagnosis counselling. During this time, participants were approached and invited to partake in the study by either by the doctoral candidate (Dr Sarah Rayne) or by a research assistant (MSc or PhD in social science) employed for the purpose. After post-test counselling, the research assistant introduced themselves and discussed the invitation letter and consent form. When the invitation was accepted the questionnaire was administered and on completion of the questionnaire, data would be captured and these responses, together with their clinical examination at diagnosis, were then linked to their diagnostic histological specimen.

Appendix D: Student declaration for published papers

As per the University of Witwatersrand requirements for dissertations that include published work a student declaration is included.

Declaration: Student's contribution to manuscripts

I, Sarah Louise Rayne, student number 545345, declare that this thesis is my own work and that I was the primary contributor to all research findings published in the article(s) which are included in my thesis.

Sarah Louise Rayne (PHD Candidate)
Thursday, 31 January 2019

_____

Deirdre Kruger (Supervisor)
Thursday, 31 January 2019

Appendix E: Co-author declaration for published papers

As per the University of Witwatersrand requirements for dissertations that include published work a declaration from each co-author is included.

By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

The co-authors for the publications include (in alphabetical order):

Benn C

Fearnhead K

Firnhaber C

Kruger D

Schnippel K

Wright K

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Tuesday, 17 April 2018

Factors influencing delay in presentation in women with a diagnosis of breast cancer in South Africa and their impact on cancer stage at presentation

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy, by Sarah Louise Rayne

As per the University of Witwatersrand requirements for dissertations that include published work a declaration from each co-author is included.

1. Rayne S, Schnippel K, Wright K, Kruger D, Firnhaber C, Benn C. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa. J Glob Oncol 2016;3:125–34. doi:10.1200/JGO.2015.002691.

2. Rayne S, Schnippel K, Benn C, Kruger D, Wright K, Firnhaber C. The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa. J Cancer Educ 2017. doi:10.1007/s13187-017-1234-3.

3. Rayne S, Schnippel K, Kruger D, Benn C, Firnhaber C Delay to diagnosis and breast cancer stage in an urban South African breast clinic. Submitted to South African Medical Journal *Accepted*

4. Rayne S, Schnippel K, Grover S, Kruger D, Benn C, Firnhaber C The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa. Submitted to South African Journal of Surgery *Accepted with revision*

5. Rayne S, Schnippel K, Fearnhead K, Grover S, Kruger D, Benn C, Firnhaber C Unravelling the South African breast cancer story: the relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting. Submitted to Journal of Surgical Research *Under review*

By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

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Factors influencing delay in presentation in women with a diagnosis of breast cancer in South Africa and their impact on cancer stage at presentation

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By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

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By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

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By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

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Thursday, 19 April 2018

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A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy, by Sarah Louise Rayne

As per the University of Witwatersrand requirements for dissertations that include published work a declaration from each co-author is included.

1. Rayne S, Schnippel K, Wright K, Kruger D, Firnhaber C, Benn C. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa. J Glob Oncol 2016;3:125–34. doi:10.1200/JGO.2015.002691.

2. Rayne S, Schnippel K, Benn C, Kruger D, Wright K, Firnhaber C. The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa. J Cancer Educ 2017. doi:10.1007/s13187-017-1234-3.

3. Rayne S, Schnippel K, Kruger D, Benn C, Firnhaber C Delay to diagnosis and breast cancer stage in an urban South African breast clinic. Submitted to South African Medical Journal *Accepted*

4. Rayne S, Schnippel K, Grover S, Kruger D, Benn C, Firnhaber C The effect of beliefs about breast cancer on stage and delay to presentation: Results from a prospective study in urban South Africa. Submitted to South African Journal of Surgery *Accepted with revision*

5. Rayne S, Schnippel K, Fearnhead K, Grover S, Kruger D, Benn C, Firnhaber C Unravelling the South African breast cancer story: the relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting. Submitted to Journal of Surgical Research *Under review*

By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

Name: Kathryn Schnippel

Signed: _____ Date: 2018/04/19

Co-author declaration: K Wright

Department of Surgery

7 York Road, Parktown, 2193 South Africa • Telegrams "Witsmed" • Telephone (011) 717-2000 • Fax (011) 484-2717

Monday, 07 May 2018

Factors influencing delay in presentation in women with a diagnosis of breast cancer in South Africa and their impact on cancer stage at presentation

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy, by Sarah Louise Rayne

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By signing this declaration, the co-author agrees to the use of the article by the student Sarah Louise Rayne as part of her thesis.

