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MULTIMORBIDITY AND BREAST CANCER IN SUB-SAHARAN AFRICA: PROFILE AND IMPACT ON STAGE AT DIAGNOSIS AND BREAST CANCER TREATMENT DECISIONS



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Submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of

Doctor of Philosophy.

JOHANNESBURG, SOUTH AFRICA

2021

DECLARATION

I, Oluwatosin Adetayo Ayeni, hereby declare that the work in this thesis, unless otherwise acknowledged, is mine. This work is submitted, in fulfilment for the degree of Doctor of Philosophy in the Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.



Signed at the University of the Witwatersrand, Johannesburg

O.A. Ayeni

15th Day, February, 2021

DEDICATION

Dedicated to God Almighty.

Give thanks to the lord, for he is good!

His faithful love endures forever.

Psalm 107:1

ACKNOWLEDGEMENTS

There are several people who have made this PhD possible because of their amazing support. I would specifically like to extend my thanks and appreciation to the following:

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TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
ACKNOWLEDGEMENTS iv
TABLE OF CONTENTS vi
LIST OF FIGURES x
LIST OF TABLES xi
PEER REVIEWED PUBLICATIONS (PHD) xiii
POSTER PRESENTATIONS xiv
HONOURS AWARDED TO PhD CANDIDATE xv
ACRONYMS AND ABBREVIATIONS xvi
ABSTRACT xviii
PREFACE xxi
1. CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW 24
1.1. Global burden of Non-Communicable Diseases (NCDs) 24
1.2. Multimorbidity and chronic conditions 24
1.2.1. Burden of chronic conditions and multimorbidity in sub-Saharan Africa 25
1.3. Global burden of cancer 27
1.3.1. Challenges of cancer management in sub-Saharan Africa 28
1.3.2. Burden of breast cancer in sub-Saharan Africa 28
1.3.3. Burden of breast cancer in South Africa 30
1.4. Conceptual Model and Theoretical Framework 31
1.5. Literature Review 32
1.5.1. Development and risks of breast cancer 32
1.5.2. TNM staging of Breast Cancer 35
1.5.3. Early versus Advanced/Late breast cancer 36

1.5.4. Breast cancer and stage at diagnosis in sub-Saharan Africa and South Africa .37
1.5.5. Treatment of breast cancer....39
1.5.6. Chronic conditions and breast cancer....41
1.5.7. Multimorbidity and breast cancer stage at diagnosis and management....47
1.5.8. Effect of multimorbidity on patients and health systems....50
1.5.9. Socio-demographic and lifestyle factors and their impact on multimorbidity and breast cancer stage at diagnosis and outcomes....51
1.6. Overall aim....53
1.6.1. Specific objectives and hypothesis....54
2. CHAPTER TWO: METHODOLOGY....56
2.1. Paper 1/Objective 1 methodology....56
2.1.1. Study design and study setting....56
2.1.2. Study participants....59
2.1.3. Measurement of chronic conditions and classifications....59
2.1.4. Outcome measurement....60
2.2. Paper 2/Objective 2 methodology....61
2.2.1. Study design, study setting and participants.....61
2.2.2. Measurement of chronic conditions and classifications....62
2.2.3. Outcome measurement....63
2.3. Paper 3/Objective 3 methodology....64
2.3.1. Study design and study setting and participants....64
2.3.2. Characteristic of the recruitment sites in SSA....64
2.3.3. Measurement of chronic conditions and classifications....68
2.3.4. Outcome measurement....69
2.4. Data management....69
2.5. Ethical Considerations....70
3. CHAPTER THREE: PAPER 1....72

3.1. Introduction 72
3.2. Methods 75
3.2.1. Study design and study setting 75
3.2.2. Recruitment of cases and controls 76
3.2.3. Procedure 76
3.2.4. Anthropometric data and other measurements 77
3.2.5. Blood measurements 77
3.2.6. Comorbidity measurements and classifications 78
3.2.7. Outcome measurement 78
3.2.8. Statistical analysis 79
3.3. Results 80
3.4. Discussion 87
4. CHAPTER FOUR: PAPER 2 92
4.1. Introduction 92
4.2. Methods 94
4.1.1. Recruitment of participants 95
4.1.2. Study procedures 96
4.1.3. Socio-demographic and anthropometric measures 96
4.3. Statistical analysis 99
4.4. Results 100
4.5. Discussion 113
4.6. Supplementary tables 118
5. CHAPTER FIVE: PAPER 3 121
5.1. Introduction 121
5.2. Methods 123
5.2.1. Study design and study setting 123
5.2.2. Participants 124

5.2.3. Statistical methods 126
5.3. Results 126
5.3.1. Prevalence of chronic conditions and multimorbidity 127
5.3.2. Determinants of chronic conditions 133
5.3.3. Influence of pre-existing morbidities on stage at diagnosis 135
5.4. Discussion 138
5.4.1. Summary of findings 138
5.4.2. Major prevalent chronic conditions: in the population as risk factors for breast cancer and impact on prognosis 138
5.4.3. Determinants of chronic conditions 140
5.4.4. Impact on stage 141
5.4.5. Strengths and limitations 141
5.4.6. Implications on therapeutic management 141
5.5. Conclusion 142
5.6. Supplementary Tables 143
6. CHAPTER SIX: INTEGRATED DISCUSSION AND CONCLUSION 147
6.1. Key findings 147
6.2. Emerging research themes from the findings 151
6.2.1. Methodological theme 151
6.2.2. Empirical theme 153
6.3. Conceptual framework 156
6.4. Implications 159
6.5. Future research 163
6.6 Limitations 164
6.7 Conclusion 165
REFERENCES 166
APPENDICES 203

LIST OF FIGURES

Figure 1.1: Projected burden of disease in SSA, 2008 and 2030. 26
Figure 1.2: Bar Chart of Region-Specific Incidence and Mortality Age-Standardized Rates for Cancers of the Female Breast in 2018 30
Figure 1.3: Conceptual diagram showing the determinants of stage at diagnosis and treatment decision in women with breast cancer. 32
Figure 1.4: Chronic conditions and risk factors associated with multi-morbidity and its outcomes in women with breast cancer. 48
Figure 2.1: Map of Soweto, Johannesburg in Gauteng Province, South Africa 58
Figure 2.2: Map of SABCHO study centres in South Africa 62
Figure 2.3: Map of ABC-DO study centres in sub-Saharan Africa 66
Figure 4.1: Percentage of women newly diagnosed with breast cancer from each hospital site in South Africa, with none, one, two or more of obesity, self-reported hypertension, self-reported diabetes, self-reported cerebrovascular disease, self-reported asthma/COPD, HIV and self-reported prior tuberculosis. 104
Figure 5.1: The prevalence of chronic conditions in women with breast cancer in the ABC-DO cohort by age group. 131
Figure 5.2: Profile of the combination of seven pre-existing morbidities amongst breast cancer patients in ABCDO study. 132
Figure 5.3: Odds ratios of women being diagnosed with advanced stage breast cancer (stages III & IV) associated with each of the seven chronic conditions examined, by sub-Saharan Africa countries in the ABC-DO breast cancer cohort. 136
Figure 6.1: Five Stages of the Nutrition Transition 154
Figure 6.2: Revised conceptual framework for the associations of multimorbidity with stage at diagnosis and treatment decision in women with breast cancer. 157

LIST OF TABLES

Table 1.1: Breast cancer staging (American Joint Committee on Cancer). 36
Table 2.1: WHO classification of obesity 60
Table 3.1: Socio-demographic profile and disease risk in women with and without breast cancer in Soweto women. 80
Table 3.2: Frequency of metabolic diseases* in women from the SABC study, overall and by case/control status. 82
Table 3.3: Frequency of at least one metabolic disease* depression and HIV in women from the SABC study, overall and by case/control status 83
Table 3.4: Bivariate analysis of variables associated with advanced stage presentation (stages III & IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa 84
Table 3.5: Multiple logistic regression models of factors influencing advanced stage presentation (stages III and IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa 86
Table 4.1: Characteristics of the hospital sites 98
Table 4.2: Socio-demographic characteristics, prevalence of chronic conditions and stage at breast cancer diagnosis in women newly diagnosed with breast cancer in South Africa, by study-site. 101
Table 4.3: Pooled multivariate logistic regression model of socio-demographic characteristics and association with chronic conditions in women newly diagnosed with breast cancer in South Africa. 106
Table 4.4: Pooled associations between socio-demographic, geographical and behavioural factors with chronic conditions (≥2 (multimorbidity) vs. <2) in women newly diagnosed with breast cancer 107
Table 4.5: Pooled multiple logistic regression model of socio-demographic, geographical and behavioural factors associated with ≥2 chronic conditions (multimorbidity) in women newly diagnosed with breast cancer. 109
Table 4.6: Pooled bivariate analyses of the association between chronic conditions and advanced stage disease amongst women newly diagnosed with breast cancer. 110
Table 4.7: Pooled multivariate logistic regression models of chronic conditions associated with advanced stage disease (stages III-IV) in women newly diagnosed with breast cancer. 111

Table 4.8: Association between multimorbidity and first treatment received by stage at diagnosis in women newly diagnosed with breast cancer. 112
Table 5.1: Characteristics of women newly diagnosed with breast cancer in Sub-Saharan Africa, by country-site; ABC-DO breast cancer cohort.....128
Table 5.2: Prevalence of pre-existing chronic conditions in women newly diagnosed with breast cancer in Sub-Saharan Africa, by country-site; ABC-DO study. 128
Table 5.3: Associations of socio-demographic characteristics with each chronic conditions, among breast cancer patients in Sub-Saharan Africa, ABC-DO study. ORs are mutually adjusted. 134
Table 5.4: Multiple logistic regression models of chronic conditions and presence of multimorbidity (≥2 chronic conditions) as predictors of advanced stage breast cancer (stages II & IV) in women newly diagnosed with breast cancer in Sub-Saharan Africa, ABC-DO breast cancer cohort. 137
Table 6.1: Summary of research findings per study objectives 148

PEER REVIEWED PUBLICATIONS (PHD)

Paper 1 (Chapter 3, article published in South African Journal of Medicine. 2019)

Ayeni, O.A., Joffe, M., Cubasch, H., Rinaldi, S., Taljaard, C., Vorster, E., Romieu, I. and Norris, S.A., 2019. Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: Results from the SABC study. *SAMJ: South African Medical Journal, 109(4), pp.264-271.*

Paper 2 (Chapter 4, article published in International Journal of Cancer. 2020)

Ayeni, O.A., Norris, S.A., Joffe, M., Cubasch, H., Nietz, S., Buccimazza, I., Singh, U., Čačala, S., Stopforth, L., Chen, W.C. McCormack, V.A., O'Neil, D.S., Judith S. Jacobson, J.S., Neugut, A.I., Ruff, P., and Micklesfield, L.K. The multimorbidity profile of South African women newly diagnosed with breast cancer. *Published online: October 2019, International Journal of Cancer, 147*(2), pp.361-374.

Paper 3 (Chapter 5)

Ayeni, O.A., Norris, S.A., Joffe, M., Cubasch,H., Galukande, M., Zietsman, A., Parham, G., Adisa, C., Anele, A., Schüz, J., Anderson, B.O., Foerster, M., PhD[9], dos Santos Silva, I., McCormack, V.A., Pre-existing morbidity profile of women newly diagnosed with breast cancer in sub-Saharan Africa: African Breast Cancer—Disparities in Outcomes (ABC-DO) study. *Published online ahead of print, Nov 12 2020, International Journal of Cancer, doi: 10.1002/ijc.33387.*

POSTER PRESENTATIONS

Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: results from the SABC study. *Breast Interest Group of Southern Africa (BIGOSA) 2019 Annual Scientific Meeting, Johannesburg, South Africa. Oct, 2019*

The multimorbidity profile of South African women newly diagnosed with breast cancer *Breast Interest Group of Southern Africa (BIGOSA) 2019 Annual Scientific Meeting, Johannesburg, South Africa. Oct, 2019*

The multimorbidity profile of South African women newly diagnosed with breast cancer. *The African Organization for Research and Training in Cancer (**AO**RTIC) 12th international Conference on Cancer in Africa; Maputo, Mozambique. Nov, 2019*

Multimorbidity profile of women newly diagnosed with breast cancer in sub-Saharan Africa: African Breast Cancer-Disparities in Outcomes (ABC-DO) study. *University of the Witwatersrand, Faculty of Health Sciences Virtual Research Day and Postgraduate Expo. 15th October 2020.*

HONOURS AWARDED TO PhD CANDIDATE

Postgraduate Merit Award (PMA). *University of the Witwatersrand. (2018-2020)*

ACRONYMS AND ABBREVIATIONS

ABC-DO	Africa breast Cancer Disparity in Outcomes
ART	Antiretroviral therapy
ASIR	Age-specific incidence rate
BMI	Body mass index
CBE	Clinical breast examination
CD	Communicable diseases
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COPD	Chronic obstructive pulmonary disease
DALYs	Disability-adjusted life-years
DPHRU	Developmental Pathways for Health Research Unit
ELISA	Enzyme-linked immunosorbent assay
HICs	High income countries
HIV	Human immunodeficiency virus
HR	Hormone responsive
HSES	Household socio-economic status
ICD	Infectious chronic diseases
KZN	KwaZulu-Natal
LMICs	Low and middle income countries
NADC	Non-AIDS defining cancer
NCDs	Non-Communicable diseases
NHLS	National Health Laboratory Services
OR	Odds ratio
QOL	Quality of life
SABC	South African Breast cancer
PLHIV	People living with HIV
SABCHO	South African Breast Cancer and HIV Outcomes
SBE	Self-breast examination
SD	Standard deviation
SDGs	Sustainable development goals

SEP	Socio-economic position
SSA	Sub-Saharan Africa
UN	United Nations
WHO	World Health Organization

ABSTRACT

Background

Multimorbidity (the co-occurrence of two or more chronic conditions in one person) poses a challenge to patient care in South Africa and sub-Saharan African (SSA) countries in transition. Breast cancer remains the most common cancer among women worldwide and is a major contributor to women's cancer deaths. The mortality-to-incidence ratios are among the highest globally, mainly due to advanced stage at diagnosis and suboptimal management.

Presence of existing chronic conditions at the time of breast cancer diagnosis may further challenge breast cancer control in SSA. Multimorbidity in women with breast cancer can be burdensome, may negatively influence time to and stage at presentation, negatively impact treatment decisions and outcomes. Multimorbidity in breast cancer patients may present challenging considerations for targeted patient-oriented prevention, diagnosis, treatment, disease control and improved outcome control strategies. The burden of multimorbidity in women with breast cancer, its determinants and impact on stage at diagnosis and cancer treatment decisions in South Africa and SSA is yet to be understood.

Aim

The overall aim of this thesis was to determine the prevalence and patterns of chronic conditions and multimorbidity in women with breast cancer and its associations with stage at diagnosis and cancer treatment decisions in SSA.

The following specific study objectives addressed this aim: 1) To characterize and compare socioeconomic factors and chronic conditions among women with breast cancer from Soweto, South Africa and their age and neighbourhood matched controls; 2) To assess the multimorbidity burden of women newly diagnosed with breast cancer in 5 public hospitals in South Africa and the associations of these chronic conditions and multimorbidity with breast cancer stage at diagnosis and first breast cancer treatment received; 3) To determine profiles

and patterns of chronic conditions and multimorbidity in women newly diagnosed with breast cancer in 5 countries in SSA and their associations with stage at diagnosis.

Methods

This thesis utilizes three cohorts with increasing context and environmental complexity for women with breast cancer, to address its objectives and test the same hypotheses in order to identify unique and universal findings. The first is a single country local region cohort,

The second comprises a regional five site cohort from different regions of the same country and the third covers five countries in SSA with varying income status.

Cohort 1 (Objective 1) is a population based case-control study on breast cancer among black women, in Soweto, South Africa. Cohort 2 (Objective 2) is a cohort of women newly diagnosed with breast cancer at 5 academic public hospitals in Gauteng and KwaZulu Natal provinces of South Africa. Cohort 3 (Objective 3) is a multi-country cohort of women newly diagnosed with breast cancer in SSA.

Data on sociodemographic factors, self-reported chronic conditions, blood pressure and anthropometric measurements, HIV-status and point-of-care lipid and glucose levels were collected. Sociodemographic associations with individual chronic conditions and multimorbidity (≥2 of chronic conditions) were explored. Associations between individual chronic conditions and multimorbidity with stage at diagnosis of breast cancer (advanced (III-IV) vs. early (I-II)) were analysed using multivariable logistic regression models. Finally, association of multimorbidity with first breast cancer treatment received was determined.

Result

The prevalence of multimorbidity in these three cohorts of women with breast cancer ranged from 27-44%. For individual chronic conditions the prevalence was higher for hypertension (range: 32-59%), obesity (35-57%), and HIV (16-22%) than for diabetes (7-14%), tuberculosis (4-7%) and asthma/ chronic obstructive pulmonary disease (COPD) (4-5%). There is a steady

increasing trend for hypertension and obesity with increasing wealth status of country. Older women and those with higher socioeconomic status were more likely to have obesity, hypertension, diabetes and multimorbidity and were less likely to be HIV positive, this finding is consistent across settings. In the multivariable regression model, multimorbidity was not associated with advanced stage breast cancer at diagnosis across settings but for self-reported hypertension there was less likelihood of being diagnosed with advanced stage disease in the adjusted models across settings. Obesity was also associated with early stage breast cancer at diagnosis only in the multi-country cohort. Women with multimorbidity were less likely to have surgery, less likely to receive chemotherapy and more likely to receive endocrine therapy compared to women without multimorbidity in those with early stage breast cancer, p=0.003.

Conclusion

The prevalence of multimorbidity is high among patients with breast cancer across different settings in SSA, mainly driven by socio-demographic factors, notably higher socio-economic status across different settings. These universal findings are particularly worrying and require urgent intervention. There is need to further understand the down-staging impact of hypertension and obesity on stage at diagnosis and the impact of multimorbidity on breast cancer outcomes. Multimorbidity had a significant negative impact on first treatment received in those with early stage disease, which may negatively impact survival outcomes.

PREFACE

I have never shied away from intellectual stimulation. However, my interest in pursuing a PhD was not really concrete until I serendipitously found myself in the company of Dr Maureen Joffe and the Non-Communicable Disease Research (NCDRD) team of the Wits Health Consortium in 2016. A timely recommendation by Prof Tobias Chirwa, the then Head of the Division of Epidemiology and Biostatistics and stimulating discussions with great minds, among others, kindled my interest and ultimately culminated in this thesis.

While in medical school and during my internship years in the Academic hospital back home in Nigeria, I have always pondered on why most of the women we see with breast cancer present with very advanced stage disease and what could have contributed to the delay in presentation and diagnosis. Finding myself in South Africa in 2014 and after deciding that going back to school was the easiest and fastest way of integrating into the society, I decided to pursue a master's degree in Epidemiology in the School of Public Health. Grappling with multiple health challenges has its deleterious consequences, not least for women living in Africa. There is a research gap in the field of breast cancer in Africa in relation to multimorbidity and its effects and this PhD thesis intends to fill at least part of that gap.

This PhD thesis should be of interest particularly to medical and public health practitioners, health system managers and policy makers, epidemiologists and specialists involved in communicable and non-communicable diseases management in general.

Summarised below is the outline of this thesis:

PART 1: INTRODUCTION

Chapters 1 and 2 include the background of the study comprising the problem statement, introduction of key concepts, conceptual framework, literature review and methods for this series of studies.

PART 2: EMPIRICAL CHAPTERS

Chapters 3-5 contain details of the studies undertaken and papers published during the course of the PhD.

1. Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: results from the SABC study - chapter 3.
2. The multimorbidity profile of South African women newly diagnosed with breast cancer – chapter 4.
3. Pre-existing morbidity profile of women newly diagnosed with breast cancer in Sub-Saharan Africa: African Breast Cancer—Disparities in Outcomes (ABC-DO) study – chapter 5.

PART 3: INTEGRATED DISCUSSION AND CONCLUSION

Chapter 6 comprises an integrated discussion of the thesis, it includes the main research findings, and identification of critical themes, a re-evaluation of the conceptual frameworks used in this thesis, relevance and implication of the study findings and concludes with the study strengths and limitations.

PART ONE: INTRODUCTION

"Strength does not come from winning. Your struggles develop your strengths. When you go through hardships and decide not to surrender, that is strength" – Mahatma Gandhi

1. CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

1.1. Global burden of Non-Communicable Diseases (NCDs)

Non-communicable diseases (NCDs) account for approximately 41 million deaths each year, equivalent to 71% of all deaths globally with over 80% of deaths occurring in low and middle income countries (LMICs)(World Health Organization, 2017). Among NCDs, the four top killers that together account for over 80% of all premature NCDs deaths include cardiovascular diseases (17·9 million deaths annually), cancers (9·0 million), chronic respiratory diseases (3·9 million), and diabetes (1·6 million) (Forouzanfar et al., 2016). The burden of NCDs continue to rise especially in LMICs and most deaths occur in the productive years resulting in barriers in achieving developmental goals which include economic stability, poverty reduction and health equity (Beaglehole et al., 2011). The global recognition of the growing challenges posed by NCDs is reflected in the United Nations (UN) Sustainable Development Goals (SDGs), which include a target of 30% reduction in premature deaths due to major NCDs by 2030 (United Nations, 2019). Like in High Income countries (HICs), the major NCDs that are becoming an epidemic in LMICs are cardiovascular diseases, chronic lung diseases, type 2 diabetes, cancer and depression (Islam et al., 2014, Mendenhall et al., 2017, Haregu et al., 2019). Some of these major NCDs are preceded by unhealthy lifestyle behaviours followed by the emergence of metabolic risk factors and disease. The risk factors associated with NCDs are increasing age, overweight and obesity linked to dietary and sedentary lifestyles, raised blood pressure, raised blood glucose levels, raised blood cholesterol levels and abnormal lipid distributions (Ezzati and Riboli, 2013, Allen et al., 2017)

1.2. Multimorbidity and chronic conditions

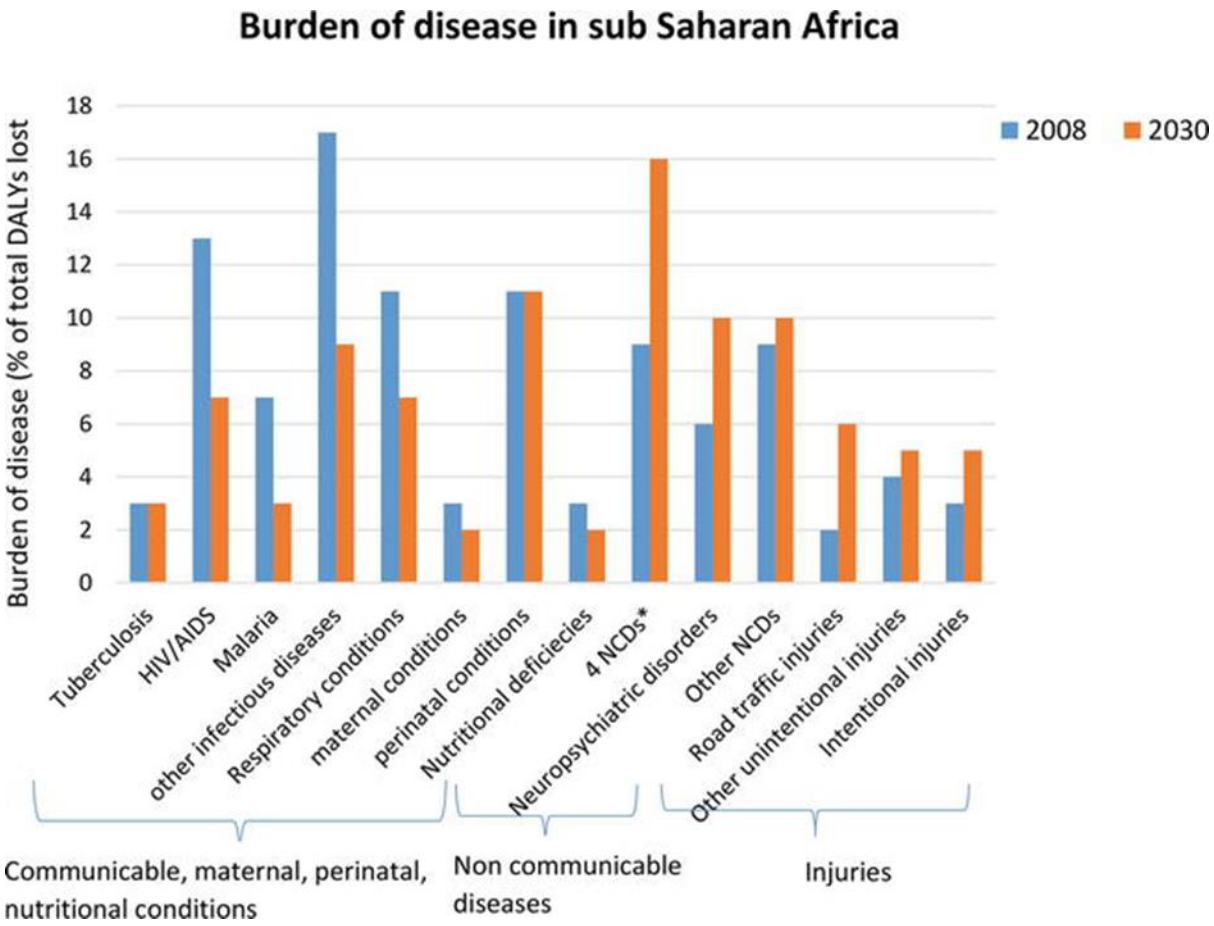
Multimorbidity has been defined as the co-occurrence of two or more chronic conditions in one person (World Health Organization, 2016a). The term “multimorbidity” is often used to

describe the coexistence of at least two medical conditions without referring to a well-defined index disease under study. In this dissertation, the term "multimorbidity" is operationally defined as: "Any existence of two or more chronic or long-term conditions in addition to breast cancer which is the disease under study". Chronic condition is defined as "any single chronic or long-term medical condition that exists at the time of breast cancer diagnosis".