Name: Kathryne Wright

Signed:_____ Date: ____05/05/18_____

Appendix F: Clearance to reproduce article published in Journal of Cancer Education

Sarah Rayne

From: Arthur Michalek <jceditor1@gmail.com>
Sent: 18 April 2018 14:13
To: Sarah Rayne
Subject: Re: JCED: Your manuscript entitled The effect of access to information on beliefs surrounding breast cancer in South Africa

I have no objection to the use of this publication in Ms. Rayne's dissertation. I wish the good Dr-to-be well and great future success. Thank you.

Art

On Tue, Apr 17, 2018 at 9:45 AM, Sarah Rayne <rayne.sarah@gmail.com> wrote:

> Dear Editors/Publishers of Journal of Cancer Education
>
> Ref.: Ms. No. JCED-D-16-00293R3
>
> The effect of access to information on beliefs surrounding breast cancer in South Africa Journal of Cancer Education
>
> This article (attached) was part of a study completed in fulfilment of the requirements for the degree of Doctor of Philosophy, by Sarah Louise Rayne. The full thesis (by publications) is due for submission to the Faculty of Health Sciences, University of Witwatersrand, South Africa.
>
> I would be grateful for permission for the article to be reproduced as part of this PhD, both as a chapter and in its PDF format as an appendix. The final PhD will be logged in the library of the University of the Witwatersrand.
>
> Best Wishes
>
> Dr Sarah Rayne
>
> BSc MBChB MRCS(Eng) MMed FCS(SA)
>
> **Specialist Surgeon** | Helen Joseph Hospital
>
> **Associate Professor** | Department of Surgery | University of the Witwatersrand
>
> Johannesburg | South Africa

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Appendix G: Ethical clearance certificate M111121

Primary ethics approval was sought from the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg, South Africa and was received om 25/11/2011 with extension and amendments approved on 19/11/2014.

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 13005, 13th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Phillip Tobias Building, 2nd Floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050 www.wits.ac.za. Fax +27 (0)11-717-1265

19 November 2014

Dr Sarah Rayne
Private Bag X47
Auckland park
Johannesburg
2006

Sent by email to: [illegible]

Dear Dr Rayne

Re: **Protocol Ref no: M111121**
Protocol Title: Factors Affecting Presentation In Patients Subsequently Diagnosed with Breast Cancer
Principal Investigator: Dr Sarah Rayne

Additional projects on the above mentioned programme

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amendments on the above mentioned protocol as detailed in your letter received

The following documents were received:

- Consent form
- Research protocol
- Information sheet.

Thank you for keeping us informed and updated.