1.2.1. Burden of chronic conditions and multimorbidity in sub-Saharan Africa

Many LMICs, including those in sub-Saharan Africa (SSA), are undergoing rapid epidemiological transition with an associated rising burden of NCDs (Mensah and Mayosi, 2013, Mendenhall and Weaver, 2014, Bigna et a.,. 2019, Gouda et al., 2019, Gyasi ey al., 2020). In SSA, over one million deaths are attributed to cardiovascular diseases each year and about 48% of the adult population in some SSA countries are hypertensive (Daniel et al., 2011, Roth et al., 2015, Roth et al., 2018). The prevalence of diabetes which was previously thought to be rare in rural Africa is increasing and projected to rise from 12·1 million in 2010 to 23·9 million in 2030; impaired glucose tolerance is expected to rise from 26.9 million in 2010 to 47·3 million in 2030, a 75.8% rise (Aguiree et al., 2013). The global burden of disease study showed depression increased by 37.5% between 1990 and 2010, predominantly because of population growth and ageing (Ferrari et al., 2013). Depression is also on the increase in SSA with prevalence similar to those reported from HICs (Tomlinson et al., 2009, Camara et al., 2015; Guerra et al., 2016, Duthé et al., 2016) especially among people living with human immunodeficiency virus (PLWHIV) (Bernard et al., 2017).

Figure 1.1: Projected burden of disease in SSA, 2008 and 2030.



Source of data: Authors from (World Health Organization, 2008) 4 NCDS: Cardiovascular diseases, cancer, diabetes and chronic respiratory diseases.

The SSA NCD epidemic is emerging and rapidly overtaking the existing infectious chronic disease (ICD) epidemics of tuberculosis and human immunodeficiency virus (HIV) (Levitt et al., 2011, Peer, 2015, Nyirenda, 2016) (Figure 1-1). It is projected that NCDs will overtake communicable diseases, maternal and neonatal diseases as the leading cause of morbidity and mortality in SSA by 2030 (Holmes et al., 2010, Nugent et al., 2018, Bigna and Noubiap, 2019). The devastating impact is an increase in disability-adjusted life-years (DALYs) due to NCDs in SSA, from 90·6 million DALYs in 1990 to 151·3 million DALYs in 2017 (Gouda et al., 2019).

HIV/Acquired immunodeficiency syndrome (AIDS) is a leading cause of morbidity and mortality in SSA (Roth et al., 2018). The global HIV epidemic and burden is disproportionately concentrated in SSA, where in 2017 approximately 75% of deaths and about 65% of new infections occurred and almost 71% of PLWHIV resided (Roth et al., 2018, James et al., 2018). There is a wide variation in the estimates of HIV prevalence across SSA with the highest prevalence concentrated in southern Africa countries (James et al., 2018). In South Africa, the HIV prevalence rate for adults aged 15 to 49 is 19.0% (STATSSA, 2018). With successful SSA antiretroviral (ARV) rollout programmes, HIV is becoming a well-managed chronic disease associated with increased life expectancy and increased age and lifestyle-associated multimorbidity. The double burden of communicable diseases and NCDs could have a devastating impact on a region that already has significant healthcare resource constraints unless appropriate intervention strategies are put in place to respond effectively to these changing health needs.

1.3. Global burden of cancer

Cancer is one of the major causes of morbidity and mortality globally with an estimated 18.1 million incident cases in 2018 and approximately 9.6 million deaths; it is expected to rank as the leading cause of death globally and the single most important barrier to increasing life expectancy in all countries of the world in the 21st century (Bray et al., 2018). According to the world health organization (WHO), cancer is currently the second leading cause of NCD deaths accounting for 22% of the total (World Health Organization, 2018). By 2025, over 20 million newly diagnosed cancer cases are expected annually (Morgan et al., 2018). Cancer was ranked as the first or second cause of premature death in almost 100 countries worldwide (Bray et al., 2019) with clustering occurring in LMICs, mainly in Africa, South-East Asia and Eastern Mediterranean regions (Martinez et al., 2017).

In LMICs, due to demographic and epidemiologic transitions associated with increasing life expectancy and westernized lifestyle transitions, the cancer incidence is rapidly rising with high mortality as a result of advanced stage at diagnosis.

1.3.1. Challenges of cancer management in sub-Saharan Africa

Sub-Saharan Africa contains 13% of the world's population, carries more than 24% of the global disease burden, with only 3% of the health workforce globally and less than 1% of the global financial resources to cope with its disease burden(Edge et al., 2014, Agyepong et al., 2017). It has few formalized cancer control programs, and insufficient infrastructure and personnel to cope with steadily increasing cancer incidences (Edge et al., 2014, Stefan, 2015). The economic burden of cancer is profound; it includes high costs of treatment as well as costs to society and families faced with loss of productivity and income associated with premature death and increased caregiver burdens (Luengo-Fernandez et al., 2013, de Oliveira et al., 2018, Longacre et al., 2018). The cost of cancer management thus poses unique challenges in SSA, due to insufficient resources to cope with increasing health system demands.

1.3.2. Burden of breast cancer in sub-Saharan Africa

There is a scarcity of high-quality data on the incidence and mortality associated with breast cancer in SSA due to a limited number of population-based cancer registries in the region (Forman et al., 2013). However, the few available estimates indicate that both incidence of breast cancer and breast cancer death in SSA is increasing (Ferlay et al., 2015, Bray et al., 2018).

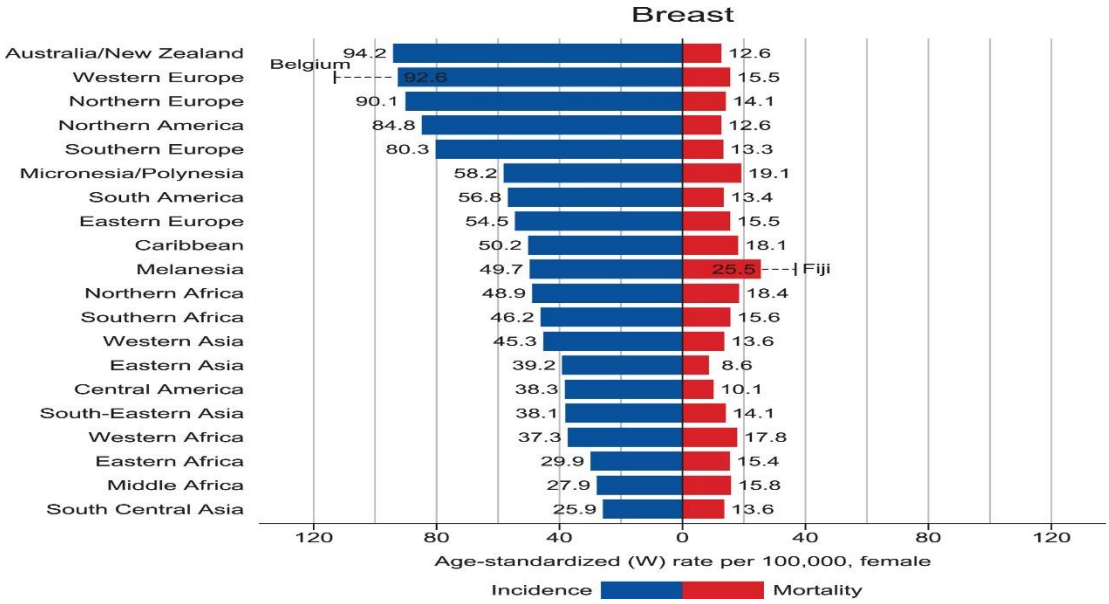
Breast cancer remains the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide, with an estimated 2.1 million cases diagnosed in 2018 and over 625,000 deaths accounting for 6.6% of the total female deaths from cancer globally (Bray et al., 2018). Although breast cancer was once considered a disease of affluence, its reported

incidence is rising rapidly in LMICs where almost half of the total breast cancer cases and 58% of deaths now occur (Bray et al., 2018).

South Africa has the highest age-standardized incidence rate (ASIR) of breast cancer in SSA with 35.9 per 100,000 (South African National Cancer Registry, 2016). The GLOBOCAN ASIR of breast cancer per 100,000 is modelled at 46.2 among Southern Africa women, 37.3 among Western African women and 29.9 among East Africa women. These rates are substantially lower than those reported for North America and Europe; 54.5 in women from Eastern Europe, 84.8 in North American women and 92.6 in women from Western Europe (Bray et al., 2018) (Figure 1.2) probably due to under-reporting linked to absence of population screening. These rates are substantially lower than those reported for North America and Europe; 54.5 in women from Eastern Europe, 84.8 in North American women and 92.6 in women from Western Europe (Bray et al., 2018) (Figure 1.2) probably due to under-reporting linked to absence of population screening. There's also lower incidences in the older age-groups in SSA due to fewer reproductive (early age at first birth, more children and longer duration of breast feeding compared with women from HICs) and lifestyle factors.

In contrast to the relatively lower reported incidence rate, the mortality in SSA (15.6 per 100,000 in Southern Africa) is estimated to be as high as that recorded in Western and Eastern Europe (15.5 per 100,000) and much higher than that in Northern America (12.6 per 100,000) (Figure 1.2).

Figure 1.2: Bar Chart of Region-Specific Incidence and Mortality Age-Standardized Rates for Cancers of the Female Breast in 2018



Source: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries (Bray et al., 2018).

In HICs, breast cancer generally has a favorable prognosis at 80% 5-year survival among African-American black women and 91% among Caucasian women (Howlader et al., 2015). This is due to population screening, early stage at diagnosis and good diagnostic and treatment resources. In contrast, the 5-year survival estimates for SSA are below 50% due to late stage at diagnosis and inadequate diagnostic and treatment programmes (Anyanwu, 2000, Swaminathan et al., 2011, Popoola et al., 2012, Anele et al., 2014, Galukande et al., 2015).

1.3.3. Burden of breast cancer in South Africa

As in other parts of the world, breast cancer is the most common cancer among women in South Africa accounting for 22.6% of all female cancers (South African National Cancer Registry, 2016). Breast cancer incidence among South African women is reported by the National laboratory-based Cancer Registry at 35.9 per 100 000 (ASIR) and accounts for 16% of cancer

deaths amongst women. The incidence of breast cancer among South African women is steadily increasing and large differences in incidence among different ethnic groups are reported. In 2016, the ASIR for Blacks, Mixed race, Asians, and Whites were 22.6, 48.8, 50.9 and 84.6 per 100,000, respectively (South African National Cancer Registry, 2016)

1.4. Conceptual Model and Theoretical Framework

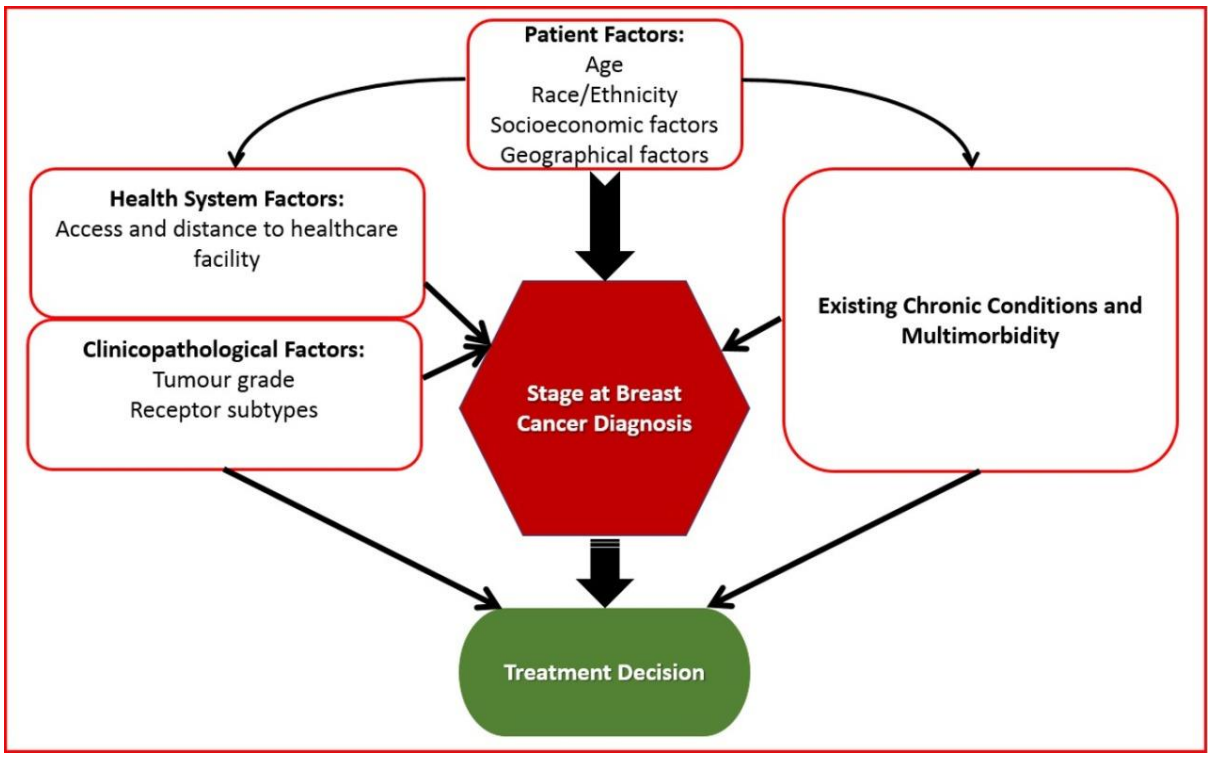
Multimorbidity and its determinants have been widely investigated especially in the elderly and in primary care settings both in HICs (Salisbury et al., 2011, Violan et al., 2014, Roberts et al., 2015, Picco et al., 2016, Sakib et al., 2019) and LMICs (Wang et al., 2015, Nunes et al., 2018) but only few studies have been undertaken in SSA (Ataguba, 2013, Alaba and Chola, 2013) and none have specifically looked at the burden of multimorbidity in women with breast cancer.

Barriers and factors influencing stage at presentation of breast cancer have been described extensively in the literature from HICs and LMICs, but only a limited number of studies in SSA have been published on this topic (Jedy-Agba et al., 2017, Joffe et al., 2018, McKenzie et al., 2018a). Several studies from HICs have also focused on individual chronic conditions as a form of barriers to care and their negative effect on stage at breast cancer diagnosis (Vaeth et al., 2000, Sheppard et al., 2011, Gurney et al., 2015) but few have focused on multimorbidity as a whole and its association with breast cancer stage at diagnosis and treatment received (Meneses et al., 2015). The burden of multimorbidity in SSA women with breast cancer and the effect of multimorbidity on stage at breast cancer presentation and treatment approaches need to be investigated and better understood in order to seek optimum patient management solutions in limited-resource settings.

The conceptual framework of the thesis (Figure 1.3) illustrated below highlights the various factors that may contribute to stage at breast cancer diagnosis and treatment decisions. These

factors have been grouped into patient factors, their existing chronic conditions and multimorbidity, their breast cancer clinical factors and health system factors. This conceptual framework was an adaptation of the classic bio-psychosocial theoretical model (Engel, 1981) and Andersen model of total patient delay (Andersen et al., 1995) and its applications in cancer diagnosis (Walter et al., 2012). It incorporates patient factors, disease factors and health care provider factors that impact stage at breast cancer diagnosis. This study goes a step further by including the effect of these factors on treatment decisions.

Figure 1.3: Conceptual diagram showing the determinants of stage at diagnosis and treatment decision in women with breast cancer.



1.5. Literature Review

1.5.1. Development and risks of breast cancer

Breast cancer is a malignant tumour that starts in the cells of the breast. It is a heterogeneous group of tumours presenting with varying characteristics, responses to treatment and associated

treatment options and prognosis (Goldhirsch et al., 2013). Like many other cancers, there are several factors that can increase the risk of developing breast cancer. Established breast cancer risk factors include age; gender; family history and genetic predisposition; reproductive history; postmenopausal overweight and obesity; lack of physical activity and alcohol consumption (Tirona et al., 2010, Barnard et al., 2015, Tamimi et al., 2016)**.**

Being a woman is the main risk factor for breast cancer as it is about 100 times more likely to occur in women than in men. Increasing age inevitably increases one's risk of breast cancer as evinced by the fact that most breast cancers are diagnosed in women aged 55 years and older.

Hormone responsive (HR) breast cancers use oestrogen for growth (Zardavas and Piccart, 2015), respond heterogeneously to treatment (Ying et al., 2013, Saleh et al., 2014) and represent the majority (approximately 70%) of incident cases (Dickens et al., 2014, Howlader et al., 2014). They have oestrogen (ER) and progesterone (PR) receptors, predictive for response to long term targeted endocrine treatments, proven to substantially increase survival (Charehbili et al., 2014, Levasseur et al., 2015). Oestrogen is the main regulator of cell proliferation in normal breast tissue through its receptors. The aetiology of hormone receptor positive tumours are suggested to be linked to cumulative estrogen exposure and associated sex hormonal-related risk factors (Ritte et al., 2013). These tumours respond positively to anti-hormonal therapy that blocks the oestrogen receptor for oestrogen uptake (Williams and Lin, 2013). Other mechanisms by which estrogen can cause breast cancer is by induction of aneuploidy and direct genotoxic effects through a cytochrome P450-mediated metabolic activation thereby increasing mutation rates (Kulendran et al., 2009).

A woman’s risk of breast cancer is increased if she has a family history of the disease. The highest risk is associated with increasing number of first degree relatives diagnosed with breast cancer at a young age (under age 50) (Colditz et al., 2012). Overall, about 5–10% of breast cancers are linked to gene mutations inherited from a parent. The most common cause of

hereditary breast cancer is an inherited mutation in the breast cancer (BRCA) 1 or 2 gene mutation (Colditz et al., 2012, Allison et al., 2012). Women with a BRCA1 mutation have a 55–65% lifetime risk of developing breast cancer while for women with a BRCA2 mutation, the lifetime risk is 45% (Feng et al., 2018). Also, majority of African breast cancer genetic studies remain restricted to the investigation of BRCA1 and BRCA2 genes and differences in their mutations spectrum (Abbad et al., 2018). In SSA, there is a gap in the availability of routine genetic testing and counselling services and inaccurate reporting of a family history of cancer.

Reproductive history such as early menarche, nulliparity, late age at first birth, short duration of breast feeding and late menopause are known risk factors for breast cancer (Tirona et al., 2010, Barnard et al., 2015, Tamimi et al., 2016)**.** Recent findings from the South African Breast Cancer (SABC) study shows that none of these reproductive factors were associated with breast cancer in the whole cohort; however, restricting the analysis to HIV-negative pre-menopausal women, later age at first pregnancy and longer time between menarche and first full-time pregnancy were inversely related to breast cancer risk (Romieu et al., 2021).

In addition, diabetic patients have hyperinsulinemia which has been associated with increased breast cancer risk, and may impact cancer proliferation and morphology (De Bruijn et al., 2013). Use of postmenopausal hormone replacement therapy (HRT) with combined estrogen and progestin is known to increase risk of breast cancer, in particular when therapy is initiated close to menopause (Chlebowski et al., 2013). Many risk factors, medical conditions (e.g. obesity, diabetes mellitus in post-menopausal women) and some pharmacological treatment such as digoxin use (Ahern et al., 2014) may therefore increase breast cancer risk.

1.5.2. TNM staging of Breast Cancer

American Joint Committee on Cancer (AJCC) has classified breast cancer using the tumour, node, metastasis (TNM) staging system (Amin and Edge, 2017). The TNM staging takes into account the size of the tumour (T), involvement of lymph node (N), and the presence or absence of metastasis (M). Staging is used for treatment decision making and prognostic assessments.

Tumour Size (T)

Tumour size (T) is an important component in staging breast cancer, treatment decision making and is also a predictor of survival; smaller tumours are associated with better prognosis (Narod, 2012). T0 means there is no evidence of the primary tumor while Tis means the cancer is "in situ" (the tumour has not grown into healthy breast tissue). T1 size is < 2 centimetres (cm) in diameter, T2 size is 2-5cm in diameter, T3 size is >5cm in diameter whereas T4 size involves a tumour of any size with extension to the chest wall or skin.

Lymph node involvement (N)

Regional lymph node involvement is important in the staging of breast cancer because breast cancer can spread through the lymphatic system to the lymph nodes. NX is when the lymph node cannot be assessed, N0: if there is no lymph node involvement, N1: involvement of the ipsilateral lymph node, N2: if the ipsilateral lymph nodes are matted or fixed to other structures, N3: involvement of the ipsilateral infraclavicular lymph node (s), or ipsilateral supraclavicular lymph node(s) or involvement of ipsilateral internal mammary lymph node(s), (Table 1.1).

Metastases (M)

The M component of the TNM staging is determined by the absence (M0) or presence of metastases (M1) to distant body organs (Table 1.1). In cases where metastases cannot be assessed, it is reported as MX.

Table 1.1: Breast cancer staging (American Joint Committee on Cancer).

AJCC Anatomical/ Prognostic Staging			
Stage	**T**	**N**	**M**
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

- *T1 includes T1mi (Tumour ≤ 1 mm in greatest dimension)
- ** T0 and T1 tumours with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

1.5.3. Early versus Advanced/Late breast cancer

Stage I breast cancer: The cancer is still relatively small (T size < 2cm) and either has not spread to the lymph nodes or have only a tiny area of cancer spread in the sentinel lymph node (the first lymph node to which cancer is likely to spread).

Stage II breast cancer: These breast cancers are larger than stage I cancers (T size 2-5cm) and/or have spread to a few nearby lymph nodes.

Stage III breast cancer: Termed locally advanced breast cancer. These tumours are larger (T size > 5cm) or they have spread to many nearby lymph nodes.

Stage IV breast cancer: The cancer has spread beyond the breast and nearby lymph nodes to other parts of the body.

Stages I and II are termed "Early stage" breast cancer while stages III and IV are termed "Advanced/Late Stage" breast cancer. Table 1-1 shows the various combinations of T, N and M to give stages I, II, III and IV.

1.5.4. Breast cancer and stage at diagnosis in sub-Saharan Africa and South Africa

The mortality to incidence ratios of breast cancer in SSA is the highest globally, due mainly to advanced stage at diagnosis, concurrent multimorbidity (the co-existence of two or more chronic conditions) and suboptimal management (Torre et al., 2015, Lancet, 2018). Research has found that early detection and early stage at diagnosis is the most important factor for better prognosis of several kinds of cancer including breast cancer (Chu et al., 1996). Approximately 61% of women from SSA present with advanced stage breast cancer at diagnosis with poor prognostic outcomes (McKenzie et al., 2018a).

Primary prevention of breast cancer is aimed at controlling the exposure to known risk factors for breast cancer (Colditz and Bohlke, 2014). However, many of the established risk factors for breast cancer (e.g. reproductive-related factors) are not amenable to change in modern societies. Hence, primary prevention of breast cancer has been restricted to established modifiable risk factors such as lack of physical activity, postmenopausal excess weight, alcohol intake, use of exogenous hormones, exposure to ionizing radiation and prophylactic hormone treatments for patients assessed to be at high risk for breast cancer. Primary prevention, while

important in cancer control, is not likely to prevent most breast cancers in SSA. Thus, early detection to improve the survival and outcomes from breast cancer remains the cornerstone of breast cancer control in the region (Harford, 2011, World Health Organization, 2020).

The goal of secondary prevention of breast cancer is either to detect asymptomatic breast cancer through mammographic screening or to detect symptomatic breast cancer at an early stage when treatment is more effective and also more likely to lead to better survival (Kolak et al., 2017). In early stage disease, breast cancer is largely asymptomatic (Di Gioia et al., 2015) and population based mammography screening programs have been implemented in HICs which has led to an increase in the proportions of early stage breast cancers diagnosed (Berry et al., 2005). In SSA population-wide breast cancer screening is neither affordable nor feasible due to resource constraints as previously mentioned (Harford et al., 2011, Tsu et al., 2013). Furthermore, mammography is less effective for the younger population of SSA due to greater breast tissue density in younger women. In addition, tumour stage at first presentation is typically far more advanced compared to HICs settings (McCormack et al., 2013, Jedy-Agba et al., 2016). In settings that cannot afford population based mammographic screening the main methods of secondary prevention of breast cancer used are self-breast examination (SBE) and provider initiated clinical breast examination (CBE). CBE has been recommended in LMICs for women 40 years of age and older, to attain SDG 3 to reduce by one third mortality from cancer and other NCDs by 2030 (Mittra et al., 2010, Morgan et al., 2018). The Breast Health Global Initiative recommends CBE as a diagnostic tool and a necessary resource for both LMICs and HICs (Anderson et al., 2011). Both SBE education for communities and CBE education for providers can contribute to increase in the awareness of breast cancer and earlier stage at diagnosis, particularly in SSA where the general knowledge among communities and primary care providers is limited (McKenzie et al., 2018b, Sayed et al., 2019). Prior to the onset

of mammography screening in the USA, improvements in the stage at breast cancer diagnosis and survival were largely due to detection of palpable breast cancers through SBE and CBE and also breast education programmes (Shulman et al., 2010). In LMICs, CBE has also been demonstrated to downstage breast cancer, including in our own Chris Hani Baragwanath Academic Hospital (CHBAH) setting (Mittra et al., 2010, Miller et al., 2014, Murugan et al., 2014, Murillo et al., 2016, Gadgil et al., 2017); however, its effect on breast cancer mortality is still under investigation.

1.5.5. Treatment of breast cancer

The aim of treatment for women with breast cancer is to prolong survival with an emphasis on reducing treatment-related side effects as much as possible. A detailed description of the treatment options for breast cancer is beyond the scope of this dissertation. Standard treatments available in HICs and Middle Income South Africa include breast surgery, systemic chemo- and endocrine therapy, radiation therapy, and palliative care (Anderson et al., 2011). Significant transformations have occurred in the systemic management of breast cancer in the past decade with the use of targeted- and immune-therapy that has significantly improved survival (Ju et al., 2018). The treatment approaches are highly dependent on stage at diagnosis of breast cancer (Maughan et al., 2010), however; other comorbid chronic conditions at diagnosis and age-related frailty factors might impact treatment decisions.

It is important to emphasize surgery is the mainstay of treatment for early stage breast cancer (stages I & II) and consists of either breast conserving surgery (BCS) or mastectomy and assessment of axillary lymph nodes. For locally advanced stage breast cancer (stage III), neoadjuvant chemotherapy or endocrine therapy is given to downsize the tumour in an attempt

for BCS, or to enable subsequent surgery for initially inoperable but non-metastatic breast cancer (DOH South Africa, 2017, Vanderpuye et al., 2017, Ruff et al., 2018)

Although radiotherapy is an important component of any oncology treatment programme, in many countries in SSA the access to radiotherapy machines is often nonexistent, and chemotherapy is too often unaffordable. Studies revealed that out of all African countries, less than 50% provided radiotherapy services and most of these services were concentrated in Egypt and Southern Africa (Abdel-Wahab et al., 2013). Overall, there is one radiotherapy machine per million people in Africa compared to 6.12 and 14.9 in Western Europe and North America respectively (Kunene and Mahlangu 2017). Such constraints have necessitated the preclusion of breast conserving surgery approaches for African countries which require post-operative radiation oncology treatment to prevent disease recurrence.

Decisions for first breast cancer treatment received and the influence of multimorbidity on such decisions were examined in this thesis. Decisions about breast cancer treatment plans are also influenced by pre-existing chronic diseases at the time of diagnosis which may restrict certain therapies (e.g. cardiac diseases and anthracyclines, trastuzumab, which necessitate routine cardiac ejection fraction measurements and where ejection fractions of less than 50% preclude these some chemotherapy agents) (Lee et al., 2011, O'Connor et al., 2012). A study conducted in the USA exploring the associations between chronic conditions and concordance with breast cancer treatment guidelines reported that women who had chronic conditions at the time of breast cancer diagnosis had 43% concordance with treatment guidelines while those without any additional morbidity had 70% concordance with treatment guidelines for breast cancer (Kimmick et al., 2014).

1.5.6. Chronic conditions and breast cancer

Metabolic diseases and breast cancer

Metabolic syndrome (excess fat around the waist, high blood sugar, abnormal cholesterol levels and high blood pressure) has been associated with increased breast cancer risks especially in post-menopausal women (Bhandari et al., 2014, Wani et al., 2017, Gezgen et al., 2012, Agnoli et al., 2015) and the prevalence of metabolic diseases in women with breast cancer could be as high as 40% (Wani et al., 2017). However, epidemiologic studies linking metabolic syndrome to cancer in SSA are scarce.

Overweight/Obesity and breast cancer

Overweight and obesity have been defined as excessive or abnormal fat accumulation that present a risk to health. A crude measure of obesity is the body mass index (BMI) which is a person's weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI ≥ 25 is considered overweight and a BMI of ≥ 30 is generally considered obese (World health organization, 2020a). According to the WHO, more than 1.9 billion adults were overweight in 2016 of which over 650 million were obese. Globally, obesity has nearly tripled since 1975 (World health organization, 2020c) and it is projected that by 2030 about 2.16 billion individuals will be overweight and 1.12 billion will be obese (Alwan, 2011). SSA has been spared from this epidemic until recently as it battled with infectious diseases such as HIV and tuberculosis, as well as under-nutrition; however, over the last century there has been a rapid rise in the prevalence of overweight and obesity and their associated chronic conditions (Tabarés Seisdedos, 2017). The prevalence of overweight and obesity varies from country to country within SSA from as low as 6.7% of the female population in Madagascar, 19.9% in Zambia, 19.9% in Uganda, 25.4% in Nigeria, to 27.9% in Namibia (Neupane et al., 2016). In

South Africa, overweight and obesity have reached epidemic proportions with 68% of women over 15 years of age being either overweight or obese (SADHS, 2016).

The emerging prevalence of obesity in SSA has been largely attributed to the rising economic development, urbanization and women empowerment (Biadgilign et al., 2017, Neupane et al., 2016) ultimately leading to nutritional transition (Steyn and Mchiza, 2014). Inappropriate diet and physical inactivity are major contributors to the rise in obesity prevalence (Alwan and MacLean, 2009) and these dietary habits and behaviours have been associated with the adoption of a more western lifestyle (Micklesfield et al., 2013). The following factors have been identified to increase risk of obesity in women in SSA: African ethnicity, being married, higher socio-economic status, inadequate/lack of exercise and expenditure on unhealthy food while smoking was associated with reduced risk of obesity (Sartorius et al., 2015). Overweight and obesity are also risk factors for other NCDs and breast cancer especially in post-menopausal women (Nagrani et al., 2016, Picon-Ruiz et al., 2017) with a significant relative risk (RR) ranging from 1.26 to 2.52 (Morimoto et al., 2002, Van den Brandt et al., 2000). It has also been associated with a worse disease free and overall survival (Lee et al., 2019). Obesity is a known risk factor for HR breast cancers, which are slower growing and less likely to be diagnosed at advanced stage (Babu et al., 2018, Nattenmüller et al., 2018). Studies from Africa (Amin, 2016) and HICs (Leung et al., 2016, Cui et al., 2002) did not show significant associations between obesity and advanced stage breast cancer.

Hypertension and breast cancer

High blood pressure, also known as hypertension, is a medical condition in which the blood vessels have persistently raised pressure (World health organization, 2020b). It is the most common cardiovascular disorder affecting about 1 billion people worldwide and remains the

highest contributor to the global burden of disease and mortality accounting for 9.4 million deaths annually (Dzudie et al., 2017, Hendriks et al., 2012, Lim et al., 2012). In some SSA countries, approximately 48% of the adult population are hypertensive (Danaei et al., 2011, Nyirenda, 2016). South Africa has the highest burden of hypertension in people > 50 years of age in SSA (Lloyd-Sherlock et al., 2014, Prados-Torres et al., 2014) with 46% of the women hypertensive (SADHS, 2016). The major determinants of hypertension in LMICs are older age, lower education, overweight and obesity (Peltzer and Pengpid, 2018, Olatunbosun et al., 2000). In breast cancer patients, the prevalence of hypertension could be as high as 37% (Kozłowska et al., 2019), a large observational study conducted in the USA showed the possibility of increased risk of breast cancer in women on treatment for hypertension (Largent et al., 2010). Studies have focused on the associations of hypertension and increased breast cancer risk (Yang et al., 2017, Han et al., 2017) but very little is known about the association (if any) of hypertension and stage at breast cancer diagnosis.

Diabetes and breast cancer

Diabetes is a metabolic disease characterized by increased levels of blood glucose, which leads over time to serious damage to the blood vessels, heart, eyes, nerves and kidneys. Type 2 diabetes is the most common type, usually in adults, occurring when the body becomes resistant to or doesn't make enough insulin (World Health Organization, 2020a).

Diabetes has emerged as a high prevalent chronic disease in SSA. It is estimated that the number of people affected by diabetes in SSA will rise from 15.9 million people in 2017 to 40.7 million by 2045 (International Diabetes Federation, 2017). In South Africa, diabetes accounted for 7% of natural causes of deaths in South African women (SADHS, 2016). Known risk factors for diabetes include old age, obesity and genetic predisposition (Forouhi and

Wareham, 2010, American Diabetes Association, 2014). There is a 20% increased risk of breast cancer in women with diabetes (Lega et al., 2018) and approximately 16% of patients who are older than 65 years of age also have type 2 diabetes (Yancik et al., 2001). Breast cancer patients with type 2 diabetes have been reported to significantly present with advanced-stage breast cancer at diagnosis compared to those without diabetes (Lipscombe et al., 2015).

High cholesterol levels and breast cancer

Cholesterol is a type of fat found in the blood. Raised cholesterol increases the risk of heart diseases and stroke by narrowing the blood vessels, thereby increasing the risk of developing a blood clot. The prevalence of hypercholesterolaemia varies across populations from 4% to 40% in women (Tolonen et al., 2004). The relationship between high cholesterol and breast cancer risk is far from conclusive with contrasting findings from large studies from HICs (Kitahara et al., 2011, Carter et al., 2017). The UK Algorithm for Co-morbidity, Associations, Length of Stay and Mortality (ACALM) registry demonstrated that women above 40 with high cholesterol were 45% less likely to develop breast cancer than those without high cholesterol (Carter et al., 2017) and of those who developed breast cancer, those with high cholesterol had 40% lower risk of death (Carter et al., 2017); in contrast to this finding, a study from a Korean registry found high cholesterol to have a positive association with breast cancer in women (Kitahara et al., 2011).

HIV and breast cancer

HIV/AIDS is a leading cause of disease burden (James et al., 2018) and the most common cause of death in SSA (Roth et al., 2018). With increasing access and use of antiretroviral therapy (ART) in SSA, the number of AIDS related deaths have steadily declined (Kharsany and Karim, 2016). With HIV now a chronic disease, it together with breast cancer among

women in particular, pose a great burden on the resources and health services in SSA (Mayosi et al., 2009). Breast cancer is a non-AIDS defining cancer (NADC) (Mitsuyasu, 2014).

Younger age groups and lower socio-economic status have been associated with HIV infection in SSA (Fox, 2010, Ibrahim et al., 2019). The pathogenesis of breast cancer in PLWHIV appears to be multifactorial, with the association between HIV and risk of breast cancer remaining controversial among various studies of low case volumes (Phelps et al., 2001, Sarhan et al., 2010, Spano et al., 2012, Pantanowitz et al., 2011). It is not clear what role immunosuppression may play in the pathogenesis of breast cancer (Shivkumar et al., 2005). One may also not be able to eliminate the possibility that immunodeficiency may protect PLWHA from developing breast cancer (Palan and Shousha, 2011). It is however suggested that immune deficiency due to HIV does not increase the risk of breast cancer (Grulich et al., 2007).

A comparatively large study among 1,000 South African women of African descent suggested that HIV does not affect breast cancer receptor subtype distribution nor stage at diagnosis (Cubasch et al., 2013) while another South African multi-ethnic cohort suggested that HIV positive patients were more likely to be diagnosed with advanced stage breast cancer (Phakathi et al., 2019).

HIV positive women are more likely to have immunosuppression during chemotherapy and radiotherapy treatment of breast cancer. Reports from high- and low-income countries suggest that HIV/ART may adversely affect chemotherapy tolerance; immunosuppression observed with concurrent ART, in particular, zidovudine and protease inhibitors (Grover et al., 2017, Ngidi et al., 2017) may lead to chemotherapy dose reductions, treatment delays, or early treatment discontinuation (Langenhoven et al., 2016, Ngidi et al., 2017, Grover et al., 2017), thereby ultimately reducing survival.

Tuberculosis and breast cancer

In 2018, approximately 10.0 million people fell ill with tuberculosis globally, with an estimated 1.2 million deaths among HIV-negative people and an additional 251 000 deaths among HIV-positive people (World health organization, 2019). Tuberculosis and breast cancer presenting simultaneously or one after the other could create clinical as well as therapeutic challenges. A study reported the recurrence rate for tuberculosis to be 7.3% after completing treatment in breast cancer patients (Shu et al., 2019).

Depression and breast cancer

Depression is among the leading causes of disability affecting about 121 million people worldwide (Massie, 2004). About 33% of women with breast cancer have been reported to experience psychological distress (Knobf, 2007) and the prevalence of anxiety and depression among breast cancer patients ranges from 1.5% to 50% depending on definitions and methods of assessment (Zainal et al., 2013, Massie, 2004). Studies have indicated that depression before the diagnosis of breast cancer was associated with increased mortality for advanced stage breast cancer (Hjerl et al., 2003, Liang et al., 2017). Many studies have focused on prevalence of depression in women with breast cancer after diagnosis and during treatment (Knobf, 2007, Purkayastha et al., 2017, Pilevarzadeh et al., 2019) but few studies from HICs have examined the presence of depression before breast cancer diagnosis and its association with stage at diagnosis (Watson et al., 1999, Hjerl et al., 2003, Kanani et al., 2016, Liang et al., 2017). The prevalence of depression at diagnosis of breast cancer was 9.4% (Liang et al., 2017) with a higher Hazard ratio (HR) for mortality in women with depression ranging from 1.23-1.42 compared to women without depression at breast cancer diagnosis (Watson et al., 1999, Hjerl et al., 2003, Kanani et al., 2016, Liang et al., 2017). Determination of prevalence of depression among breast cancer patients at diagnosis is needed in SSA because chronic illnesses

complicate treatment and undetected depression at diagnosis may lead to poor adherence to treatment recommendations and poor outcomes.

Asthma/COPD and breast cancer risk

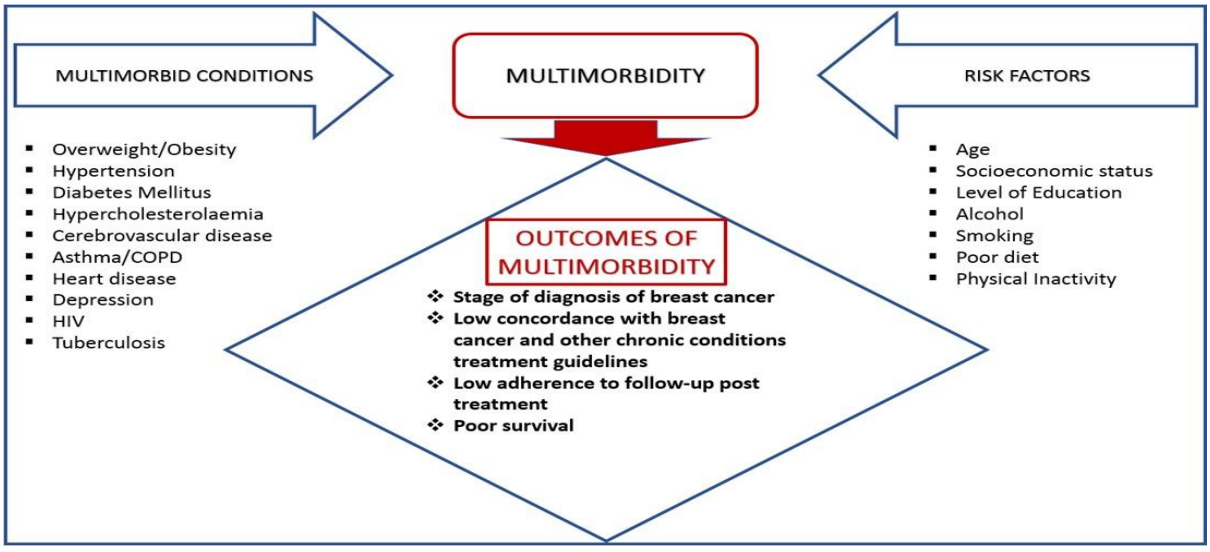
Asthma and COPD are associated with an abnormal inflammatory response of the lungs. A high lung cancer risk has been reported among COPD patients while other cancers not associated with smoking such as breast cancer have not been shown to be associated with COPD (Schneider et al., 2010). The lung is a common site for breast cancer metastases and approximately 60% of metastatic breast cancer patients suffer lung or bone metastasis in their life (Gennari et al., 2005). In particular, 60–70% of women with metastatic breast cancer who eventually died were diagnosed with lung metastasis (Dan et al., 2016). Pre-existing inflammation in the lungs seen in smokers or in people with lung diseases such as asthma/COPD may increase the risk of lung tumour and metastatic cancers (El Rayes et al., 2015).

1.5.7. Multimorbidity and breast cancer stage at diagnosis and management

There are several hypotheses regarding how chronic conditions may affect stage at cancer diagnosis. The ‘surveillance effect' suggests that increased contact with physicians/health services due to the presence of chronic conditions may result in earlier diagnosis of cancer (Vaeth et al., 2000, Gross et al., 2006). Patients with chronic conditions are likely to require frequent hospital visits and thus have more opportunity to undergo screening and also have early symptoms of cancer investigated. A contrasting hypothesis is the ‘competing demands' hypothesis, which suggests the presence of chronic conditions can distract patients and/or clinicians to such an extent that the early symptoms and signs of cancer may go unnoticed (Fleming et al., 2005, Gurney et al., 2015).

Survival after breast cancer diagnosis is mainly determined by disease-related factors such as stage at diagnosis, breast cancer subtypes and pre-existing chronic conditions (Møller et al., 2008). In breast cancer patients, the prevalence of metabolic syndrome can be as high as 40% (Wani et al., 2017) and up to 50% of women with breast cancer are likely to experience psychological distress and depression (Knobf, 2007, Zainal et al., 2013). In HIV-endemic populations such as South Africa, HIV prevalence among women with breast cancer is approximately 20% (Cubasch et al., 2013). There is a scarcity of data on the prevalence of multimorbidity in women with breast cancer in SSA with much of the data coming from HICs (Agnoli et al., 2015) or other LMICs outside SSA (Massie, 2004, Zainal et al., 2013, Wani et al., 2017). There is a need to investigate the burden of multimorbidity in women with breast cancer in SSA countries in different stages of lifestyle transition to inform feasible management strategies in constrained public health systems. Figure 1.4 highlights and summarizes common multimorbid conditions and risk factors associated with multimorbidity, and the outcomes of multimorbidity.

Figure 1.4: Chronic conditions and risk factors associated with multi-morbidity and its outcomes in women with breast cancer.



Source: Adapted from Meneses et al. (2015)

These chronic conditions may negatively affect the stage at diagnosis of breast cancer, treatment modality options, and prognosis (Sheppard et al., 2011, Søgaard et al., 2013, Gurney et al., 2015, Sarfati et al., 2016) (Figure 1.4), but the evidence regarding the degree and course of this effect on stage at diagnosis in HICs is highly inconsistent (Fleming et al., 2005, Gurney et al., 2015).

Down-staging is central to improving breast cancer survival, but achieving this goal may be challenging both for patients and health care providers in the face of the growing number of people with one or more chronic illnesses, in addition to their breast cancer, at the time of diagnosis (Maskarinec et al., 2011). Further, the high prevalence of other chronic conditions in a given population may compromise patient-oriented breast cancer prevention, diagnosis and treatment strategies (Patnaik et al., 2011, Ritchie et al., 2011, Prados-Torres et al., 2014). In HICs, an increase in the risk of being diagnosed with distant metastases has been reported in breast cancer patients with chronic conditions (Gurney et al., 2015), also women with diabetes and psychiatric disorders in HICs had 19% and 20% increased odds of advanced stage breast cancer at diagnosis respectively (Fleming et al., 2005).

The pattern of higher comorbidity levels being associated with earlier stage at breast cancer diagnosis has most commonly been reported in settings where screening occurs for breast cancer detection (Vaeth et al., 2000). There are thus several competing patient psychosocial factors, disease characteristics and health system factors that may impact stage at breast cancer diagnosis (Fleming et al., 2005). Despite increasing recognition of the impact of coexisting chronic conditions on the risks and prognosis of breast cancer, challenges remain in our understanding and optimum management of multimorbidity among breast cancer patients in SSA. While much of the focus of breast cancer outcomes and survivorship has been based on

management and cancer surveillance activities, less attention has been given to chronic conditions and multimorbidity in women with breast cancer. Furthermore, because most of these findings come from HICs, the relationship between these chronic conditions and stage at breast cancer diagnosis and treatment outcomes is not well known in South Africa and SSA. There is thus a need to describe and quantify the presence and potential clustering of chronic conditions in breast cancer patients and identify their impact and those of other socio-demographic, clinical and lifestyle patient factors on stage at diagnosis and treatment options within the public health systems in South Africa and SSA.

1.5.8. Effect of multimorbidity on patients and health systems

With increasing life expectancy in SSA, the number of people afflicted with multimorbidity is rapidly increasing and the burden is worse in the most socioeconomically disadvantaged communities (Weimann et al., 2016, Kunna et al., 2017). Women with multimorbidity are at higher risk for inadequate disease management due to fragmented management of each disease within overburdened health systems. Patients often have to bear huge out of pocket costs (McPhail, 2016) and there is the increased risk of poor adherence to polypharmacy for the patients, adverse drug reactions, and potential drug-drug, drug-gene and drug-enzyme interactions may all affect treatment efficacy (Mercer et al., 2016, Bahar et al., 2017). Further, patients with multimorbidity may be at additional risk of sub-standard care due to a high possibility of obtaining conflicting advice on care and treatment (Doessing and Burau, 2015, Valderas et al., 2019). The prevalence and burden of multimorbidity, its determinants and impact on healthcare is well established in HICs (Salisbury et al., 2011, Schäfer et al., 2012, King et al., 2018, Kingston et al., 2018), but there are fewer studies in LMICs (Thienemann et al., 2020, Eyowas et al., 2019) especially in SSA (Alaba and Chola, 2013).

In many SSA countries, health systems remain fragmented, fragile and under-resourced, and limited in capacity and infrastructure to tackle the increasing burden of NCDs (Peck et al., 2014, Gouda et al., 2019). As the prevalence of NCDs increases across SSA, existing barriers to treatment will become ever more apparent.

1.5.9. Socio-demographic and lifestyle factors and their impact on multimorbidity and breast cancer stage at diagnosis and outcomes

Increasing age is a well-known risk factor for developing multimorbidity and cancer (Marengoni et al., 2011, Sakib et al., 2019, Violan et al., 2014, Barnett et al., 2012, Meneses et al., 2015) and it is the strongest risk factor for many chronic diseases (Fabbri et al., 2015). Blood vessels lose their flexibility with increase in age making them more susceptible to chronic diseases such as hypertension.

Socioeconomic status has been linked to morbidity, mortality, health services utilization and access to care, and its association with differences in health outcomes are embedded in the larger issue of health disparities linked with social disadvantage (Adler and Stewart, 2010). There have been contradicting findings on the relationship between socioeconomic status and multimorbidity, but most of the findings from both HICs and LMICs have leaned towards multimorbidity being associated with low socioeconomic status (Alaba and Chola, 2013, Violan et al., 2014, Jackson et al., 2015, Pathirana and Jackson, 2018). Some studies from LMICs have however reported higher prevalence of multimorbidity (Khanam et al., 2011) overweight/obesity, hypertension and diabetes (Price et al., 2018) among people with higher socioeconomic status.

In breast cancer patients, it has been suggested that higher morbidity and mortality with lower survival rates among African-American women (compared with Caucasian women) are due to factors associated with lower socioeconomic status and advanced stage at diagnosis (Fregene and Newman, 2005). As socioeconomic status improves, breast cancer clinical stage at diagnosis has been shown to decrease and 5-year survival rates to increase (Neal and Allgar, 2005, Bairati et al., 2007). In South Africa, studies have shown that patients with lower levels of education, poor knowledge and awareness of breast cancer, and those from poorer communities (Čačala and Gilart, 2017) are more likely to present with advanced stage breast cancer probably because they do not understand the magnitude of the disease or that a lump in the breast can be malignant.

The relationship between ethnicity and multimorbidity has been investigated in multiracial communities in HICs and it has shown that compared with the Caucasians, the prevalence of multimorbidity was slightly higher in black persons (Rocca et al., 2014, Meneses et al., 2015) and slightly lower in Asians (Rocca et al., 2014). Ethnicity and stage at breast cancer diagnosis may also be mediated by lower socioeconomic status; black women in the USA have poorer breast cancer survival rates than whites (79% vs. 92%), and these gaps persist even when adjusting for stage at diagnosis (Howlader et al., 2012). These ethnic disparities in breast cancer stage at diagnosis have been shown to disappear when controlling for socioeconomic status (Bradley et al., 2002).