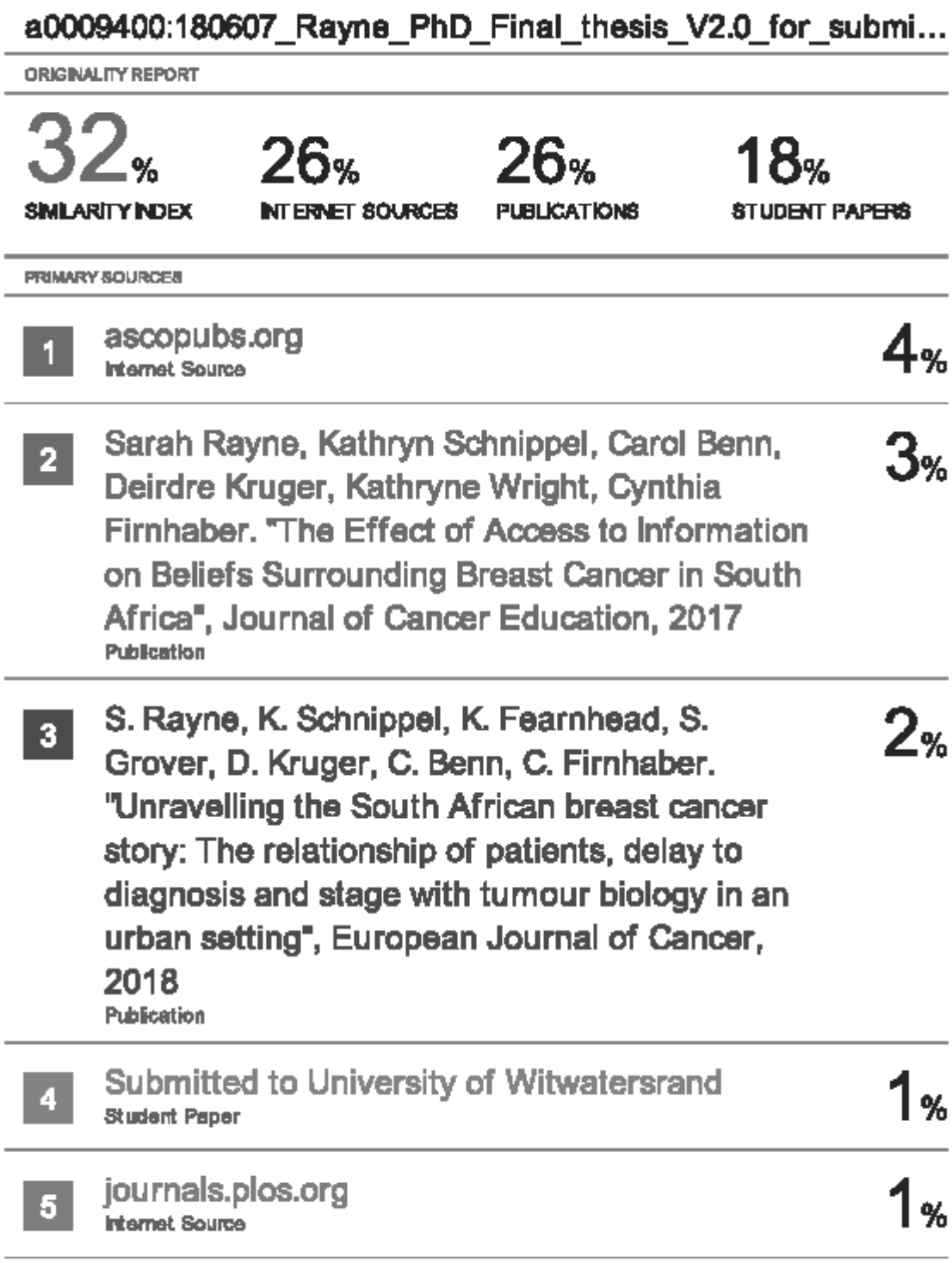
UNIVERSITY OF THE WITWATERSRAND OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH 19 NOV 2014 RESEARCH OFFICE JOHANNESBURG

Yours Sincerely.

Mr Langutani Masingi
Administrative Officer
Human Research Ethics Committee (Medical)

Appendix H: Originality report

As per the University of Witwatersrand requirements this thesis (excluding journal articles) has been submitted to Turnitin. A copy of the Turnitin report cover page is included.



a0009400:180607_Rayne_PhD_Final_thesis_V2.0_for_submi...

ORIGINALITY REPORT

32%	26%	26%	18%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	ascopubs.org Internet Source	4%
2	Sarah Rayne, Kathryn Schnippel, Carol Benn, Deirdre Kruger, Kathryne Wright, Cynthia Firnhaber. "The Effect of Access to Information on Beliefs Surrounding Breast Cancer in South Africa", Journal of Cancer Education, 2017 Publication	3%
3	S. Rayne, K. Schnippel, K. Fearnhead, S. Grover, D. Kruger, C. Benn, C. Firnhaber. "Unravelling the South African breast cancer story: The relationship of patients, delay to diagnosis and stage with tumour biology in an urban setting", European Journal of Cancer, 2018 Publication	2%
4	Submitted to University of Witwatersrand Student Paper	1%
5	journals.plos.org Internet Source	1%

Sarah Rayne

From: Deirdre Kruger <Deirdre.Kruger@wits.ac.za>
Sent: 08 June 2018 10:57
To: Sarah Rayne
Cc: 'Cindy Firnhaber'
Subject: Plagiarism report
Attachments: TURNITIN_180607_Rayne_PhD_Final_thesis_V2.0 _for_submission_excl_lit_review_from_protocol_and_appendices_for_Turnitin.docx.pdf

Importance: High

Hi Sarah

Herewith your Turnitin plagiarism report attached. I have removed the two published papers from this submission, as well as the Chapter 2 which was from your protocol, all of which would already have been submitted to a paper repository.