Most chronic conditions share common risk factors such as behavioral/lifestyle factors (alcohol consumption, smoking, unhealthy diet, physical inactivity) and biological factors (overweight/obesity) (Lim et al., 2012, Sliwa et al., 2008). Targeting these modifiable risk factors can prevent and reduce the incidence of most of the chronic conditions and cancer

(Kontis et al., 2014). Harmful alcohol intake is associated with increased risk of raised blood pressure and cholesterol levels and contribute to increase in weight (Nelson et al., 2013). According to WHO, about six million people die from tobacco use yearly (World Health Organization, 2016b). The harmful substance in tobacco lead to plaque depositions. These plaques line the walls of arteries, narrowing them and hence obstructing the flow of oxygen in the body. There are several other mechanisms proposed to explain the harmful role of smoking which include changes in gut irrigation, mucosal damage, and impaired mucosal immune response (Berkowitz et al., 2018).

Researchers have examined the associations between lifestyle factors such as alcohol consumption and smoking with multimorbidity, but findings have been inconsistent (Fabbri et al., 2015). Smoking was associated with a higher risk of multimorbidity in a study from HICs (Taylor et al., 2010) while it was associated with lower odds of multimorbidity in a South African study (Alaba and Chola, 2013).

1.6. Overall aim

The overall aim of this thesis was to determine the prevalence and patterns of chronic conditions and multimorbidity in women with breast cancer and its associations with stage at diagnosis and cancer treatment decisions in SSA. These findings will add to the sparse epidemiological data reported on multimorbidity and breast cancer in South Africa and SSA and will enable interventions to be developed to optimize patient treatments, quality of life and outcomes.

1.6.1. Specific objectives and hypothesis

The following specific study objectives addressed this aim:

The first objective (Paper 1- Chapter 3) was to characterize and compare socioeconomic factors and chronic conditions among women with breast cancer from Soweto, South Africa with their age and neighbourhood matched controls.

Hypothesis: Socioeconomic factors and chronic conditions are not predictors of stage at breast cancer diagnosis among women in Soweto, South Africa.

The second objective (Paper 2- Chapter 4) was to assess the multimorbidity burden of women newly diagnosed with breast cancer in 5 public hospitals in South Africa and the associations of these chronic conditions and multimorbidity with breast cancer stage at diagnosis and first breast cancer treatment received.

Hypothesis: Multimorbidity is not a predictor of stage at breast cancer diagnosis and first breast cancer treatment received in South Africa women.

The third objective (Paper 3- Chapter 5) was to determine profiles and patterns of chronic conditions and multimorbidity in women newly diagnosed with breast cancer in 5 countries in SSA and their associations with stage at diagnosis.

Hypothesis: Chronic conditions and multimorbidity have no effect on stage at diagnosis of breast cancer in SSA.

This chapter has highlighted the importance of evaluating the pattern and profile of chronic conditions and multimorbidity in the most common cancer affecting women in SSA. It has also highlighted the need to investigate the effect of these conditions on stage at breast cancer diagnosis because early diagnosis and optimum treatment is key to survival

CHAPTER 2: METHODOLOGY

2. CHAPTER TWO: METHODOLOGY

This chapter presents the study design, settings, analysis plan and ethical considerations of the methodological approaches used. This thesis utilizes three cohorts with increasing context and environmental complexity for women with breast cancer, to address its objectives and test the same hypotheses in order to identify unique and universal findings using quantitative methodology.

I was actively involved in data collection for the SABCHO study (Paper 2) and the ABC-DO study in the South African site (Paper 3). I also served as project manager on these breast cancer projects for a team of interviewers, patient navigators and data entry clerks, and in the process developed considerable skills in research project operationalization. These studies were chosen for these analyses because they are all breast cancer studies in sub-Saharan Africa (SSA) with a wealth of information on patients' socio-demographics, clinical presentation, diagnosis and treatment records, chronic conditions and multimorbidity which are all relevant to my PhD research. The abbreviated materials and methods are presented for each objective, with detailed methodologies described in the empirical chapters 3 to 5.

2.1. Paper 1/Objective 1 methodology

Objective 1: To characterize and compare chronic conditions among women with breast cancer from Soweto, South Africa with their age and neighbourhood matched controls

2.1.1. Study design and study setting

This is the primary analysis of data previously collected for The South Africa Breast cancer (SABC) study cohort between 2014 and 2017. The SABC study is coordinated by the International Agency for Research on Cancer (IARC), in collaboration with the Chris Hani Baragwanath Academic Hospital (CHBAH), University of the Witwatersrand, North-West

University, and the University of Southampton. The primary aim of the SABC study is to assess the influences of diet, physical activity, and body size on breast cancer in South Africa. It is a population based case-control study established in Soweto (Figure 2.1), Johannesburg, Gauteng province, South Africa.

Gauteng (Figure 2.1) is the smallest province in South Africa in terms of land coverage but has the highest population and population density (Mubiwa and Annegarn, 2013). Gauteng is the centre of South Africa's trade and economic networks and it is referred to as the financial hub of South Africa. It produces about 34% of South Africa's gross domestic product (GDP) and close to 10% of the SSA's GDP (Landau and Gindrey, 2008). Gauteng province is landlocked and is home to the city of Johannesburg, the largest city in South Africa covering an area of approximately 1,644 km² (Abrahams et al., 2018). South Western Township (So-We-To) (Figure 2.1) was developed to accommodate black people who were displaced from their homes in the city of Johannesburg after passing into law the racial segregation policy on residential areas known as Group Areas Act of 1950 (Lewis, 1966). Soweto is the largest township in South Africa with an estimated population of 1.3 million citizens, 50-80% of whom are indigent (Harrison and Harrison, 2014). Soweto covers an area of approximately 150 km², constitutes just over 9% of the city of Johannesburg and has an estimated density of approximately 8,667 people/km² compared to the 1,962 people/km² for the whole Johannesburg.

Figure 2.1: Map of Soweto, Johannesburg in Gauteng Province, South Africa



The study centres are the Soweto CHBAH Breast Clinic and the CHBAH Wits Medical Research Council (MRC)/ Developmental Pathways for Health Research Unit (DPHRU) unit of the Faculty of Health Sciences. Women with breast cancer (cases) were recruited at the Breast clinic. CHBAH is the largest public hospital in South Africa where more than 90% of patients treated are black. CHBAH boasts of specialist tertiary clinics and clinician specialists, infrastructure and pathology laboratory services that are not readily available in other African settings. More than 85% of patients are referred from public sector primary and secondary care facilities located within a 30-60 km radius from CHBAH; the rest are referred from private general practitioners or self-referred.

2.1.2. Study participants

Cases: Consenting women ≥18 years of age, with histologically confirmed incident cases of invasive primary breast cancer, newly diagnosed at the CHBAH breast clinic.

Controls: Women with no previous cancer diagnosis, age-matched to within 5 years and from the same neighbourhood as the cases, which served as a proxy for similar socio-economic status were eligible for participation. Controls were recruited by community volunteers at churches and community centres.

2.1.3. Measurement of chronic conditions and classifications

The main chronic conditions measured include obesity, hypertension, hyperglycaemia, hyperlipidaemia, depression and HIV infection. Obesity was determined by calculating BMI from the weight and height using the WHO obesity cut-offs (World Health Organization, 2000) (Table 2.1). The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression and other major depressive symptoms. Only seven of the nine questions from the PHQ were used. The two questions 'Feeling down, depressed or hopeless' and 'Moving or speaking so slowly that other people could have noticed' were omitted because they did not perform well on test-retest reliability assessments (Familiar et al., 2015). Patients were assessed to be depressed if they answered yes to 4 of the 7 PHQ questions asked or if depression was self-reported.

Table 2.1: WHO classification of obesity

Classification	BMI (kg/m²)	Risk of comorbidities
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal range	18.5 to 24.9	Average
Overweight	≥ 25	
Pre-obese	25.0 to 29.9	Increased
Obese class 1	30.0 to 34.9	Moderate
Obese class 2	35.0 to 39.9	Severe
Obese class 3	≥ 40.0	Very severe

	Waist circumference (cm)	
Comorbidity risk	**Women**	**Men**
Above action level 1	≥80	≥94
Above action level 2	≥88	≥102

Source: World Health Organization. Obesity: preventing and managing the global epidemic (WHO Technical Report Series 894).

2.1.4. Outcome measurement

The primary outcome measurement was stage at diagnosis of breast cancer (advanced stage "III & IV" versus early stage "I & II") from the CHBAH Breast clinic database records. Stage was assessed clinically at presentation as part of the triple assessment breast cancer diagnostic workup (Mazari et al., 2018).

Statistical analysis

Categorical variables were described and reported using Pearson's $\chi 2$ and Fisher's exact tests. Means and standard deviations (SDs) were computed for continuous variables using Student's t-test to report differences between groups, frequencies of metabolic diseases in the cohort were

analysed and reported. To examine associations with advanced-stage breast cancer, we used multivariable logistic regression models. Odds ratios (ORs) were examined in three models in a stepwise fashion in our multivariate analysis, with r2 values (coefficient of determination) reported as explained variation. Analysis was performed by me using Stata version 14 (StataCorp, USA).

2.2. Paper 2/Objective 2 methodology

Objective 2: To assess the multimorbidity burden of women newly diagnosed with breast cancer in 5 public hospitals in South Africa and the associations of these chronic conditions and multimorbidity with breast cancer stage at diagnosis and first breast cancer treatment received.

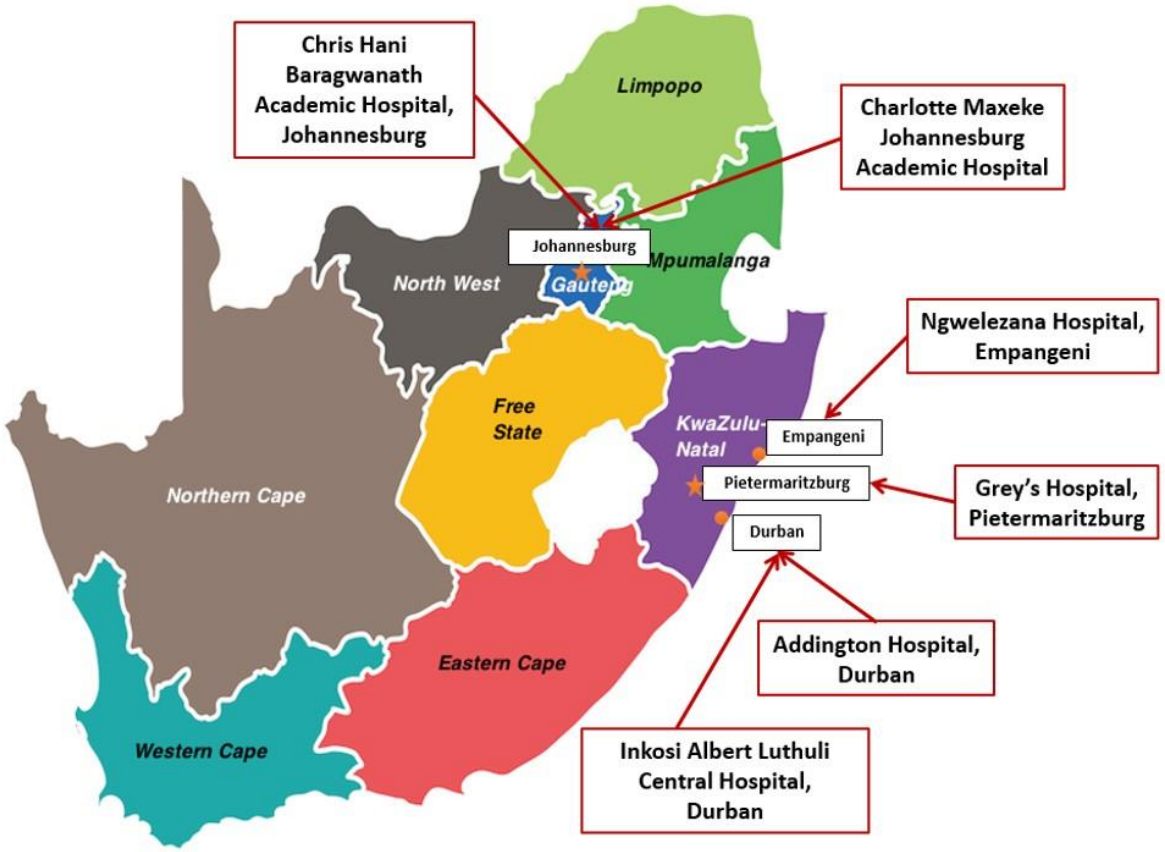
2.2.1. Study design, study setting and participants.

This is the primary data analysis of the ongoing prospective study of breast cancer patients across five public hospital sites in the South Africa Breast Cancer and HIV Outcomes (SABCHO) study (Cubasch et al., 2016b). This study is being conducted in two provinces in South Africa: 1) Gauteng province at the CHBAH and Charlotte Maxeke Johannesburg academic hospital (CMJAH) surgical breast units, 2) Kwazulu-Natal Province at Inkosi Albert Luthuli central hospital and Addington hospitals in Durban, Grey's hospital in Pietermaritzburg and Ngwelezane hospital in Empageni (Figure 2.2). The aim of the SABCHO study is to determine the factors influencing outcomes of breast cancer including HIV.

Gauteng province was previously described in objective 1. Kwazulu-Natal province occupying the South-Eastern part of South Africa and covering approximately 92,100 km2 in area was created in 1994 when the Zulu of KwaZulu (known as "Place of the Zulu" in Zulu language) and Natal Province were merged (Berry, 2013). It borders with three other provinces, and the countries of Eswatini, Mozambique and Lesotho and enjoys a long shoreline beside the Indian

Ocean. It is the second most populous province in South Africa. Its capital is Pietermaritzburg, and its largest city is Durban (the third most populous city in South Africa after Johannesburg and Cape Town). The key characteristics of each hospital site are summarized in chapter 4. Consecutive women ≥18 years of age, who resided in South Africa for ≥ 5 years and were newly diagnosed with invasive breast cancer were eligible for enrolment in the SABCHO study.

Figure 2.2: Map of SABCHO study centres in South Africa



2.2.2. Measurement of chronic conditions and classifications

Seven chronic conditions were evaluated: hypertension, obesity, diabetes, asthma/COPD, cerebrovascular disease, HIV infection and tuberculosis. HIV status was tested using ELISA through the NHLS. Obesity was defined as a body mass index (BMI) ≥30.0 kg/m². Participants were asked if they have ever been diagnosed with tuberculosis and whether they had ever been

diagnosed with the other four chronic conditions (hypertension, diabetes, asthma/COPD and cerebrovascular disease).

Intrinsic breast cancer receptor subtyping included Allred scoring for definition of oestrogen and progesterone receptor (ER and PR) status (Harvey et al., 1999) and the human epidermal growth factor receptor 2 (HER2) gene amplification (Vance et al., 2009). The receptor subtype definitions were as follows: "Luminal A (ER+ and/or PR+, HER2-, and Ki67 ≤14), Luminal B (ER+ and/or PR+, HER2-, Ki67 >14% or ER+ and/or PR+, HER2+, any Ki67), HER2-enriched (ER-, PR- and HER2+, any Ki67) and triple negative (ER-, PR-, HER2- and any Ki67).

2.2.3. Outcome measurement

Multimorbidity was defined as having ≥ 2 of these seven chronic conditions. The stage at diagnosis was grouped into early stage (stages I & II) and advanced/late stage (stage lll & lV). First treatment received was coded as primary surgery, neoadjuvant chemotherapy and neoadjuvant endocrine therapy.

Statistical analysis

Determinants of each chronic condition and multimorbidity were examined in a multisite-pooled analysis using bivariate and multivariate logistic regression. Odds ratios (OR) for multimorbidity were examined in three models by adding potentially associated factors in a stepwise fashion. In Model 1, we examined all sociodemographic factors, model 2 included sociodemographic and geographical factors and model 3 included sociodemographic, geographical factors and behavioural factors. Finally, multivariable logistic regression models were used to examine associations of chronic conditions and multimorbidity with advanced-stage breast cancer (Stage III–IV). ORs were examined in two models (Model A [unadjusted] and Model B (which was adjusted for age, ethnic, highest level of education and hospital site). We further examined the associations between multimorbidity and first treatment received by

their stage at diagnosis using Pearson's Chi-squared test. Analysis was performed by me using Stata version 15 (StataCorp Ltd, College Station, TX).

2.3. Paper 3/Objective 3 methodology

Objective 3: To determine profiles and patterns of multimorbidity in women newly diagnosed with breast cancer in 5 countries in SSA and their associations with stage at diagnosis.

2.3.1. Study design and study setting and participants

This prospective African Breast Cancer-Disparities in Outcomes study (ABC-DO) was conducted in six hospital settings across 5 SSA countries namely: Windhoek Central Hospital, Namibia; Abia State University Teaching Hospital, Aba and the Federal Medical Centre, Owerri, Nigeria; Chris Hani Baragwanath Academic hospital (CHBAH), Soweto, South Africa; Mulago Hospital and the Uganda Cancer Institute, Kampala, Uganda; and the Cancer Diseases Hospital and University Teaching Hospital, Lusaka, Zambia (Figure 2.3). Women ≥18 years of age, with clinically/histologically confirmed newly diagnosed breast cancer who provided written consent to participate in the study and access their medical records and tumour tissue were enrolled. The aim of the ABC-DO study is to determine the proximal and distal factors that explain poor breast cancer survival in SSA and which ones can most effectively be targeted to improve survival.

2.3.2. Characteristic of the recruitment sites in SSA

Namibia: A Southern African upper MIC, bordering the South Atlantic Ocean, between South Africa and Angola (Figure 2.3). It covers an area of approximately 823,290 km2, abounds on natural minerals and has a population of about 2.5 million citizens. However, unemployment rates are 20% and extreme socio-economic inequalities persist, despite generous public

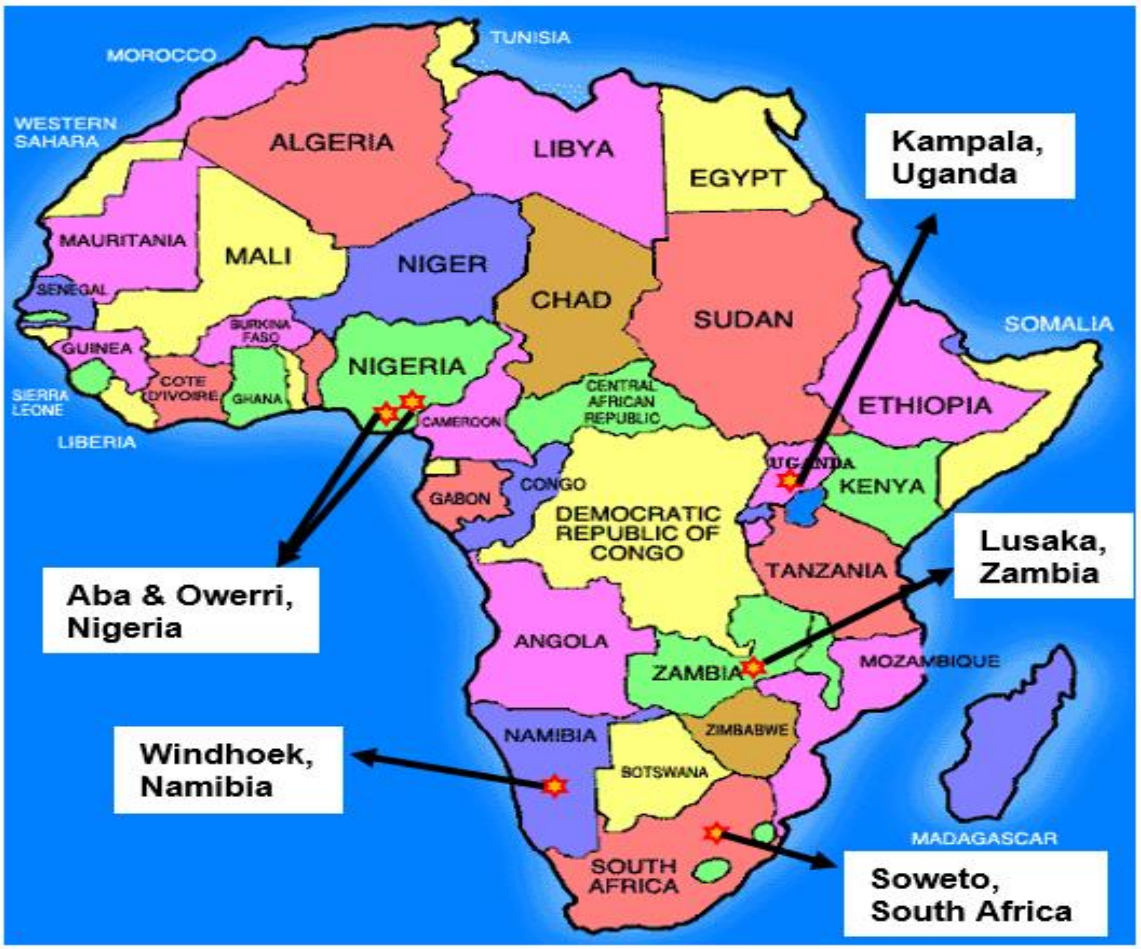
spending on social programs (Shaninga, 2019). Namibia's population is ethnically diverse comprising of the Ovambo (50%), Kavangos (9%), Herero (7%), Damara (7%), mixed European and African ancestry (6.5%), European (6%), Nama (5%), Caprivian (4%), San (3%), Baster (2%) and Tswana (0.5%) (Central Intelligence Agency, 2020). The majority (55%) of Namibians are rural dwellers and live in the northern parts of the country (Liber, 1998). Windhoek is the central capital city of Namibia, has a population of approximately 431,000 people and its healthcare services are mainly Government funded (Allcock et al., 2019). Windhoek Central Hospital (WCH), the recruitment centre for this study is the main cancer treatment centre for public patients in Namibia and the largest referral hospital in Namibia (The Elective Network, 2020). Some patients attending this hospital travel up to 700km/ 9hours drive to WCH to access health care. However, unique to Namibia is a government-funded hospital bus which brings patients from throughout the country to WCH for diagnosis and treatment. Patients attending the breast clinic are 25% European, 25% Ovambo, 10% Damara, 9% Herero and others.

Nigeria: A West African country, bordering the Gulf of Guinea, between Republic of Benin and Cameroon (Figure 2.3). Covering a land area of approximately 910,768 km^2, it is the most populous nation in Africa with over 200 million people. Nigeria has more than 250 ethnic groups with the major ones being Hausa (30%) in Northern Nigeria, Yoruba (15.5%) in Southwest Nigeria and Igbo (15.2%) in Southeast Nigeria. Nigeria is a lower MIC, SSA's largest economy, yet 62% of the population live in extreme poverty (Balogun and Seeni, 2018). The local, state and federal governments provide primary, secondary, and tertiary levels of care respectively; however, there is poor coordination of healthcare services and high reliance on out of pocket health payments as a means of financing health care in Nigeria (Aregbeshola and Khan, 2018). Due to the deplorable state of the health care system in the country, medical tourism is fast becoming a norm among many Nigerians (Abubakar et al., 2018).

Two hospitals located in two different states in southeast Nigeria served as recruitment centres for this study.

1) The Maratha Clinic at the Abia State University Teaching Hospital is a tertiary referral centre typically providing cancer diagnostics and therapy. This hospital serves about 6 million people with up to 50 km radius.
2) Federal Medical Centre, Owerri, Imo state is a tertiary health institution that serves approximately 1.5 million people in the city and its environs. It also provides cancer diagnostics and treatment.

Figure 2.3: Map of ABC-DO study centres in sub-Saharan Africa



South Africa: Located at the southern tip of Africa. It is bordered by Botswana, Eswatini, Mozambique, Namibia and Zimbabwe; and surrounds the small Kingdom of Lesotho (Figure

2.3). South Africa has a population of approximately 59.6 million (Stats, 2020) and a land area of 1,214,470 km^2. The racial distributions are black African (80.9%), mixed race (8.8%), white (7.8%) and Indian/Asian (2.5%) (Zuberi et al., 2016). South Africa, with the most diversified and industrialized economy in Africa is an upper MIC, one of only eight such countries in Africa. South Africa has made tremendous progress in reducing poverty since 1994 when it gained its independence, however, high levels of inequality, unemployment and poverty still persist especially among black South Africans (Orthofer, 2016, Sulla and Zikhali, 2018). South Africa has a dual health system, with private insurance schemes covering approximately 16% of the more affluent population and the 84% majority uninsured being dependent on the Government for health care (McIntyre and Ataguba, 2012). The recruitment centre in South Africa is the breast unit of the Chris Hani Baragwanath Academic hospital (CHBAH), Soweto in Johannesburg, Gauteng province, South Africa. This hospital has been described in objective 1.

Uganda: Located in East-Central Africa, east of the Democratic Republic of the Congo and west of Kenya (Figure 2.3). With a land mass area of 197,100 km^2 and a population of approximately 35 million, its population density is high in comparison to other African nations. The majority of the population is concentrated in the southern and central parts of the country, along the shores of Lake Albert and Lake Victoria (Mwakikagile, 2009). Uganda is a LIC with 25% of its population urban and 20% living in extreme poverty (Statistics, 2016). Health care delivery at government hospitals in Uganda is free; however, frequent broken equipment and stock-outs require patients to pay for most of their care (Anderson et al., 2017). Kampala is the largest city and capital of Uganda, situated in the southern part of the country, just north of Lake Victoria.

Patients were enrolled at the breast clinic of the Mulago National hospital. This hospital is the teaching facility of the Makerere University College of Health Sciences. It serves as a National referral hospital for the whole country. This hospital and the Ugandan Cancer Institute are Uganda's only public diagnostic and treatment hospitals for breast cancer. Patients are referred from hospices throughout the country to this hospital which provides free treatment.