Your similarity index is 32% with a maximum single matches of 4%, 3% and 2% from your published manuscripts or conference proceedings. The rest is 1% or less - this is acceptable within our Department.
For PG submissions - Please only print out the Turnitin report pages in the attached report showing the similarity indices (page 74 onwards), as well as this email stating that your plagiarism report is acceptable within the Department of Surgery.

Kind regards,
Deirdré

Dr. Deirdré Kruger
BSc PGCHE PhD (UK)

Specialist Scientist and Research Coordinator (Surgery)
University of the Witwatersrand
Wits Medical School - Department of Surgery
Rm 9M09, 7 York Road, Parktown, Johannesburg, 2193.
Tel: +27 (0) 11 717 2376
Email: deirdre.kruger@wits.ac.za

Appendix H: Supervisor's approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG | FACULTY OF HEALTH SCIENCES

CERTIFICATE OF SUBMISSION FOR EXAMINATION SIGNED BY SUPERVISORS OF HIGHER DEGREES CANDIDATES

Full name	Sarah Louise Rayne		
Student number	545345		
Candidate for the degree of: ____PhD_____ *has submitted his/her thesis/dissertation/research report* Entitled: ___Factors influencing delay in presentation in women with a diagnosis of breast cancer in South Africa and their impact on cancer stage at presentation _____ _____			
Contact no	0727768553	E-mail	Rayne.sarah@gmail.com

Mark with an X on appropriate box	Yes	No
Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?	Yes	
To the best of your knowledge are you able to verify that: This is the candidate's work except as otherwise stated by the candidate?	Yes	
The substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university	Yes	
The candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions	Yes	
Have examiners been nominated and approved?	Yes	

I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee/Committee for Research on Human Subjects and the Number of the Certificate of Approval is: ____M111121_____

List all publications, which your student have published in peer-reviewed journals from his/her postgraduate research report/dissertation/thesis during the course of his/her studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

1

1. Rayne S, Schnippel K, Wright K, Kruger D, Firnhaber C, Benn C. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa. J Glob Oncol 2016;3:125–34. doi:10.1200/JGO.2015.002691.

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Name of Supervisor: Dr Deirdre Kruger — Telephone: 0761278049

Signature: _____ — E-mail: deirdre.kruger@wits.ac.za

Date: 08/06/18

Name of Supervisor: Adj Prof Carol Benn — Telephone: 0833213385

Signature: _____ — E-mail: drbenncarol@gmail.com

Date: 07/06/18

Name of Supervisor: Assoc Prof Cynthia Firnhaber — Telephone: +1 (303) 917 0613

Signature: Cynthia S Firnhaber — E-mail: csfirnhaber@gmail.com

Date: 07/06/18

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG | FACULTY OF HEALTH SCIENCES

IMPORTANT NOTICE WITH REGARD TO THE SENATE STANDING ORDERS:

A.22 Submission against advice of Supervisor

If the Supervisor is not prepared to agree to the submission of a thesis, the candidate shall still be entitled, if he or she wishes, to submit it for examination. When a thesis is submitted against the advice of the Supervisor, this should be recorded in the minutes of the Faculty Graduate Studies Committee. In such a case, no internal examiners are appointed but a Supervisor's report will still be required. After the examination process, the external examiner(s) will be advised by the Chairperson of the Faculty Graduate Studies Committee that the thesis was submitted against the advice of the Supervisor.

A.24 *Nomination of Examiners*:

Nomination of examiners should take place at least six weeks before submission of the thesis or dissertation. *(The Postgraduate Office will not accept any submission for examination without the confirmed appointment of the nominated examiners.)*

A.25 Confidentiality of names of examiners (both external and internal)

The names of the examiners should be confidential during the examination process and may only be revealed to the candidate with the acquiescence of the examiner once the final version of the thesis has been submitted to the Faculty and the process has been completed.

End of thesis