Zambia: A Southern African country located south of the Democratic Republic of the Congo and east of Angola (Figure 2.3). It has a population of approximately 17 million and a land mass area of 743,398km^2. Zambia has one of the highest levels of urbanization in SSA, with high density mainly in the central area and 44.6% of total population living in urban areas. Zambia is a lower MIC with much economic diversion but the majority of Zambian people live in poverty (Chitonge, 2016). Healthcare is free in government hospitals in Zambia; however, out-of-pocket payments are still significant (Masiye et al., 2016). Lusaka is the capital city with 2.7 million citizens and it is located in the Southern part of the country. The breast clinic of the University Teaching Hospital, Lusaka served as the enrolment centre in Zambia. This teaching hospital is the largest hospital in Zambia and is a centre for specialist referral throughout the country (Ministry of Health, 2015).

2.3.3. Measurement of chronic conditions and classifications

We examined the presence of seven chronic conditions: hypertension, obesity, diabetes, asthma/ COPD, heart disease, HIV infection and tuberculosis. Body height and weight were measured at enrolment, and obesity was defined as a BMI ≥30.0 kg/m². Patients were asked if they had ever been diagnosed and treated for tuberculosis and whether they had ever been diagnosed and treated with hypertension, diabetes, asthma/COPD and heart disease.

2.3.4. Outcome measurement

Multimorbidity was defined as having ≥ 2 of these seven chronic conditions, in addition to breast cancer. Breast cancer stage at diagnosis was determined using the American Joint Committee on Cancer (AJCC) TNM staging system (Amin et al., 2017) and categorized as early (stages I&II) and advanced (stages III &IV).

Statistical analysis

The pattern and prevalence of each chronic condition were described by site and (for the Namibia site) by site race group using Pearson's chi-squared and Fisher's exact tests. Associations of sociodemographic factors with each chronic condition and with multimorbidity were examined using logistic regression analysis. Logistic regression was also used to examine whether each chronic condition and multimorbidity were associated with advanced stage breast cancer (Stages III and IV), as compared to early-stage breast cancer (Stages I and II). Variables for which P values were <0.1in bivariate analysis with advanced stage breast cancer were evaluated and ORs were assessed adjusting for each covariate, HIV status, age and country (as a proxy for level of health care). Analysis was performed by me using Stata version 15 (StataCorp Ltd, TX).

2.4. Data management

Details of the exact analytical approaches used for these analyses are described in chapters 3 to 5, however additional information about specific analytical and data management component is provided in this section. Data collected in this series of studies was extracted from each of the individual study databases following approval from the gate keeper of each study. Data were analysed by myself and the findings from the analysis were further discussed and reviewed with supervisors and co-authors. Data management included conducting quality

checks and cleaning of data pertaining to all key variables at relevant time points for each cohort. Data were evaluated for accuracy, consistency and outliers. Data manipulation for each cohort included the creation of new variables (e.g. wealth index scores from several household ownership variables) and the recoding of existing variables as well as transforming or converting variables (e.g. continuous variables to categorical variables). Analysis was performed using Stata version 15 (StataCorp Ltd, Texas, USA).

2.5. Ethical Considerations

Each objective for this PhD forms part of a larger study which was approved by different ethics committees. An application was submitted to the University of the Witwatersrand's Human Research Ethics Committee (Medical) for approval of the PhD protocol specifically (HREC Clearance: M180326 – Appendix 2).

PART TWO: EMPIRICAL CHAPTER

"It is health that is the real wealth, and not pieces of gold and silver." – Mahatma Gandhi

3. CHAPTER THREE: PAPER 1

Ayeni, O.A., Joffe, M., Cubasch, H., Rinaldi, S., Taljaard, C., Vorster, E., Romieu, I. and Norris, S.A., 2019. Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: Results from the SABC study. *SAMJ: South African Medical Journal, 109(4), pp.264-271.*

3.1. Introduction

Globally, approximately 41 million people die from non-communicable diseases (NCDs) each year with over 85% of deaths occurring in low and middle income countries (LMICs) including South Africa (SA) (World Health Organization, 2018). In SA, 39% of total deaths in 2010 were due to NCDs with the number of deaths similar to deaths from the combination of Human immunodeficiency virus (HIV) and tuberculosis (Nojilana et al., 2016). It is projected that death from NCDs will be five times those from communicable diseases in LMICs by the year 2030 (World Health Organization, 2008). Most deaths occur in the productive years compromising the World Health Organization (WHO) defined developmental goals, which include economic stability, poverty reduction and health equity (Beaglehole et al., 2011). The major NCDs burden in LMICs are hypertension, cardiovascular diseases, chronic lung diseases, type 2 diabetes, cancer and depression which increases with age (Daar et al., 2007). Risk factors such as alcohol consumption, smoking, dietary factors, lack of exercise and excess weight are responsible for a large share of the global disease burden mediated directly or through conditions such as higher weight/body mass index (BMI), high blood pressure, elevated cholesterol and blood glucose levels (Ezzati and Riboli, 2013). It is worrisome that in SA this rapidly increasing NCDs burden is occurring at the same time as the large number of HIV-infected population well managed on antiretroviral treatment, is aging (Hofman, 2014, Mayosi et al., 2009).

Cancer is one of the major causes of morbidity and mortality globally with an estimated 14.9 million incident cases in 2013 and approximately 8.2 million cancer deaths making cancer among the leading causes of death globally (Ferlay et al., 2015). According to the WHO, cancer is the second leading cause of NCD deaths accounting for 21% of all NCD deaths (Stewart and Wild, 2017). Breast cancer remains the most common cancer among women worldwide and is a major cause of women's cancer deaths. In LMICs the mortality to incidence ratios are comparatively high, due mainly to advanced stage at diagnosis and suboptimal management (Torre et al., 2015). Countries in Sub-Saharan Africa (SSA) including SA are yet to identify cancer as a priority, allocating limited resources mainly into HIV, tuberculosis and other infectious disease management (Edge et al., 2014, Farmer et al., 2010, Hanna and Kangolle, 2010, Jemal et al., 2012, Kantelhardt et al., 2008, Levitt et al., 2011). Yet the burden of cancer and NCDs in this region is rapidly increasing (Nyirenda, 2016).

Existing lifestyle risk factors and the metabolic syndrome (high blood sugar, high blood pressure, abnormal cholesterol levels and excess fat around the waist) have been associated with breast cancer risks especially in post-menopausal women (Bhandari et al., 2014, Gezgen et al., 2012, Wani et al., 2017, Agnoli et al., 2015). Studies conducted in LMICs have shown that the prevalence of the metabolic syndrome in breast cancer patients can be as high as 40% (Wani et al., 2017). It has also been reported that about a third of women with breast cancer are likely to experience psychological distress (Knobf, 2007). Studies have shown that the prevalence of anxiety and depression ranges from 1.5% to 50% among women with breast cancer depending on definitions and methods of assessment of psychological disorders (Massie, 2004, Zainal et al., 2013).

There have been conflicting reports on association of education with breast cancer. Older studies have shown that women with higher education are at increased risk of developing breast cancer compared to those with low education (Heck and Pamuk, 1997, Hussain et al., 2008, Massie, 2004, Mouw et al., 2008, Zainal et al., 2013). However, studies conducted in LMICs have reported the reverse (Ogundiran et al., 2010, Ozmen et al., 2009).

Studies have shown that stage at cancer diagnosis is affected by other health conditions, but the direction and magnitude of this effect is highly inconsistent (Terret et al., 2009). Several competing mechanisms such as the surveillance hypothesis, psychological hypothesis, competing demand hypothesis and death from other cause hypothesis may impact stage at diagnosis (Fleming et al., 2005).

The interplay between metabolic diseases, depression, HIV and breast cancer influences cancer treatment decisions and patients' tolerance and adherence to treatment (Klabunde et al., 2007, Satariano and Ragland, 1994). Furthermore, the presence of metabolic diseases, depression and HIV have also been reported to negatively influence survival in breast cancer patients (Satariano and Ragland, 1994, Yancik et al., 2001, Houterman et al., 2004, Nagel et al., 2004). Metabolic diseases are largely preventable by eliminating risk factors like harmful alcohol use, tobacco use, physical inactivity and unhealthy diet. There is need for a better understanding of the prevalence of metabolic diseases, depression and HIV among SA populations for better health policies and service integration (Shisana et al., 2014).

We have conducted a population based case control study primarily to describe and compare the burden of metabolic diseases, HIV infection and depression in women with and without breast cancer. However, because the covariates analysed could possibly be associated with

stage at breast cancer diagnosis, we further analysed these covariates to determine their effect on stage at breast cancer diagnosis. The aim of this study is to describe and compare the burden of metabolic diseases, depression and HIV among women newly diagnosed with invasive breast cancer at the Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa with their age and residential neighbourhood matched controls and to determine factors associated with advanced stage breast cancer diagnosis.

3.2. Methods

3.2.1. Study design and study setting

The South Africa Breast cancer (SABC) study is a population based case-control study set up in Soweto, home to a high-density urban population of SA, to study the aetiology of breast cancer in South African black women. The SABC study is coordinated by the International Agency for Research on Cancer (IARC), in collaboration with the University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, North-West University, and the University of Southampton.

Women were recruited at the Breast Unit of the CHBAH between December 2014 and June 2017. CHBAH is the largest public hospital in SA with >90% of patients being black and it boasts of infrastructure, with pathology laboratory services and professional skills that are not easily available in other African settings. About 85% of patients presenting at CHBAH are referred from public sector primary and secondary care facilities within a 30-60 km radius, the rest of the patients are either self-referred or referred from private general practitioners. Controls were recruited from the same communities as the cases.

3.2.2. Recruitment of cases and controls

Eligibility criteria:

Cases: Women ≥18 years of age with a histologically confirmed newly diagnosed breast cancer that provided written consent and met all inclusion and exclusion criteria were enrolled. Exclusion criteria were pregnancy or breastfeeding, chronic renal disease, a prior cancer diagnosis or inability to answer questions.

Controls: Women ≥18 years of age who were selected among the population living in Soweto, and who matched the cases on age (±5 years) and area of residence. Controls were recruited by community volunteers at churches and community centres.

For all subjects, fasting blood samples were collected prior to the start of any treatment (for cases), fractionated into serum, plasma, red blood cells and buffy coats, and stored at -80°C. At the same time, spot urine samples were collected from all subjects, aliquoted and stored at -80°C.

3.2.3. Procedure

Investigators and trained study staff conducted face-to-face interviews. We collected detailed information on socioeconomic status during infancy and early childhood, health and reproductive history (number of births, age at each birth, age at menarche, and duration of breastfeeding for each birth), history of benign breast disease, use of exogenous hormones, smoking habits, alcohol intake, maximum attained body weight, body silhouette at different ages, physical activity (household and recreational) and hours per day spent sedentary (e.g. watching television), diet, occupation, environmental exposures, ethnicity, and family history of cancer. In particular, self-reported demographics, comorbidities (hypertension, diabetes, cardiovascular disease, tuberculosis, hypercholesterolemia and depression) and,

socioeconomic indicators were collected (education level, household socioeconomic score determined from motor vehicle ownership, household possessions (refrigerator, microwave, cell phone and landline telephone, washing machine, bed, cooking facilities) with the score calculation described in the legend to table 1. The patient health Questionnaire (PHQ-9) was used to assess depression and other major depressive symptoms, the validity of the questionnaire has been tested in studies conducted in South Africa and a similar study in Mexican women (Cholera et al., 2014, Familiar et al., 2015, Bhana et al., 2015). Only seven of the nine questions from the PHQ were used. The two questions "Feeling down, depressed or hopeless" and "Moving or speaking so slowly that other people could have noticed?" were omitted as these questions did not perform well on test-retest reliability assessments (Familiar et al., 2015). Patients were assessed to be depressed if they answered yes to 4 of the 7 PHQ questions asked or if depression was self-reported.

3.2.4. Anthropometric data and other measurements

Body weight, standing and sitting height, waist and hip circumferences were measured. Pulse and blood pressure were measured according to the American Heart Association recommendations (Goff et al., 2014). Participants were seated, and three consecutive readings were taken.

3.2.5. Blood measurements

Fasting plasma glucose and lipids (total cholesterol and high density lipoprotein) were measured enzymatically with a glucose oxidase method and cholesterol oxidase method respectively using RANDOX DAYTONA PLUS (United Kingdom) automated clinical chemistry analyzer method. The coefficient of variation for the laboratory technician was less than 2% for the assays. Cases and controls were measured in the same batch. HIV status was

either measured by HIV 1-2 rapid test (Alere Medical Co Ltd., USA) for the controls or enzyme-linked immunosorbent assay (ELISA) test for the cases through the national health laboratory services (NHLS) because the cases were enrolled through the clinic.

3.2.6. Comorbidity measurements and classifications

The main comorbidities measured include obesity, hyperlipidaemia, hyperglycaemia, hypertension, depression and HIV infection. Obesity was determined by calculating BMI from the height and weight using the WHO obesity cut-offs. BMI of <18.5 kg/m^2 was categorized as underweight, 18.5 - 24.9 kg/m^2 categorized as normal, 25 - 29.9 kg/m^2 was categorized as overweight, a BMI of >30 – 39.9 kg/m^2 was categorized as obese while BMI of ≥40 kg/m^2 was categorized as morbidly obese (World Health Organization, 2000). Dyslipidaemia was defined by measured total cholesterol level of >6.21mmols/L or high density lipoprotein (HDL) of <1.19mmols/L while a fasting glucose level of > 5.5mmols/L was considered impaired fasting glucose (Klug, 2012, Rao et al., 2004). Blood pressure (BP) was calculated using the average between the second and third BP readings. Hypertension was defined using BP readings alone which was categorized as normal (Systolic <120mmHg and diastolic <80mmHg), category 1 (Systolic 120–139mmHg or Diastolic 80–89 mmHg), category 2 (Systolic 140–159mmHg or Diastolic 90–99 mmHg) and category 3 (Systolic ≥160 mmHg or Diastolic ≥100 mmHg) (Chobanian et al., 2003). Hypertension was further defined as "No" or "Yes" (using mean systolic blood pressure of ≥140 mmHg or mean diastolic blood pressure ≥ 90 mmHg or normal blood pressure with self-reported hypertensive medication use).

3.2.7. Outcome measurement

The primary outcome measurement was stage at breast cancer presentation to Chris Hani Baragwanath Academic Hospital Breast Unit (early stage "I & II" versus advanced stage "III

& IV") which was extracted from the Breast Unit database. Stage was assessed clinically at diagnosis, it was primarily coded according to Tumour-Node-Metastasis (TNM) classification and then converted to Manchester staging.

3.2.8. Statistical analysis

Differences in demographics, socio-economic factors, metabolic diseases, depression and HIV between the breast cancer and the control groups were described and reported using Pearson's chi squared and Fisher's exact tests for categorical variables. Means and standard deviations were computed for continuous variables using the Student's t-test to report differences in groups. Frequencies of number of metabolic diseases in the cohort were analysed and reported, frequencies of metabolic diseases, depression and HIV in breast cancer patients were also analysed with stage at breast cancer diagnosis as the outcome variable. To examine associations with advanced stage breast cancer, we used multivariable logistic regression models. Variables for which p-values were <0.1 in bivariate analysis were included in our multivariate models. ORs were examined in 3 models in our multivariate analysis, with R-squared values (coefficient of determination) reported as explained variation. We added in a stepwise fashion socio-demographic factors (Age and household socioeconomic status), dyslipidaemia, hypertension and HIV to examine the association between these factors and advanced presentation of breast cancer. Analysis was performed using Stata version 14 (StataCorp Ltd, Texas, USA).

Ethics: This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Approval Number: Ml40980, dated: 10th November 2014) and by the IARC ethics committee.

3.3.Results

A total of 798 women (399 cases and 399 controls) were correctly matched to both neighbourhood and age to within 5 years. In the first year of recruitment, controls were enrolled independently of case matching in accordance with a predictive recruitment algorithm developed from a prior analysis of patients enrolled on a prior study (Dickens et al, 2014). A summary of the characteristics of the cohort is shown in table 3.1.

Table 3.1: Socio-demographic profile and disease risk in women with and without breast cancer in Soweto women.

Variables	Total (N=798)	Participants		p-value
		Breast cancer (N=399)	Control (N=399)	
Age (year), Mean (SD)	54.6 (12.9)	54.6 (12.8)	54.7 (12.9)	0.939
Level of education, n (%)				
Completion of Primary education and below	167 (20.9)	97 (24.3)	70 (17.5)	0.023[a]
Completion of Secondary education	617 (77.3)	298 (74.7)	319 (80.0)	
Some tertiary education	14 (1.8)	4 (1.0)	10 (2.5)	
[b]Household SES (assets score, 0-8), Mean (SD)	5.4 (1.3)	5.4 (1.3)	5.5 (1.3)	0.182
BMI (kg/m^2), n (%)				
[c]Underweight & Normal (<24.9)	150 (18.8)	82 (20.5)	68 (17.0)	0.649
Overweight (25.0 – 29.9)	192 (24.1)	93 (23.3)	99 (24.8)	
Obese grade (30.0 – 39.9)	215 (26.9)	105 (26.3)	110 (27.6)	
Morbidly obesity (≥ 40)	241 (30.2)	119 (29.8)	122 (30.6)	
Waist circumference (cm), Mean (SD)	94.6 (13.8)	93.4 (13.8)	95.9 (13.7)	0.009
Abdominal adiposity (Waist circumference in cm), n (%)				
< 80	117 (14.7)	64 (16.0)	53 (13.3)	0.271
≥80	681 (85.3)	335 (84.0)	346 (86.7)	
Dyslipidaemia (TC and HDL in mmol/L), n (%)				

TC ≤ 6.21	731 (91.6)	368 (92.2)	363 (91.0)	0.523
TC > 6.21	67 (8.4)	31 (7.8)	36 (9.0)	
HDL ≤ 1.3	597 (74.8)	310 (77.7)	287 (71.9)	0.061
HDL > 1.3	201 (25.2)	89 (22.3)	112 (28.1)	
HYPERTENSION (BP reading alone in mmHg, patient hypertensive on medications excluded), n (%)				
Normal (<120/<80)	167 (36.5)	84 (36.4)	83 (36.7)	0.323
Category 1 (120-139/80-89)	142 (31.1)	79 (34.2)	63 (27.9)	
Category 2 (140-159/90-99)	99 (21.7)	43 (18.6)	56 (24.8)	
Category 3 (>=160/>=100)	49 (10.7)	25 (10.8)	24 (10.6)	
Hypertension (using either BP reading or medication use), n (%)				
No	309 (38.7)	163 (40.8)	146 (36.6)	0.217
Yes	489 (61.3)	236 (59.2)	253 (63.4)	
Fasting glucose (mmol/L), n (%)				
≤5.5	422 (52.9)	212 (53.4)	210 (52.6)	0.828
>5.5	376 (47.1)	185 (46.6)	189 (47.4)	
Missing	2	2	0	
Risk of depression (using either PHQ-9 score or self-reported depression), n (%)				
No	711 (89.1)	364 (91.2)	347 (87.0)	0.053
Yes	87 (10.9)	35 (8.8)	52 (13.0)	
HIV Infection, n (%)				
Negative	642 (80.5)	333 (83.5)	309 (77.4)	0.032
Positive	156 (19.5)	66 (16.5)	90 (22.6)	

SABC = South Africa Breast Cancer; SD = standard deviation; SES = socioeconomic status; BMI = body mass index; TC = total cholesterol; HDL = high-density lipoprotein; BP = blood pressure;
PHQ-9 = Patient Health Questionnaire-9.
*Significant at p<0.05
[a]Fisher's exact test
[b]SES: Household socio-economic status (possessions) score determined from: (motor vehicle=1, fridge=1, microwave=1, land telephone=1, washing machine=1, cell phone=1, bed=1, gas/electric stove=1) Denominator= 8 (1 for Yes, 0 for No)
[c]19 people are underweight

The overall mean age ± standard deviation (SD) was 54.6 ±12.9. Educational level, HIV status and waist circumference differed significantly between the two groups. Those in the control group were more likely to have schooled beyond primary education compared to the breast cancer patients, p=0.023. Over a fifth (22.6%) of those in the control group were HIV infected while in the breast cancer group it was 16.5%, p=0.032. The mean waist circumference in the control group was 95.9±13.7 while in the breast cancer group it was 93.4±13.7, p=0.009. There were no significant differences in household SES, nutritional status (BMI), level of hypertension, dyslipidaemia, fasting plasma glucose and assessment of depression between the two groups. In the total cohort, the majority (81.2%) of the participants were overweight or obese, 85.3% (681) had abdominal adiposity, 8.4% (102) had elevated total cholesterol, 74.8% (597) had low HDL, 47.1% (376) had impaired fasting plasma glucose, 61.3% (489) were hypertensive of which 43.2% (341) were on treatment, while 10.9% (87) were assessed to be depressed (Table 3.1).

Table 3.2: Frequency of metabolic diseases* in women from the SABC study, overall and by case/control status.

Number of metabolic diseases, n	Total (N=798), n (%)	Breast cancer (N=399), n (%)	Controls (N=399), n (%)	P value
0	72 (9.0)	42 (10.5)	30 (7.5)	0.285
1	192 (24.1)	101 (25.3)	91 (22.8)	
2	304 (38.1)	139 (34.9)	165 (41.3)	
3	197 (24.7)	99 (24.8)	98 (24.6)	
4	33 (4.1)	18 (4.5)	15 (3.8)	
Total	798 (100)	399 (100)	399 (100)	

SABC = South Africa Breast Cancer.
*Defined as obesity (body mass index ≥30 kg/m2), dyslipidaemia (total cholesterol >6.21 mmol/L), hypertension (blood pressure ≥140/≥90 mmHg or medication use) and hyperglycaemia (fasting glucose >5.5 mmol/L).

In determining the number of metabolic diseases reported in the whole cohort, only 9% (72) of the women had no metabolic disease, 24.1% (192) had one metabolic disease, 38.1% (304) had

two metabolic diseases, 24.7% (197) had three metabolic diseases and 4.1% (33) presented with 4 metabolic diseases (Table 3.2). There were no significant differences in the number of metabolic diseases between the cases and the controls, p=0.285.

Table 3.3: Frequency of at least one metabolic disease* depression and HIV in women from the SABC study, overall and by case/control status

At least one MD, D, HIV	Total (N=798), n (%)	Breast cancer (N=399), n (%)	Control (N=399), n (%)	P value
MD (+), D (-), HIV (-)	542 (68.4)	285 (72.2)	257 (64.7)	0.036
MD (+), D (-), HIV (+)	103 (13.0)	41 (10.4)	62 (15.6)	
MD (+), D (+), HIV (-)	58 (7.3)	23 (5.8)	35 (8.8)	
MD (-), D (-), HIV (+)	27 (3.4)	15 (3.8)	12 (3.0)	
MD (+), D (+), HIV (+)	23 (2.9)	8 (2.0)	15 (3.8)	
MD (-), D (-), HIV (-)	39 (4.9)	23 (5.8)	16 (4.0)	
Total	792 (100.0)	395 (100.0)	397 (100.0)	
**Not shown	6	4	2	

SABC = South Africa Breast Cancer; MD = metabolic disease; D = depression.
*Obesity, hyperlipidaemia, hypertension or hyperglycaemia.
**D (+), MD (-), HIV (-) and D (+), HIV (+), MD (-) combinations.

When combining at least one metabolic disease, depression and HIV, 2.9% (23) of the women presented with these 3 diseases in the whole cohort and this proportion was almost doubled in the control group 3.8% (15) compared to the breast cancer group 2.0% (8). The majority 72.2% (285) of the women from the breast cancer group and 64.7% (257) of women from the control group presented with metabolic diseases alone (HIV negative and no evidence of depression). Women with no metabolic disease, depression and HIV were 5.8% (23) and 4.0% (16) from the breast cancer group and the control group respectively. The distribution of metabolic diseases, depression and HIV was significantly different between the breast cancer and control groups, p value=0.036 (Table 3.3).

In the bivariate analysis among women from the breast cancer group (Table 3.4), for every unit increase in household socioeconomic status asset score there was a 21% reduction in the odds of presenting with an advanced stage breast cancer, (OR 0.79, 95%CI: 0.67±0.92).

Table 3.4: Bivariate analysis of variables associated with advanced stage presentation (stages III & IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa

	Bivariate analysis	
Variables	**OR (95% CI)**	**P-value**
Age (years)	0.99 (0.97-1.00)	0.162
Level of education		
Completion of Primary education and below	3.47 (0.35- 34.51)	0.384
Completion of Secondary education	2.77 (0.28-26.90)	
Some tertiary education	Reference	
Household SES (asset score)	0.79 (0.67-0.92)	0.002*
BMI (kg/m^2)		
Underweight & Normal (<24.9)	Reference	0.343
Overweight (25.0 – 29.9)	0.80 (0.4 4-1.45)	
Obese grade (30.0 – 39.9)	0.59 (0.33-1.05)	
Morbidly obesity (≥ 40)	0.74 (0.42-1.31)	
Waist circumference	0.99 (0.98-1.00)	0.167
Abdominal adiposity (Waist circumference in cm)		
< 80	1.41 (0.82-2.41)	0.212
≥80	Reference	
Dyslipidaemia (TC and HDL in mmol/L)		
TC ≤ 6.21	2.53 (1.13-5.63)	0.018*
TC > 6.2	Reference	
HDL ≤ 1.3	1.77 (1.09-2.87)	0.019*
HDL > 1.3	Reference	
HYPERTENSION (BP reading alone in mmHg, patient hypertensive on medications excluded)		
Normal (<120/<80)	Reference	0.516
Category 1 (120-139/80-89)	1.15 (0.62-2.14)	

Category 2 (140-159/90-99)	0.65 (0.31-1.37)	
Category 3 (>=160/>=100)	0.89 (0.37-2.19)	
Hypertension (using either BP reading or medication use)		
No	1.64 (1.09-2.46)	0.015*
Yes	Reference	
Impaired fasting glucose (mmol/L)		
≤5.5	Reference	0.217
>5.5	1.28 (0.86-1.90)	
Risk of depression (using either PHQ-9 score or self-reported depression)		
No	1.31 (0.65-2.66)	0.437
Yes	Reference	
HIV status		
Negative	Reference	0.041*
Positive	1.75 (1.01-2.99)	

OR = odds ratio; CI = confidence interval; BMI = body mass index; TC = total cholesterol; HDL = high-density lipoprotein; BP = blood pressure; PHQ-9 = Patient Health Questionnaire-9.
*Significant at $p<0.05$

Women with total cholesterol ≤6.21mmol/L and HDL ≤1.3mmol/L had a higher risk for advanced stage disease (OR 2.53, 95% CI: 1.13- 5.63 and OR 1.77, 95% CI: 1.09-2.87, respectively). Women who were HIV positive but not hypertensive were also more likely to present with advanced stage disease, (OR 1.64, 95% CI: 1.09 -2.46) and (OR 1.75, 95% CI: 1.01-2.99) respectively.

Table 3.5: Multiple logistic regression models of factors influencing advanced stage presentation (stages III and IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa

Variables	Bivariate analysis OR (95% CI)	Model 1, sociodemographic OR (95% CI)	Model 2, comorbidities OR (95% CI)	Model 3, sociodemographic +comorbidities OR (95% CI)
Sociodemographic				
Age in years	0.99 (0.97-1.00)	0.99 (0.97-1.00)		0.99 (0.98-1.02)
Household socio-economic status (asset score)	0.79 (0.67-0.92)*	0.79 (0.67-0.92)*		0.81 (0.69-0.95)*
Comorbidities				
Dyslipidaemia (TC in mmol/L)				
≤ 6.21	2.53 (1.13-5.63)		2.46 (1.10-5.54)*	2.18 (0.96-4.96)
> 6.21	Reference		Reference	Reference
Hypertension (using either BP reading or medication use)				
No	1.64 (1.09-2.46)*		1.56 (1.04-2.35)*	1.50 (0.96-2.35)
Yes	Reference		Reference	Reference
HIV status				
Negative	Reference		Reference	Reference
Positive	1.75 (1.01-2.99)*		1.60 (0.93-2.77)	1.44 (0.80-2.57)
r^2		0.0286	0.0335	0.0486

OR = odds ratio; CI = confidence interval; TC = total cholesterol; BP = blood pressure.
*Significant at $p<0.05$

Variables significant in the bivariate analysis were further explored in Table 3-5 in individual and combined logistic regression models controlling for age. Socio-demographic factors (model 1) independently explained 2.9% of the variance and household socioeconomic status was shown to partially influence the likelihood of advanced stage at diagnosis. Comorbid factors (model 2) explained 3.3% of the variance, with patients with no dyslipidaemia and patients with no hypertension having greater odds of advanced-stage presentation. In the final model with all factors included (model 3), 4.9% of the variance was explained. The associations of advanced stage breast cancer with household socioeconomic status was slightly attenuated on adjustment (OR 0.81, 95% CI: 0.69-0.95), whereas associations with hypertension, dyslipidaemia and HIV were no longer significant in mutually adjusted models (Table 3.5).

3.4. Discussion

In this study, we found that there was a high burden of metabolic diseases, depression and HIV in women with and without breast cancer in Soweto. About two third of the whole cohort has two or more metabolic diseases and 10.2% had at least one metabolic disease and depression. The prevalence of metabolic diseases and depression were comparable in women with breast cancer and those without breast cancer. Women with breast cancer had lower education levels compared to their controls. There was a significant difference in the waist circumference and HIV status between the two groups while levels of obesity, hyperlipidaemia, hypertension, hyperglycaemia and depression were similar. The combination of at least one metabolic disease, depression and HIV differed between the breast cancer group and the control group. A higher household socioeconomic asset score was protective against advanced stage breast cancer at presentation while hypertension, dyslipidaemia and HIV had no significant influence on stage at presentation.

Our study demonstrated that women with breast cancer were significantly less educated than their controls; this is in support of literature reports that showed less educated women and women with low SES to be at increased risk for breast cancer (Ogundiran et al., 2010, Ozmen et al., 2009). This is partly due to change in reproductive factors and lifestyle modification. We reported a high prevalence of comorbidity among Soweto women in general corroborating findings from previous studies in South Africa from different settings (Gaziano et al., 2017, Heerden et al., 2017). About a fifth of our whole cohort were HIV infected, while almost 14% of breast cancer patients with at least one metabolic disease and depression were also infected with HIV. This further supports the fact that our population is undergoing a double burden involving an epidemiologic overlap of NCDs and infectious diseases.

Studies have reported association between metabolic diseases and risk of breast cancer especially in post-menopausal women (Agnoli et al., 2015, Sheean et al., 2017). There was no significant difference in our study with regards to individual metabolic disease component (obesity, Dyslipidaemia, Hypertension and Hyperglycaemia) and also in the number of metabolic diseases presented with between women with and without breast cancer; however, the proportion of women presenting with metabolic diseases is so high in both groups that significant differences are hard to detect. Several factors like physical activity, dietary intake, smoking and alcohol intake could explain the high prevalence of metabolic diseases in our study and these lifestyle behaviours will be the focus of our future article.

Women with higher socioeconomic status presented with early stage breast cancer disease. It has been reported that intention to seek medical care is not entirely dependent on education and socio-economic status but on complex personal, social factors and previous health care seeking

habit (Khakbazan et al., 2014). Appropriate targeted interventions to address inequalities evident in stage at breast cancer diagnosis may help in improving stage at diagnosis.

Cost of care in breast cancer patients with metabolic diseases, depression and HIV can place a big burden on the limited health care resources in the public hospitals in South Africa. Controlling cost of care and significant patient out of pocket costs should be of great concern among public and private managers and policy makers. The integrated chronic disease management (ICDM) model was introduced as a response to the dual burden of HIV/AIDS and NCDs in South Africa. However, the aim for which the ICDM model was initiated i.e. to use the HIV programme as leverage for scaling up services for NCDs is yet to be achieved (Ameh et al., 2017). The majority of patients experiencing multiple comorbidities visit the health care facilities more frequently, navigation and coordination of care in these patients can be very difficult and ultimately they are vulnerable to sub-optimal quality of care. Our results highlight the necessity for health system integration of services and continuity of care (Boyd et al., 2005). The management of breast cancer patients burdened with metabolic diseases, depression and HIV may result in further fragmentation of care, as cancer treatment is complex and multidisciplinary in nature. It is thus essential for patient management to extend beyond the cancer domain and include the high burden of other communicable and non-communicable diseases. The coordination and integration of care for cancer and other comorbid conditions is fundamental to cost effective health care delivery for patients and health systems alike as previously identified (Walsh et al., 2010, U.S. Department of Health and Human Services, 2010). Shared hospital appointments, community based cancer care, collaboration with primary health care services may all be helpful in improving coordination of care for breast cancer patients and these may improve the survival outcomes in these patients.

Poor quality of life and survival among women with breast cancer may be exacerbated by multiple comorbidities (Fu et al., 2015). Other factors that may adversely affect outcomes include large out of pocket expenses such as transport costs, loss of wages and employment that may result in poor adherence to multiple treatments and adverse drug interactions that may affect cancer treatment efficacy and tolerance. Breast cancer survivors with comorbidities are more likely to experience adverse outcomes due to non-completion of radiation therapy and are less likely to initiate and complete chemotherapy (Giordano et al., 2006, Gold et al., 2008).

The limitations to this study include the fact that it was conducted in Soweto, which might not make our findings generalizable to the whole population in South Africa. Some bias are possible in our recruitment and exposure assessment, however our participation rate was high (91.3%) and women were not aware of our research hypothesis. Therefore, misclassification is most likely random. Simultaneous testing of several hypotheses was carried out in our analysis to assess differences in socio-demographic factors and metabolic diseases, depression and HIV across stage at breast cancer presentation. This could reduce the significance value to very precise levels and increases the chances of a false negative error (Type 2 error) (Giordano et al., 2006); however, our focus was more on the actual effect size rather than the level of significance and our analysis was focused on a single primary end point. Despite these limitations, knowledge gained from this study on prevalence of metabolic diseases, depression and HIV in women from Soweto with and without breast cancer and our finding on the importance of household socioeconomic asset score in relation to stage at breast cancer diagnosis highlights the need for better community awareness and screening for these metabolic diseases, depression, HIV and other chronic diseases, for further research on treatment compliance in patients with breast cancer, tolerance and efficacy, survival outcomes and integration of care for multi-comorbidities.

In conclusion, South African women with breast cancer from socioeconomically disadvantaged communities are burdened with metabolic diseases, depression and HIV. There is a need for research on treatment efficacy and tolerance, coordination of care for easier navigation in our complex health care system.

4. CHAPTER FOUR: PAPER 2

Ayeni, O.A., Norris, S.A., Joffe, M., Cubasch, H., Nietz, S., Buccimazza, I., Singh, U., Čačala, S., Stopforth, L., Chen, W.C. McCormack, V.A., O'Neil, D.S., Judith S. Jacobson, J.S., Neugut, A.I., Ruff, P., and Micklesfield, L.K. The multimorbidity profile of South African women newly diagnosed with breast cancer. *Published online: October 2019, International Journal of Cancer*, *147*(2), pp.361-374.

4.1. Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, accounting for 6.6% of all cancer deaths (Bray et al., 2018). In South Africa, it is also the most common cancer among women, accounting for 20.8% of all female cancers. Age-standardized annual incidence rates are 18 per 100,000 in black women, 49 in women of mixed ancestral, 57 in the Asian women, and 88 in white South African women (South African National Cancer Registry, 2014).

The strongest determinant of breast cancer survival is stage at diagnosis (Cubasch et al., 2018, Iqbal et al., 2015, McKenzie et al., 2018a) and over 50% of women in South Africa have advanced stage disease at diagnosis (Joffe et al., 2018). A similar situation exists across sub-Saharan Africa (SSA), attributable in part to modifiable factors which include lack of early diagnosis strategies at the primary care level, (Opoku et al., 2012) inadequate knowledge and awareness of breast cancer, inadequate access to care, socioeconomic factors, (Joffe et al., 2018, Merkin et al., 2002, McKenzie et al., 2018a) as well as tumour biology (Curtis et al., 2008).

In addition to late diagnosis, another challenge to breast cancer control in South Africa may be the presence of chronic conditions at the time of breast cancer diagnosis. Multimorbidity has been defined as the presence of two or more chronic conditions in the same individual (World

Health Organisation, 2016). In South Africa, the effective treatment of infectious diseases, such as human immunodeficiency virus (HIV), has extended life expectancy, leading to increases in the prevalence of age-related chronic conditions. The number of people with two or more chronic conditions, such as cancer, hypertension, diabetes, obesity, HIV and tuberculosis is also growing rapidly and the burden is worse in poor communities (Mayosi et al., 2009). Patients with multimorbidity are at higher risk for inadequate disease management due to independent management of each disease within overburdened health systems, significant out of pocket costs and poor adherence for the patients who are likely to have to take more medications, adverse drug reactions, and potential drug-drug, drug-enzyme and drug-gene interactions affecting treatment efficacy (Bahar et al., 2017, World Health Organisation, 2016). Further, patients with multimorbidity may be at additional risk of sub-standard care due to a high possibility of obtaining conflicting advice on care and treatment (McCormick and Boling, 2005, Starfield et al., 2003). The burden of multimorbidity, its determinants and impact on healthcare is well established in high income countries, (Salisbury et al., 2011, Schäfer et al., 2012) but there are few studies in low and middle income countries (Alaba and Chola, 2013, Khanam et al., 2011). Many women with breast cancer have other chronic diseases at the time of their breast cancer diagnosis, and these conditions may affect the stage at diagnosis of breast cancer, treatment modality, and prognosis (Gurney et al., 2015, Sheppard et al., 2011, Sarfati et al., 2016, Søgaard et al., 2013). It has been demonstrated that patients with cancer and other chronic diseases have reduced quality of life and survival (Braithwaite et al., 2012, Søgaard et al., 2013, Fu et al., 2015).

In our previous work describing the prevalence of multimorbid health conditions among 798 black South African women with and without breast cancer, although multimorbidity prevalence in cases was not higher than in the age-matched general population, the prevalence

in cases were themselves high: 79.5% were overweight or obese, 59.2% were hypertensive, 46.6% had impaired fasting plasma glucose, 16.5% were HIV positive and 64.2% had ≥2 chronic conditions (Ayeni et al., 2019a). Other South African studies reported that the prevalence of multimorbidity increases with age (Oni et al., 2015) and is associated with higher household income (Alaba and Chola, 2013).

The prevalence and patterns of multimorbidity in a given cancer patient population have important implications for targeted patient-oriented prevention, diagnosis, treatment, disease control and improved outcome strategies (Prados-Torres et al., 2014). The aim of this study is four-fold: (i) to describe the prevalence and patterns of multimorbidity in women newly diagnosed with breast cancer in five public hospitals in South Africa; (ii) to determine socio-demographic factors associated with different chronic conditions; (iii) to determine the factors associated with multimorbidity; and (iv) to assess whether multimorbidity is associated with breast cancer stage at diagnosis and first treatment received.

4.2. Methods

We used data from a cohort of women enrolled in the ongoing South African Breast Cancer and HIV Outcomes study (SABCHO) collected between January 2016 and April 2018 (Cubasch et al., 2016). Five public hospital breast centres across Gauteng and KwaZulu-Natal provinces served as recruitment sites: Chris Hani Baragwanath Academic Hospital (Soweto hospital, Johannesburg), Charlotte Maxeke Johannesburg Academic Hospital (Central Johannesburg hospital), Addington Hospital and Inkosi Albert Luthuli Central Hospital in Durban (KwaZulu-Natal (KZN) Durban hospitals), Grey's Hospital, Pietermaritzburg (KZN Pietermaritzburg hospital) and Ngwelezane Hospital (KZN rural hospital). The tertiary hospitals where all patients were enrolled on the study and received their treatments are located

in city centres. The Central Johannesburg, KZN Durban hospitals and KZN Pietermaritzburg hospital all provide diagnostic services, surgery, chemotherapy, radiation therapy and endocrine treatments. The Soweto hospital, Johannesburg provides diagnostic, surgical and endocrine treatment services and patients have to travel to the Central Johannesburg hospital for chemotherapy and radiation treatments. The KZN rural hospital provides only diagnostic services, endocrine treatments and follow up surveillance of patients following surgical, chemotherapy and radiation therapy treatments at KZN Durban hospitals located more than 200km away. In the KwaZulu-Natal province most patients undergo diagnostic procedures in the district referral hospitals and surgery is performed either at district hospitals or at the tertiary hospital centres. Some Patients have to bare out of pocket transport costs to access their treatment while others travel using hospital transport. The women differ in education and socioeconomic status with the more rural communities accessing the KZN Pietermaritzburg and KZN rural hospitals generally less educated and more impoverished than urban communities" The patient referral demographics for each participating hospital are shown in Table 4.1.

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Approval Number: Ml50351, dated: 6th May 2015), and the Institutional Review Board of Columbia University (protocol number AAAQ1359, dated 1st January 2016). This study was performed in accordance with the Declaration of Helsinki.

4.1.1. Recruitment of participants

Women who were newly diagnosed with invasive breast cancer, were ≥18 years of age and had resided in South Africa for ≥ 5 years were eligible for enrolment in the SABCHO study. Patients who had a previous cancer diagnosis (excluding non-melanoma skin cancer or non-

invasive cervical cancer), had previously received > 1 month of radiotherapy or chemotherapy, had previously received any endocrine therapy, or were unable to give informed consent, were excluded.

4.1.2. Study procedures

Women were enrolled on the day of the diagnostic visit following voluntary written informed consent. Participants consented to HIV testing. Those who tested positive were referred for ART initiation prior to commencement of cancer treatment. Those who refused HIV testing were still included in the study and HIV status was recorded as unknown.

4.1.3. Socio-demographic and anthropometric measures

Trained study staff collected detailed socio-demographic information (age, self-identified ethnicity, marital status, employment status, highest level of education completed, residential address); reproductive history (number of full term pregnancies, age at first full-term pregnancy, use of oral and injectable contraceptives, use of hormone replacement therapy) and behavioural factors (alcohol consumption, smoking). Tumour American Joint Committee on Cancer (7th edition) stage, grade, receptor status and first treatment received data were extracted from medical records (Edge and Compton, 2010). Participants were grouped by stage at diagnosis as early (I-II) or advanced (III-IV).

Household socio-economic scores were determined using self-reported home ownership, car ownership, possession of a washing machine or microwave, presence of a flush toilet inside the home and presence of indoor running water. We assigned a score of 1 for each of these items and the scores were added out of a total of six. We documented the residential address

of each participant at enrolment and computed the shortest straight-line distance to the enrolling hospital in kilometres (km).

We assessed seven chronic conditions: obesity, hypertension, diabetes, cerebrovascular disease, asthma/COPD, HIV infection and tuberculosis. HIV status was tested using the enzyme-linked immunosorbent assay through the National Health Laboratory Services. Body weight and height measurements were measured at enrolment, and obesity was defined as a body mass index (BMI) ≥30.0 kg/m2.

Table 4.1: Characteristics of the hospital sites

	Soweto hospital, Johannesburg[1]	Central Johannesburg hospital[2]	KZN Durban hospitals[3]	KZN Pietermaritzburg hospital[4]	KZN rural hospital[5]
Location	Johannesburg (Gauteng province)	Johannesburg (Gauteng province)	Durban (KwaZulu-Natal Province)	Pietermaritz-burg (KwaZulu-Natal Province)	Empageni (KwaZulu-Natal Province)
Main population catchment area (N)	Soweto (3 million)	Johannesburg, East and Central (1.5 million)	Durban metropolitan, (3.5 million)	Western KwaZulu-Natal and distant rural communities (3.5 million),	Uthungulu, Umkhanyakude, Zululand (3 million)
Surgery	Surgery performed at this hospital	Surgery performed at this hospital	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital
Oncology capacity (Chemotherapy and radiotherapy)	None. Patients are referred to Central Johannesburg hospital	Full oncology capacity	Full oncology capacity	Full oncology capacity	None. Patients are referred to KZN Durban hospitals.

[1]Chris Hani Baragwanath Academic Hospital, Soweto Johannesburg
[2]Charlotte Maxeke Johannesburg Academic Hospital
[3]Addington Hospital and Inkosi Albert Luthuli Central Hospital, Durban, KwaZulu-Natal
[4]Grey's Hospital, Pietermaritzburg, KwaZulu-Natal
[5]Ngwelezane Hospital, KwaZulu-Natal

Patients were asked if they were ever treated for tuberculosis and whether they had ever been diagnosed and treated for the other four conditions (hypertension, diabetes, cerebrovascular disease and asthma/COPD). We defined multimorbidity as having ≥ 2 of these seven chronic conditions.

4.3. Statistical analysis

Determinants of each chronic condition and multimorbidity (≥2 chronic conditions) were examined in a multisite-pooled analysis using bivariate and multivariate logistic regression. Odds ratios (OR) for multimorbidity were examined in 3 models by adding potentially associated factors in a stepwise fashion. Model 1 we examined all socio-demographic factors (age, ethnicity, marital status, highest level of education, employment status and household socio-economic status). Model 2 included socio-demographic and geographical factors (hospital site and residential distance from the hospital), and model 3 included socio-demographic, geographical factors and behavioural factors (alcohol intake and smoking). Finally, multivariable logistic regression models were used to examine whether chronic conditions and multimorbidity were associated with advanced stage breast cancer (stage III-IV). We included in the multivariate models variables for which p-values were <0.1 in bivariate analysis with advanced stage breast cancer. ORs were examined in two models (model A (unadjusted) and model B (which was adjusted for age, race, highest level of education and hospital site). We further examined the associations between multimorbidity and first treatment received (primary surgery, neoadjuvant chemotherapy or neoadjuvant endocrine therapy) by their stage at diagnosis using Pearson's Chi-squared test. Analysis was performed using Stata version 15 (StataCorp Ltd, Texas, USA).

4.4. Results

A total of 2281 women were included in the study: 795 (34.9%) from Soweto, Johannesburg hospital, 511 (22.4%) from Central Johannesburg hospital, 435 (19.1%) from KZN Durban hospitals, 462 (20.2%) from KZN Pietermaritzburg hospital and 77 (3.4%) from KZN rural hospital (Table 4.2). The mean age at diagnosis was 56.2 ± 14.3 years; women from the two Johannesburg hospitals compared to the KZN cities hospitals (Durban and Pietermaritzburg) were significantly younger and more likely to be married. In the combined sample, the majority (76.9%) of women were black Africans while KZN Durban hospitals had the highest percentage of Asians (39.4%) compared to other sites, and central Johannesburg hospital had the highest number of white women (17.0%).

In the combined sample, most of the women had at least a high school education (72.3%), but there was a significant difference between the sites as 52.1% of women attending KZN rural hospital had only completed primary education. Overall >50% of women were unemployed; women from the Johannesburg hospitals and KZN Durban hospitals had higher HSES than women from KZN Pietermaritzburg and KZN rural hospitals. Participants from KZN Pietermaritzburg hospital had the furthest distance to travel and women from Soweto, Johannesburg hospital travelled the shortest distance (84.1 vs. 12.8km) (Table 4.2). There was a significant difference between the sites for smoking and alcohol consumption, with the KZN rural hospital reporting the least for both compared to the other sites.

Table 4.2: Socio-demographic characteristics, prevalence of chronic conditions and stage at breast cancer diagnosis in women newly diagnosed with breast cancer in South Africa, by study-site.

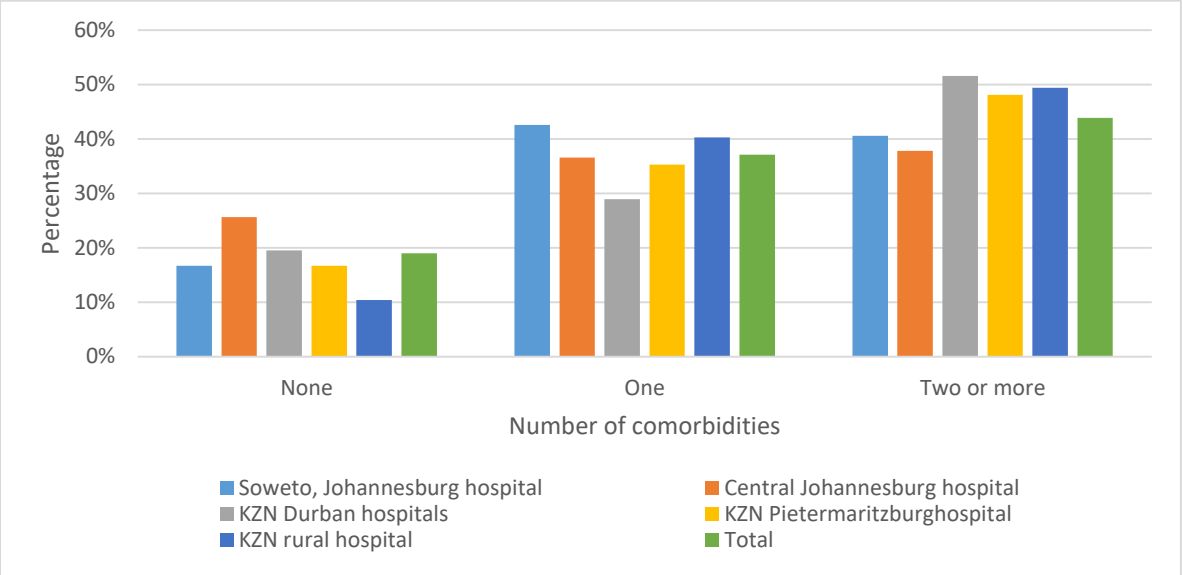
	Soweto, Johannesburg Hospital (n=795)	Central Johannesburg hospital (n=511)	KZN Durban hospitals (n=436)	KZN Pietermaritzburg hospital (n=462)	KZN rural hospital (n=77)	Total N=2281	P value
Age in years, mean ± SD	55.1 ± 14.3	55.3 ± 14.2	58.1 ± 13.6	57.3 ± 14.7	55.6 ± 14.8	56.2 ± 14.3	0.002
Ethnicity							
Asian	7 (0.9%)	18 (3.5%)	172 (39.4%)	63 (13.6%)	1 (1.3%)	261 (11.4%)	<0.001
Black	734 (92.3%)	378 (74.0%)	203 (46.6%)	364 (78.8%)	75 (97.4%)	1,754 (76.9%)	
Mixed	42 (5.3%)	28 (5.5%)	17 (3.9%)	18 (3.9%)	0 (0.0%)	105 (4.6%)	
White	12 (1.5%)	87 (17.0%)	44 (10.1%)	17 (3.7%)	1 (1.3%)	161 (7.1%)	
Marital status							
Married/co-habiting	329 (41.5%)	212 (41.5%)	156 (36.1%)	140 (30.5%)	24 (31.2%)	861 (37.9%)	0.001
Unmarried	464 (58.5%)	299 (58.5%)	276 (63.9%)	319 (69.5%)	53 (68.8%)	1,411(62.1%)	
Highest level of education							
Completion of informal/primary education	192 (24.2%)	90 (17.8%)	127 (29.7%)	180 (39.2%)	38 (52.1%)	627 (27.7%)	<0.001
Completion of high school/any tertiary education	602 (75.8%)	416 (82.2%)	301 (70.3%)	279 (60.8%)	35 (47.9%)	1,633 (72.3%)	
Employment status							
Unemployed	583 (73.3%)	335 (65.6%)	342 (78.4%)	373 (80.7%)	63 (81.8%)	1,696 (74.4%)	<0.001
Employed	212 (26.7%)	176 (34.4%)	94 (21.6%)	89 (19.3%)	14 (18.2%)	585 (25.6%)	
[a]**Household socio-economic status (score 0-6), median(IQR)**	4 (2-5)	4 (3-5)	4 (2-4)	2 (1-4)	1 (1-2)	2 (3-5)	<0.001
Residential distance from hospital site (km), median (IQR)	12.8 (6.8-27.2)	19.7 (8.7-34.7)	20.4 (16.0-56.1)	84.1 (8.3-155.6)	58.9 (29.1-144.2)	20.6 (8.9-42.9)	<0.001

Have you ever consumed alcohol?							
No	616 (77.5%)	407 (79.7%)	359 (82.3%)	382 (82.7%)	68 (88.3%)	1,832 (80.3%)	0.039
Yes	179 (22.5%)	104 (20.3%)	77 (17.7%)	80 (17.3%)	9 (11.7%)	449 (19.7%)	
Have you ever smoked?							
No	718 (90.3%)	427 (83.6%)	367 (84.2%)	413 (89.4%)	74 (96.1%)	1,999 (87.6%)	<0.001*
Yes	77 (9.7%)	84 (16.4%)	69 (15.8%)	49 (10.6%)	3 (3.9%)	282 (12.4%)	
Stage at diagnosis							
Early stage (0-II)	402 (50.6%)	196 (38.4%)	172 (40.0%)	181 (39.2%)	14 (18.4%)	965 (43.9%)	<0.001
Advanced stage (III & IV)	393 (49.4%)	315 (61.6%)	258 (60.0%)	281 (60.8%)	62 (81.6%)	1309 (56.1%)	
Receptor subtype							
Luminal A	111 (14.1%)	123 (24.6%)	152 (35.0%)	71 (15.4%)	19 (24.7%)	476 (21.1%)	<0.001
Luminal B	467 (59.5%)	232 (46.4%)	172 (39.7%)	255 (55.3%)	30 (38.9%)	1156 (51.2%)	
HER2 enriched	94 (12.0%)	69 (13.8%)	50 (11.5%)	58 (12.6%)	14 (18.2%)	285 (12.6%)	
Triple negative	113 (14.4%)	76 (15.2%)	60 (13.8%)	77 (16.7%)	14 (18.2%)	340 (15.1%)	
Chronic conditions considered							
Nutritional status (BMI)							
[a]Underweight & Normal ($\leq$24.9 kg/m^2)	160 (21.8%)	98 (20.6%)	96 (23.4%)	109 (24.4%)	19 (24.7%)	482 (22.5%)	0.094
Overweight (25-29.9 kg/m^2)	160 (21.8%)	133 (28.0%)	117 (28.5%)	103 (23.1%)	17 (22.1%)	530 (24.7%)	
Obese ($\geq$ 30.0 kg/m^2)	415 (56.4%)	244 (51.4%)	197 (48.1%)	234 (52.5%)	41 (53.2%)	1,131 (52.8%)	
Self-reported hypertension							
No	487 (61.3%)	322 (63.0%)	224 (51.4%)	254 (55.0%)	51 (66.2%)	1,338 (58.7%)	<0.001
Yes	308 (38.7%)	189 (37.0%)	212 (48.6%)	208 (45.0%)	26 (33.8%)	943 (41.3%)	
HIV status							
Negative	564 (74.7%)	401 (82.5%)	342 (85.3%)	343 (75.4%)	45 (59.2%)	1,695 (78.0%)	<0.001
Positive	191 (25.3%)	85 (17.5%)	59 (14.7%)	112 (24.6%)	31 (40.8%)	478 (22.0%)	
Self-reported diabetes							
No	720 (90.6%)	465 (91.0%)	324 (74.3%)	388 (84.0%)	71 (92.2%)	1,968 (86.3%)	<0.001

Yes	75 (9.4%)	46 (9.0%)	112 (25.7%)	74 (16.0%)	6 (7.8%)	313 (13.7%)	
Self-reported prior tuberculosis							
No	742 (93.3%)	491 (96.1%)	394 (90.4%)	417 (90.3%)	70 (90.9%)	2,114 (92.7%)	0.002
Yes	53 (6.7%)	20 (3.9%)	42 (9.6%)	45 (9.7%)	7 (9.1%)	167 (7.3%)	
Self-reported asthma/COPD							
No	763 (96.0%)	482 (94.3%)	399 (91.5%)	444 (96.1%)	71 (92.2%)	2,159 (94.7%)	0.007
Yes	32 (4.0%)	29 (5.7%)	37 (8.5%)	18 (3.9%)	6 (7.8%)	122 (5.3%)	
Self-reported cerebrovascular disease							
No	773 (97.2%)	503 (98.4%)	412 (94.5%)	453 (98.1%)	74 (96.1%)	2,215 (97.1%)	0.005*
Yes	22 (2.8%)	8 (1.6%)	24 (5.5%)	9 (1.9%)	3 (3.9%)	66 (2.9%)	

- [a]HSES: Household socio-economic status (possessions) score determined from: (home ownership=1, motor vehicle=1, microwave=1, washing machine=1, flush toilet=1, indoor running water=1) Denominator= 6 (1 for Yes, 0 for No).
- [b]54 women were underweight
- KZN (KwaZulu-Natal)
- Missing values for covariates were as follows: marital status (n=9), highest level of education (n=21), BMI (n=138), HIV status unknown (n=108), stage at diagnosis (n=7).
- P value* (Fisher's exact test).
- BMI (Body mass index), COPD (Chronic obstructive pulmonary disease)
- SD (standard deviation), IQR (interquartile range), km (kilometres)

Figure 4.1: Percentage of women newly diagnosed with breast cancer from each hospital site in South Africa, with none, one, two or more of obesity, self-reported hypertension, self-reported diabetes, self-reported cerebrovascular disease, self-reported asthma/COPD, HIV and self-reported prior tuberculosis.



* KZN (KwaZulu-Natal)

Overall, 56.1% of the women presented with advanced stage breast cancer. Soweto, Johannesburg hospital was the only site where more than half (50.6%) presented at an early (stage I-II). Most (72.3%) of the women had oestrogen and progesterone receptor positive (Luminal A and B) breast cancer (Table 4.2).

At enrolment, 19.0% of the women reported no chronic conditions (hypertension, diabetes, cerebrovascular diseases, asthma/chronic obstructive pulmonary disease, tuberculosis, HIV and obesity) ranging from 10.4% in KZN rural hospital to 25.6% at Central Johannesburg hospital (Figure 4.1 and supplementary table 4.1).

In the combined sample, 52.8% of women were obese. The second most common chronic condition was hypertension (41.0%), which ranged from 34.0% at the KZN rural hospital to

48.6% at KZN Durban hospitals. HIV was the third most prevalent chronic condition (22.0%) but with considerable variation, highest (40.8%) at the KZN rural hospital and lowest at the KZN Durban hospitals (14.7%). Diabetes ranked as the fourth most prevalent chronic condition affecting 14% of women, with <10% at the two Johannesburg hospitals. Finally ranking fifth, sixth and seventh were tuberculosis, COPD/asthma and cerebrovascular disease, respectively, with each present in less than 10% of breast cancer patients at each site.

Overall, 43.9% of breast cancer patients met our definition of multimorbidity (presence of ≥2 additional chronic conditions) and KZN Durban hospitals had the highest proportion (51.6%) (Figure 4.1 and supplementary table 4.1).

Bivariate and multivariable logistic regression models of associations between socio-demographic variables and each chronic condition are presented in supplementary table 4.3 and table 4.3 respectively.

In the multivariate analysis, with every 1-year increase in age, there was an 8% increase in the odds of hypertension, 4% increase in the odds of having diabetes, 4% increase in the odds of cerebrovascular disease, 6% reduced odds of HIV and 3% reduced odds of tuberculosis. When compared to the black women, white women had reduced odds of all the chronic conditions except asthma and the Asian women had increased odds of hypertension, diabetes and asthma/COPD.

Of the three measures of socio-economic status, HSES was most frequently associated with the presence of a chronic condition. Women with higher HSES were more likely to be obese, hypertensive, diabetic, report asthma/COPD, and were less likely to be living with HIV (Table 4.3). The variance in the different chronic conditions that could be explained by age, race and socio-economic status ranged from 2% for obesity to 22% for HIV infection.

Table 4.3: Pooled multivariate logistic regression model of socio-demographic characteristics and association with chronic conditions in women newly diagnosed with breast cancer in South Africa.

Socio-demographic characteristics	Obesity (BMI ≥ 30.0 kg/m2)	Hypertension	Diabetes	Cerebrovascular disease	Asthma/COPD	HIV positive	Tuberculosis
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age in years	1.00 (0.99-1.00)	1.08 (1.07-1.09) [b]	1.04 (1.03-1.05) [b]	1.04 (1.02-1.06) [b]	0.99 (.98-1.01)	0.94 (0.93-0.95) [b]	0.97 (0.95-0.98) [b]
Race							
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Asian	0.8 (0.6-1.3)	3.3 (2.1-5.3) [b]	9.4 (4.5-19.6) [b]	1.1 (0.4-3.1)	1.0 (0.5-2.1)	0.3 (0.1-3.6)	0.8 (0.2-3.0)
Black	2.1 (1.4-2.9) [b]	2.4 (1.6-3.5) [b]	2.8 (1.4-5.8) [b]	0.6 (0.2-1.6)	0.5 (0.3-0.9) [a]	16.4 (4.0-67.2) [b]	2.5 (0.9-6.9)
Mixed	1.5 (0.9-2.6)	2.8 (1.6-5.0) [b]	4.4 (1.9-10.3) [b]	0.5 (0.1-2.8)	0.7 (0.3-1.8)	5.2 (1.1-25.7) [a]	2.0 (0.5-7.2)
Highest level of education							
Primary education and below	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Secondary and above	1.2 (0.9-1.5)	1.0 (0.8-1.2)	0.9 (0.6-1.2)	0.8 (0.4-1.4)	0.8 (0.4-1.2)	1.2 (0.9-1.6)	0.7 (0.5-1.1)
Employment status							
Unemployed	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Employed	1.2 (0.9-1.4)	0.8 (0.6-1.0)	0.7 (0.5-0.9) [a]	0.7 (0.3-1.6)	0.7 (0.4-1.2)	1.2 (0.9-1.5)	0.8 (0.6-1.2)
Household socio-economic status (score 0-6)	1.2 (1.1-1.2) [b]	1.1 (1.0-1.1) [a]	1.1 (1.0-1.2) [a]	0.9 (0.8-1.1)	1.2 (1.0-1.3) [a]	0.8 (0.8-0.9) [b]	0.9 (0.8-1.0)
R2	**0.02**	**0.19**	**0.11**	**0.06**	**0.02**	**0.22**	**0.04**

OR (Odds ratio), 95% CI (95% confidence interval), COPD (Chronic obstructive pulmonary disease), [a] Significant at p<0.05, [b] Significant at p<0.001

[a]HSES: Household socio-economic status (possessions) score determined from: (home ownership=1, motor vehicle=1, microwave=1, washing machine=1, flush toilet=1, indoor running water=1)

Denominator= 6 (1 for Yes, 0 for No).

Table 4.4: Pooled associations between socio-demographic, geographical and behavioural factors with chronic conditions (≥2 (multimorbidity) vs. <2) in women newly diagnosed with breast cancer.

Characteristics	< 2 chronic conditions N=1280	≥2 chronic conditions (multimorbidity) N=1001	Bivariate analysis OR (95% CI)	P value
Age in years, mean ± SD	54.4 ± 15.0	58.4 ±13.0	1.02 (1.01-1.03)	<0.001*
Ethnicity (%)				
Black	976 (76.2%)	778 (77.7%)	1.00 (Referent)	
Asian	130 (10.2%)	131 (13.1%)	1.26 (0.97-1.64)	<0.001*
Mixed	56 (4.4%)	49 (4.9%)	1.10 (0.74-1.63)	
White	118 (9.2%)	43 (4.3%)	0.46 (0.32-0.66)	
Marital status (%)				
Married/co-habiting	513 (40.2%)	348 (34.9%)	1.00 (Ref)	0.010*
Unmarried	763 (59.8%)	648 (65.1%)	1.25 (1.05-1.49)	
Highest level of education (%)				
Primary education and below	324 (24.4%)	303 (30.7%)	1.00 (Referent)	0.006*
Secondary education and above	949 (74.6%)	684 (69.3%)	0.77 (0.64-0.93)	
Employment status (%)				
Unemployed	921 (71.9%)	775 (77.4%)	1.00 (Referent)	0.003*
Employed	359 (28.1%)	226 (22.6%)	0.75 (0.62-0.91)	
Household socio-economic status (score 0-6), median (IQR)	3 (2-5)	4 (2-5)	1.02 (0.97-1.07)	0.488
Hospital site (%)				
Soweto, Johannesburg	472 (36.9%)	323 (32.3%)	1.00 (Referent)	<0.001*
Central Johannesburg	318 (24.8%)	193 (19.3%)	0.89 (0.71-1.11)	
KZN Durban	211 (16.5%)	225 (22.5%)	1.56 (1.23-1.97)	
KZN Pietermaritzburg	240 (18.8%)	222 (22.2%)	1.35 (1.07-1.70)	
KZN rural	39 (3.1%)	38 (3.8%)	1.42 (0.89-2.28)	
Residential distance from hospital site (km), median (IQR)	19.9 (8.7-39.5)	21.8 (9.1-48.1)	1.00 (1.00-1.01)	0.033*
Have you ever consumed alcohol? (%)				
No	1004 (78.4%)	828 (82.7%)	1.00 (Ref)	0.011*
Yes	276 (21.6%)	173 (17.3%)	0.76 (0.62-0.94)	
Have you ever smoked? (%)				0.044*

No	1106 (86.4%)	893 (89.2%)	1.00 (Ref)
Yes	174 (13.6%)	108 (10.8%)	0.77 (0.60-0.99)

OR (Odds ratio) = odds of reporting ≥2 chronic conditions compared with <2 chronic conditions, *variables significant at p<0.05.
[a]HSES: Household socio-economic status (possessions) score determined from: (home ownership=1, motor vehicle=1, microwave=1, washing machine=1, flush toilet=1, indoor running water=1) Denominator= 6 (1 for Yes, 0 for No), KZN (KwaZulu-Natal), SD (standard deviation), IQR (interquartile range), km (kilometres)

In table 4.4, bivariate logistic regression showed positive associations between multimorbidity and age, marital status, hospital sites and negative associations with ethnicity, highest level of education, employment status, alcohol consumption and smoking. These significant associations at the bivariate level were further explored in multivariate logistic regressions in three models (Table 4.5).

In model 1 (socio-demographic variables only), age contributed independently to an increased odds of multimorbidity and being white was associated with a decreased odds of multimorbidity. In model 2 (socio-demographic and geographical factors) age and white ethnicity remained significant and being Asian was associated with a lower odds of multimorbidity. Women from KZN Durban hospitals (OR=1.90, 95% CI 1.43-2.53) and KZN Pietermaritzburg hospital (OR 1.49, 95% CI 1.13-1.98) had an increased odds of having multimorbidity and the factors in model 2 were able to explain 3.1% of the variance in multimorbidity. In model 3 (socio-demographic, geographical and behavioural variables), age, white and Asian ethnicity, enrolment at KZN Durban hospitals and KZN Pietermaritzburg hospital remained significant, although higher HSES was now associated with an increased odds of multimorbidity (OR=1.06, 95% CI 1.00-1.13), none of the behavioural factors were significant in the model (Table 4.5).

Table 4.5: Pooled multiple logistic regression model of socio-demographic, geographical and behavioural factors associated with ≥2 chronic conditions (multimorbidity) in women newly diagnosed with breast cancer.

Characteristics	Model 1 (Socio-demographic factors) OR (95% CI)	Model 2 (Socio-demographic and geographical factors) OR (95% CI)	Model 3 (Socio-demographic, geographical and behavioural factors) OR (95% CI)
Age in years	**1.02 (1.01-1.03)[b]**	**1.02 (1.01-1.03)[b]**	**1.02 (1.01-1.03)[b]**
Ethnicity			
Black	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Asian	1.05 (0.79-1.38)	**0.70 (0.50-0.97)[a]**	**0.70 (0.50-0.97)[a]**
Mixed	0.99 (0.66-1.50)	0.93 (0.61-1.40)	0.97 (0.63-1.49)
White	**0.39 (0.27-0.58)[b]**	**0.34 (0.23-0.51)[b]**	**0.36 (0.24-0.54)[b]**
Marital status			
Married/co-habiting	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Unmarried	1.09 (0.90-1.30)	1.06 (0.89-1.28)	1.07 (0.89-1.29)
Highest level of education			
Primary education and below	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Secondary education and above	1.04 (0.84-1.29)	1.08 (0.87-1.35)	1.08 (0.87-1.35)
Employment status			
Unemployed	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Employed	0.93 (0.75-1.14)	0.93 (0.75-1.15)	0.93 (0.75-1.15)
Household socio-economic status (score 0-6)	1.01 (0.96-1.07)	1.06 (0.99-1.13)	**1.06 (1.00-1.13)[b]**
Hospital site			
Soweto, Johannesburg		1.00 (Ref)	1.00 (Ref)
Central Johannesburg		1.03 (0.81-1.31)	1.02 (0.80-1.30)
KZN Durban		**1.90 (1.43-2.53)[b]**	**1.89 (1.42-2.51)[b]**
KZN Pietermaritzburg		**1.49 (1.13-1.98)[a]**	**1.49 (1.12-1.97)[a]**
KZN rural		1.57 (0.94-2.63)	1.54 (0.92-2.57)
Residential distance from hospital site (km)		1.00 (0.99-1.00)	1.00 (0.99-1.00)
Have you ever consumed alcohol?			
No			1.00 (Ref)
Yes			0.85 (0.67-1.07)
Have you ever smoked?			
No			1.00 (Ref)
Yes			0.96 (0.71-1.29)
R^2	0.028	0.031	0.033

OR (Odds ratio) = odds of reporting ≥2 chronic conditions compared with <2 chronic conditions
[a] Significant at p<0.05, [b] Significant at p<0.001
KZN (KwaZulu-Natal)

Bivariate and multivariate logistic regression models of chronic conditions and multimorbidity associated with advanced stage breast cancer disease at diagnosis are presented in tables 4.6

and 4.7 respectively. In the bivariate analysis (Table 4.6), obesity and hypertension were negatively associated with advanced stage breast cancer at diagnosis. Women who were HIV positive and women who reported prior tuberculosis had positive associations with advanced stage breast cancer at diagnosis. There was no significant association between multimorbidity and advanced stage breast cancer at diagnosis (OR=0.88, 95% CI 0.74-1.04) (Table 4.6). The significant variables at p <0.1 were further explored in the multivariate model (Table 4.7).

Table 4.6: Pooled bivariate analyses of the association between chronic conditions and advanced stage disease amongst women newly diagnosed with breast cancer.

Characteristics	Bivariate analysis OR (95% CI)	P value
Obese	0.84 (0.70-0.99)	**0.041***
Self-reported hypertension	0.74 (0.62-0.87)	**<0.001***
Self-reported diabetes	0.80 (0.63-1.01)	0.064
Self-reported cerebrovascular disease	1.00 (0.61-1.64)	0.998
Self-reported asthma/COPD	0.82 (0.57-1.18)	0.286
HIV positive	1.52 (1.23-1.87)	**<0.001***
Self-reported prior tuberculosis	1.49 (1.07-2.08)	**0.019***
Multimorbidity	0.88 (0.68-1.10)	0.138

*Significant at p<0.05, COPD (Chronic obstructive pulmonary disease)

In Model A (Table 4.7), women who reported having hypertension had lower odds of advanced stage breast cancer and women who were HIV positive had higher odds of advanced stage breast cancer at diagnosis than those women without the disease.

Table 4.7: Pooled multivariate logistic regression models of chronic conditions associated with advanced stage disease (stages III-IV) in women newly diagnosed with breast cancer.

Characteristics	Model A OR (95% CI)	P value	Model B OR (95% CI)	P value
Obese	0.92 (0.77-1.09)	0.340	0.85 (0.71-1.03)	0.098
Self-reported hypertension	0.77 (0.64-0.92)	**0.005***	0.80 (0.64-0.98)	**0.036***
HIV positive	1.36 (1.09-1.71)	**0.008***	1.07 (0.83-1.38)	0.582
Self-reported prior tuberculosis	1.32 (0.93-1.88)	0.123	1.22 (0.84-1.78)	0.286
R^2	0.013		0.040	

*Significant at p<0.05, model A (unadjusted), model B (adjusted for age on presentation, race, highest level of education and hospital site)

In model B, adjusting for age, race, highest level of education and hospital site, self-reported hypertension (OR=0.80, 95% CI 0.64-0.98) was the only chronic condition associated with advanced stage breast cancer disease (Table 4.7).

In women with early stage (stages 1-II) breast cancer, there was a significantly higher proportion of women with multimorbidity who received neoadjuvant endocrine therapy (18.2%) compared to those without multimorbidity who received neoadjuvant endocrine treatment (10.5%), p=0.003 (Table 4.8).

Table 4.8: Association between multimorbidity and first treatment received by stage at diagnosis in women newly diagnosed with breast cancer.

Multimorbidity	Stages 1-II (Early stage)				Stages III & IV (Advanced stage)			
	Primary surgery	Neoadjuvant chemotherapy	Neoadjuvant endocrine therapy	P value	Primary surgery	Neoadjuvant chemotherapy	Neoadjuvant endocrine therapy	P value
	N=662 (%)	N=141 (%)	N=131 (%)		N=125 (%)	N=881 (%)	N=206 (%)	
No (< 2 chronic conditions)	372 (73.7)	80 (15.8)	53 (10.5)	**0.003**	67 (9.6)	520 (74.7)	109 (15.7)	0.184
Yes (≥ 2 chronic conditions)	290 (67.6)	61 (14.2)	78 (18.2)		58 (11.2)	361 (70.0)	97 (18.8)	
***Total**	662 (70.9)	141 (15.1)	131 (14.0)		125 (10.3)	881 (72.7)	206 (17.0)	

*Total for stages 0-II (early stage) = 934, total for stages III & IV (advanced stage) = 1212. Some 135 women had missing treatment information.
Row percentages shown

4.5. Discussion

In this study, we found that among women newly diagnosed with breast cancer from five public hospitals across South Africa, more than 80% reported at least one chronic condition and 43.9% had two or more chronic conditions. Older women, higher HSES, and women enrolled at the KZN Durban and Pietermaritzburg hospitals, had higher odds of multimorbidity, while the Asian and white women were less likely to present with multimorbidity when compared to black women. Hypertensive women were less likely to have advanced stage breast cancer at diagnosis, whilst multimorbidity was not associated with advanced stage breast cancer at diagnosis.

The burden of multimorbidity in our cohort was high with 43.9% of the whole sample reporting two or more chronic conditions. Multimorbidity is of increasing concern in South Africa and this high prevalence of non-communicable and communicable multimorbidity has significant implications for the mode of health care delivery and the health system. Severe chronic conditions narrow treatment choices and are associated with poor quality of life and survival, especially in postmenopausal women (Yancik et al., 2001, Fu et al., 2015). In South Africa chronic disease management is meant to be delivered using the integrated chronic disease management approach; (Mahomed and Asmall, 2015) however this is yet to be achieved as people with multimorbidity receive fragmented and inefficient health care delivery (Draper et al., 2014, Mahomed et al., 2016). There is a need for an effective integrated and comprehensive array of health services spanning from primary to tertiary levels.

The most common chronic condition reported in this sample of women with breast cancer was obesity (52.8%), which was much higher than report from the recent South African national

survey with obesity prevalence of 41.7% in adult women (ranging from 30.6% among the white women to 49.2% among the Asian women) (Statistics South Africa, 2016).

Our results indicate that multimorbidity in women with breast cancer is associated with socio-demographic characteristics (age, race and HSES) and hospital site where they are seeking health care. It is well accepted that multimorbidity is associated with increasing age, due to age-related chronic health conditions (Uijen and van de Lisdonk, 2008). The Asians in South Africa have been reported to have a high burden of chronic conditions, (Alaba and Chola, 2013) which is in keeping with our findings for individual chronic conditions in this population group. This is primarily the result of high prevalence of hypertension and diabetes in the Asian group; HIV prevalence was low. A study conducted among Asian South Africans living in Durban also reported a high burden of hypertension (47.5%), diabetes (20.1%), and obesity (32.4%) (Prakaschandra et al., 2016). Despite this high finding of the prevalence of individual chronic conditions in Asian women in our cohort, they were still less likely to present with multimorbidity (OR=0.70, 95% CI 0.50-0.97) compared to the black African women. This may be due to the higher prevalence of obesity in the black women, (Human Sciences Research Council, 2013) and equally high burden of hypertension. South Africa has the highest burden of hypertension in people >50 years of age in SSA, (Lloyd-Sherlock et al., 2014, Prados-Torres et al., 2014) HIV-infection and tuberculosis were almost exclusive to the black African women in our cohort. This double burden of communicable and non-communicable diseases in women with breast cancer is of concern and can ultimately affect treatment, quality of life and survival. We found that women with higher HSES were more likely to present with multimorbidity, independent of ethnicity. There is a dearth of knowledge on the association between socioeconomic status and multimorbidity in South Africa; however our finding is in contrast to other South African studies that reported that poorer women and those socioeconomically

deprived bear a greater burden of multimorbidity (Ataguba, 2013, Weimann et al., 2016). Women socioeconomically deprived had 50% increased odds of having multimorbidity compared to those not socioeconomically deprived (Weimann et al., 2016). This may be due to different definitions and mode of measurement of socio-economic status in the studies. Patients also experience varying delays within the referral network, as reflected in significant differences in the proportions of advanced stage (stages III & IV) at presentation of patients at the different sites (ranging from 50% (lowest) at the Soweto, Johannesburg hospital and 73% (highest) at the KZN Pietermaritzburg and KZN rural hospital. These challenges are compounded for patients with high multimorbidity who have to visit other clinics for their chronic medications apart for their breast cancer treatments.

Some of our findings on the association between individual chronic conditions, multimorbidity, and stage of breast cancer diagnosis are consistent with previous work in South Africa and SSA. Although obesity was associated with a reduced risk of being diagnosed with advanced stage breast cancer in the bivariate analysis, when included in the multivariable analysis with other chronic conditions this was no longer significant. This is in keeping with studies from Africa and high income countries (Leung et al., 2016, Amin, 2016, Cui et al., 2002) where obesity did not emerge as being associated with advanced stage disease at breast cancer diagnosis. Obesity is a risk factor for luminal type breast cancers, which tend to be slower growing and less likely to be diagnosed at advanced stage (Babu et al., 2018, Nattenmüller et al., 2018). Obesity is not a comorbidity that has been shown to increase contact with health services in our setting; we therefore cannot imply its protective effect from regular contact with the health facilities.

Women who reported being hypertensive were less likely to have advanced stage of breast cancer at diagnosis, before and after adjusting for potential covariates. This may imply regular contact with the health systems that may result in patient breast cancer education by the health services or a surveillance effect leading to earlier stage at diagnosis (Gurney et al., 2015). This may also be related to tumour biology because breast cancer in younger women (with less hypertension prevalence) tend to be the more aggressive subtypes (Anders et al., 2008, Assi et al., 2013, Collins et al., 2012). HIV infection, prior tuberculosis, diabetes, asthma/COPD, cerebrovascular disease and multimorbidity was not associated with advanced stage breast cancer at diagnosis.

Our findings show that multimorbidity was significantly associated with first treatment received in women with early stage breast cancer. Among women with multimorbidity with early stage breast cancer, a large proportion were placed on less aggressive neoadjuvant endocrine therapy. Older women with multimorbidity are more likely to have poor Eastern Cooperative Oncology Group (ECOG) performance status and not able to withstand the stress of surgery or chemotherapy and are therefore not likely to be placed on standard more aggressive treatments (Koroukian et al., 2011).

Some limitations need to be noted. As the data on the various chronic conditions was self-reported the prevalence of these conditions may be higher than reported. The list of chronic conditions was not comprehensive, and therefore certain health conditions may not have been detected and may result in potential confounding. We had to rely on patient self-reports of their diagnosed comorbidities and that they were on treatment. In South Africa hospital records are not electronically centralised and patient records from different clinics are not readily accessible for diagnostic and treatment details. Another limitation was that in the interview we

did not specify if the patient had a current history of tuberculosis or previous history, whilst not ideal, it was not a common prior condition so did not affect overall results, as seen in supplementary table 2 where the tuberculosis rows and columns are all relatively small. Despite these limitations, the strengths of this study include the uniquely large sample of South African women with breast cancer and inclusion of hospitals in different geographical regions. We described the burden and pattern of multimorbidity, and difference in chronic conditions between different hospital settings and have also measured factors associated with individual chronic conditions as well as multimorbidity. Further, this study provides data on the association between these chronic conditions and multimorbidity, and advanced stage breast cancer at diagnosis, in South Africa women. Our finding give important insight into demographic and socio-economic factors associated with multimorbidity in women with breast cancer in South Africa. There is need for policymakers to evaluate the effect of multimorbidity on the health system and its impact on the limited health care resources.

In conclusion, we have demonstrated a high prevalence of multimorbidity in women newly diagnosed with breast cancer from different public hospital settings in South Africa, with many of these chronic conditions being associated with socio-demographic factors. Women that were hypertensive were less likely to be diagnosed with advanced stage breast cancer. Our findings contribute to the literature in understanding socio-demographic factors associated with multimorbidity in South Africa. There is need to understand how multimorbidity may impact breast cancer outcomes.

4.6. Supplementary tables

Supplementary table 4-1: Frequency of chronic conditions (Obesity, self-reported hypertension, diabetes, cerebrovascular disease, asthma/COPD, HIV, and self-reported prior tuberculosis) in South African women newly diagnosed with breast cancer.

Number of chronic conditions	Soweto, Johannesburg hospital (n=795)	Central Johannesburg hospital (n=511)	KZN Durban hospitals (n=436)	KZN Pietermaritzburg hospital n=462	KZN rural hospital n=77	Total N=2281
0	133 (16.7%)	131 (25.6%)	85 (19.5%)	77 (16.7%)	8 (10.4%)	434 (19.0%)
1	339 (42.7%)	187 (36.6%)	126 (28.9%)	163 (35.3%)	31 (40.3%)	846 (37.1%)
2	226 (28.4%)	150 (29.4%)	133 (30.5%)	141 (30.5%)	27 (35.1%)	677 (29.7%)
3	84 (10.6%)	38 (7.4%)	78 (17.9%)	71 (15.4%)	9 (11.7%)	280 (12.3%)
4	12 (1.5%)	5 (1.0%)	13 (3.0%)	8 (1.7%)	2 (2.6%)	40 (1.8%)
5	1 (0.1%)	0 (0.0%)	1 (0.2%)	2 (0.4%)	0 (0.0%)	4 (0.1%)
Total	795 (100.0%)	511 (100.0%)	436 (100.0%)	462 (100.0%)	77 (100.0%)	2281 (100.0%)

KZN (Kwa-Zulu Natal)

Supplementary table 4-2: Pattern and combination of chronic conditions (Obesity, self-reported hypertension, diabetes, cerebrovascular disease, asthma/COPD, HIV, and self-reported prior tuberculosis) in South African women newly diagnosed with breast cancer.

	Women with 2 chronic conditions (1st column chronic condition listed + the row 2 chronic condition)										
Chronic conditions	**Do not have 1st column chronic condition**	**1st column chronic condition alone**	**Obesity**	**Hypertension**	**HIV**	**Diabetes**	**Tuberculosis**	**Asthma/COPD**	**CVD**	**1st column chronic condition + at least any 2 other chronic condition (3+ in total)**	**Total (%)**
Obesity	1012 (47.2%)	388 (18.1%)		282 (13.2%)	115 (5.4%)	20 (0.9%)	11 (0.5%)	21 (1.0%)	5 (0.2%)	289 (13.5%)	2143 (100.0%)*
Hypertension	1338 (58.7%)	215 (9.4%)	282 (12.4%)		26 (1.1%)	60 (2.6%)	14 (0.6%)	12 (0.5%)	5 (0.2%)	329 (14.4%)	2281 (100.0%)
HIV	1695 (78.0%)	175 (8.1%)	115 (5.3%)	26 (1.2%)		2 (0.1%)	42 (1.9%)	3 (0.1%)	1 (0.1%)	114 (5.2%)	2173 (100%)*
Diabetes	1968 (86.2%)	22 (1.0%)	20 (0.9%)	60 (2.6%)	2 (0.1%)		2 (0.1%)	0 (0.0%)	2 (0.1%)	205 (9.0%)	2281 (100.0%)
Tuberculosis	2114 (92.7%)	18 (0.8%)	11 (0.5%)	14 (0.6%)	42 (1.8%)	2 (0.1%)		0 (0.0%)	0 (0.0%)	80 (3.5%)	2281 (100.0%)
Asthma/COPD	2159 (94.7%)	17 (0.8%)	21 (0.9%)	12 (0.5%)	3 (0.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	69 (3.0%)	2281 (100.0%)
Cerebrovascular disease	2215 (97.1%)	5 (0.2%)	5 (0.2%)	5 (0.2%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)		48 (2.2%)	2281 (100.0%)

Missing values for covariates were as follows: obesity (n=138), HIV status (n=108)
COPD (Chronic obstructive pulmonary disease)
Row percentages (%) shown

Supplementary table 4-3: Pooled bivariate association of socio-demographic characteristics and chronic condition risk in women newly diagnosed with breast cancer in South Africa.

Socio-demographic characteristics	Obesity (BMI ≥ 30.0 kg/m2)	Hypertension	Diabetes	Cerebrovascular disease	Asthma/COPD	HIV positive	Tuberculosis
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.00 (0.99-1.00)	1.08 (1.07-1.09) [b]	1.05 (1.04-1.06) b	1.05 (1.03-1.07) [b]	1.00 (0.99-1.02)	0.93 (0.92-0.94) [b]	0.97 (0.96-0.98) [b]
Race							
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Asian	0.8 (0.5-1.2)	2.7 (1.8-4.1) [b]	8.4 (4.2-6.6)[b]	1.6 (0.6-4.1)	1.2 (0.6- 2.[3])	0.3 (0.1-3.5)	0.9 (0.3-3.3)
Black	1.6 (1.1-2.2) [a]	1.2 (0.9-1.7)	1.8 (0.9-3.6)	0.6 (0.3-1.5)	0.5 (0.3-0.9) [a]	28.7 (7.1-116.1) [b]	3.7 (1.4-10.1) [a]
Mixed	1.5 (0.9-2.5)	1.8 (1.1-3.0) [a]	3.3 (1.5-7.5)[b]	0.5 (0.1-2.5)	0.8 (0.3-1.9)	6.5 (1.3-31.2)	2.4 (0.7-8.6)
Highest level of education							
Primary education and below	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Secondary and above	1.2 (1.03-1.51) [a]	0.5 (0.4-0.6)[b]	0.6 (0.5-0.8) [b]	0.5 (0.3-0.8) [a]	1.0 (0.6-1.5)	1.7 (1.3-2.1) [b]	0.8 (0.6-1.2)
Employment status							
Unemployed	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Employed	1.3 (1.1-1.6)[b]	0.4 (0.3-0.5) [b]	0.4 (0.3-0.5) [b]	0.3 (0.2-0.7) [b]	0.7 (0.4-1.1)	2.1 (1.7-2.6) [b]	1.1 (0.5-1.5)
Household socio-economic status (score 0-6)	1.1 (1.0-1.2) [b]	1.1 (1.1-1.2) [b]	1.2 (1.1-1.3) [b]	1.0 (0.9-1.1)	1.2 (1.0-1.3) [a]	0.7 (0.6-0.8) [b]	0.8 (0.7-0.9) [b]

OR (Odds ratio), 95% CI (95% confidence interval), COPD (Chronic obstructive pulmonary disease), [a] Significant at p<0.05, [b] Significant at p<0.001

5. CHAPTER FIVE: PAPER 3

Ayeni, O.A., Norris, S.A., Joffe, M., Cubasch,H., Galukande, M., Zietsman, A., Parham, G., Adisa, C., Anele, A., Schüz, J., Anderson, B.O., Foerster, M., PhD[9], dos Santos Silva, I., McCormack, V.A., Pre-existing morbidity profile of women newly diagnosed with breast cancer in sub-Saharan Africa: African Breast Cancer—Disparities in Outcomes (ABC-DO) study. *Published online in International Journal of Cancer (IJC), Nov 2020.*

5.1. Introduction

Breast cancer is the most common malignancy and the leading cause of cancer mortality in women worldwide. It is also the most common cancer among women in sub-Saharan Africa (SSA) (Bray et al., 2018) where the incidence of this cancer is on the rise. These temporal changes form part of an epidemiological transition occurring in SSA, characterized by improved control of infectious diseases, ageing populations and increasing prevalence of risk factors for non-communicable diseases (NCD) due to economic advancement, urbanization and lifestyle modifications (Jemal et al., 2012, Black and Richmond, 2019). These syndemics also result in multimorbidity (the co-occurrence of two or more chronic comorbidities in one person) (The, 2018) at the individual level, including in breast cancer patients.

Survival after breast cancer diagnosis is determined by patient characteristics and disease-related factors such as stage at diagnosis and breast cancer subtypes (McCormack et al., 2020). In addition to these factors, studies mostly originating from high-income countries (HICs) have shown that several pre-existing morbidities are associated with lower breast cancer survival, poorer overall outcomes and they also impact on treatment recommendations and tolerance (Prados-Torres et al., 2014, Hawfield et al., 2006). These morbidities include obesity, diabetes and insulin resistance, stroke, body composition and mental health illnesses, i.e. conditions

which tend to be more common in older breast cancer patients (Nechuta et al., 2013, Cespedes Feliciano et al., 2020).

Pre-existing chronic conditions have also been linked to stage at cancer diagnosis, but the direction, degree and mechanisms of associations have not been consistent (Gurney et al., 2015, Fleming et al., 2005, Griffiths et al., 2014). The presence of pre-existing morbidities have been linked to increased risk of metastatic disease at diagnosis (Gurney et al., 2015), whereas links to earlier stage at diagnosis have been reported in settings served by population-based breast cancer screening (Vaeth et al., 2000). Some studies also noted earlier stage at diagnosis in women with hypertension (Ayeni et al., 2019b, Fleming et al., 2005), possibly arising from a 'surveillance effect' (i.e. greater clinical scrutiny upon follow-up for hypertension/ greater opportunity to seek help during health system contacts for other illnesses).

In the SSA setting, there is a paucity of data on the profile of pre-existing morbidity profiles among breast cancer patients. Such profiles are likely to differ across SSA countries at differing stages of economic, developmental and lifestyle transitions, i.e. different in SSA middle income countries (MICs) from low income countries (LICs) (Geyer and Mosidi, 2019, Defo, 2014). Further, in addition to the aforementioned conditions, the setting-pertinent infectious disease of HIV needs to be taken into account, due to the ageing HIV-positive population successfully treated with antiretroviral drugs (McCormack et al., 2018). Establishing these SSA-specific morbidity profiles of breast cancer patients will form a first step to inform priorities for feasible management strategies in constrained public health systems.

To date, we have investigated this morbidity profile among breast cancer patients diagnosed at five hospitals in South Africa and found that 44% of women had pre-existing morbidities at

diagnosis: 53% were obese, 41% hypertensive, 22% HIV-positive and 14% were diabetic. Multi-morbidities were linked to older age and higher socioeconomic status (Ayeni et al., 2019b). In the present study, we broadened our perspective to five SSA countries, including the upper MICs of South Africa and Namibia, lower MICs of Zambia and Nigeria and LIC of Uganda. Our aims were three-fold: (i) to describe the prevalence and profile of pre-existing chronic conditions and multimorbidity (at least two chronic conditions in addition to breast cancer) in women newly diagnosed with breast cancer in 5 countries in SSA; (ii) to determine the socio-demographic factors associated with individual chronic conditions and multimorbidity and (iii) to assess whether any of the individual chronic conditions or multimorbidity was associated with breast cancer stage at diagnosis.

5.2. Methods

5.2.1. Study design and study setting

Presence of pre-existing chronic conditions and multimorbidity in women newly diagnosed with breast cancer was examined within the African Breast Cancer-Disparities in Outcomes study (ABC-DO) cohort, a prospective multi-country hospital based breast cancer cohort in Southern (South Africa, Namibia and Zambia), Western (Nigeria) and Eastern (Uganda) SSA countries (McKenzie et al., 2016). Incident breast cancer patients were recruited at Windhoek Central Hospital, Namibia; Abia State University Teaching Hospital and the Maranatha private clinic, Aba and the Federal Medical Centre, Owerri, Nigeria; Chris Hani Baragwanath Academic hospital, Soweto, South Africa; Mulago Hospital and the Uganda Cancer Institute, Kampala, Uganda; and the Cancer Diseases Hospital and University Teaching Hospital, Lusaka, Zambia. The ABC-DO protocol was previously published (McKenzie et al., 2016).

5.2.2. Participants

Recruitment commenced from September through December 2014 in most centres and was completed by April 2017 except in Zambia (May 2016 through September 2017). Women ≥18 years of age with a clinically/histologically confirmed newly diagnosed breast cancer who provided written consent to participate in the study, and provided access to their medical records and tumour tissue were enrolled. ABC-DO was approved by ethics committees at each recruitment institution: IARC (IEC 13–19, IEC15–18), the London School of Hygiene and Tropical Medicine (6459), University of Witwatersrand, South Africa (M150345), Council for Science and Technology (HS 1588) and the Ministry of Health and Social Services of Namibia (17/3/3), University of Zambia Biomedical Research Ethics Committee (004-08-15), Federal Medical Centre Owerri, Abia State University Teaching Hospital and Uganda National Council for Science and Technology (HS 1588).

The present analyses of pre-existing morbidities were conducted overall and by site-race group, with Namibian women separated into black and non-black ethnic groups as these groups were different in socio-economic profile and stage distribution (McKenzie et al., 2018a). Participants from other countries were almost exclusively black women, forty-two non-black South Africans were excluded from the analysis as this group was too small to analyse separately.

Exposure and outcome data

The same face-to-face baseline questionnaire was utilized in all hospitals except in South Africa where a pre-existing survey instrument was administered and harmonized to ABC-DO specifications. For this analysis we included questions on age, self-identified ethnic group, and marital status. Educational level was categorised as primary education or none and secondary education or higher. We grouped employment into 2 categories, employed (highly

skilled/skilled, employed in South Africa) versus unemployed (unskilled, unemployed and retired in South Africa). A score for socioeconomic position (SEP) was generated from self-reported household facilities and possessions: home ownership, flush toilet, indoor running water, vehicle, electricity, gas or electric stove, refrigerator, landline phone and a bed. A score of +1 was allocated to each possession ranging from 0 (low) to 9 (high).

We examined the presence of seven chronic conditions: obesity, hypertension, diabetes, heart disease, asthma/ chronic obstructive pulmonary disease (COPD), HIV infection and tuberculosis. The 7 conditions were included because of their known association with breast cancer prognosis (obesity (Kamineni et al., 2013), diabetes (Charlot et al., 2017), HIV (Reddy et al., 2017, McCormack et al., 2020), their known impact on treatment (e.g. cardiotoxicity and worsening of hypertension (Mehta et al., 2018)) and/or their known high prevalence in the least parts of SSA where regular treatment may provide an avenue for early cancer detection (e.g. HIV and tuberculosis (Harries et al., 2010), COPD (Salvi, 2015), hypertension and heart disease (Cappuccio and Miller, 2016). Body weight and height were measured at enrolment, and obesity was defined as a body mass index (BMI) ≥30.0 kg/m². Patients were asked if they had ever been treated for tuberculosis and whether they had ever been diagnosed and treated with hypertension, diabetes, heart disease, asthma/COPD. HIV infection (yes vs. no/not known) was based on self-reports, with 90% of the cohort (apart from South Africa) reporting the later, however there was a 97% agreement with clinical records among those reported negative. In South Africa HIV status was tested as part of the diagnostic workup, using the enzyme-linked immunosorbent assay by the National Health Laboratory Services. We defined multimorbidity as having ≥ 2 of these seven chronic conditions, in addition to breast cancer.

Breast cancer stage at diagnosis was determined using the American Joint Committee on Cancer (AJCC) TNM staging system (Amin et al., 2017) and categorized for analyses as early (stages I & II) and advanced (stages III & IV).

5.2.3. Statistical methods

We described the pattern and prevalence of each chronic condition by site-race group using Pearson's chi squared and Fishers Exact tests. We examined associations of socio-demographic factors with each chronic condition and with multimorbidity (≥ 2 of these chronic conditions in addition to the breast cancer) using logistic regression analysis. Logistic regression was also used to examine whether each chronic condition and multimorbidity were associated with advanced stage breast cancer (stages III & IV), as compared to early stage breast cancer (stages I & II). Variables for which p values were <0.1 in bivariate analysis with advanced stage breast cancer were evaluated and ORs were assessed adjusting for each covariate, HIV status, age, and country (as a proxy for level of health care). Analysis was performed using Stata version 15 (StataCorp Ltd, Texas, USA).

5.3. Results

A total of 2189 women were included: 720 (33%) from South Africa, 478 (22%) (99 non-black and 379 black) from Namibia, 187 (9%) from Zambia, 382 (17%) from Nigeria and 422 (19%) from Uganda (Table 5.1). The mean age at diagnosis was 51.7±13.9, with women from Zambia, Nigeria and Uganda (range of mean age 48.4 – 49.4 years) significantly younger than women from Namibia and South Africa (range of mean age 52.5 - 57.1 years). Overall 62% of the women had at least secondary school education with the non-black Namibian (87%), South African (77%) and Nigerian (72%) women more likely to have had at least secondary education compared to black Namibian (49%), Zambian (47%) and Ugandan (42%) women. In keeping

with these low and middle income (LMIC) settings, most women had low to medium SEP with higher SEP in non-black Namibia women. Smoking prevalence was low, ranging from < 1% in Nigeria to 43% among the non-black Namibian women. Approximately 59% of the women presented with advanced stage breast cancer overall (50% in South Africa to 75% in Nigeria), with the exception of non-black Namibian women where the majority presented with early stage disease (78%) (Table 5.1).

5.3.1. Prevalence of chronic conditions and multimorbidity

Hypertension and obesity dominated as the most common chronic conditions in breast cancer patients in each country, with hypertension ranking first in all countries except in South Africa where obesity ranked as the most common pre-existing chronic condition. HIV ranked 3rd prevalent in all countries except in non-black Namibians (where asthma/COPD was in 3rd rank) and in Nigeria (diabetes ranked 3rd). Diabetes was the fourth most prevalent chronic condition in most countries except among the black Namibian women (tuberculosis was 4th) and in Nigeria (heart disease was 4th) (Table 5.2). Overall South Africa had the highest prevalence of HIV in the whole cohort (26%) (Table 5.2) with 42% of the women <50 years of age infected with HIV (Figure 5.1).

Twenty seven percent of the women newly diagnosed with breast cancer presented with multimorbidity (presence of ≥2 additional chronic conditions) ranging from 42% in South Africa to 11% in Uganda (Table 5.2). Percentages of women with multimorbidity was highest in South African women both under and over age 50, with 49% of the women ≥50 years presenting with multimorbidity in addition to breast cancer. Women from lower MICs Zambia and Nigeria and LIC Uganda had the least prevalence of multimorbidity in both age groups (Figure 5.1).

Table 5.1: Characteristics of women newly diagnosed with breast cancer in Sub-Saharan Africa, by country-site; ABC-DO breast cancer cohort

	Southern Africa (S.A.)				West Africa	East Africa	
	South Africa	**Namibia Non-Black**	**Namibia Black**	**Zambia**	**Nigeria**	**Uganda**	**Total**
	N=720 (%)	**N=99 (%)**	**N=379 (%)**	**N=187 (%)**	**N=382 (%)**	**N=422 (%)**	**N=2189 (%)**
Age in years, mean ± SD	54.5±14.3	57.1±12.4	52.5±14.6	49.4±14.2	48.8±12.2	48.4±12.6	51.7±13.9
BMI (kg/m2)	31.7±7.7	29.1±6.8	26.4±6.7	26.5±6.3	26.4±5.7	25.6±4.6	28.1±7.0
Marital status							
Married	233 (32.4)	58 (58.6)	122 (32.2)	110 (58.8)	250 (65.4)	199 (47.2)	972 (44.4)
Not married	487 (67.6)	41 (41.4)	257 (67.8)	77 (41.2)	132 (34.6)	223 (52.8)	1217 (55.6)
Received secondary education							
Yes	551 (76.5)	86 (86.9)	184 (48.5)	87 (46.5)	276 (72.3)	178 (42.2)	1362 (62.2)
No	169 (23.5)	13 (13.1)	195 (51.5)	100 (53.5)	106 (27.7)	244 (57.8)	827 (37.8)
Employment status							
Employed	202 (28.1)	98 (99.0)	346 (91.3)	73 (39.0)	357 (93.5)	331 (78.4)	1407 (64.3)
Unemployed	518 (71.9)	1 (1.0)	33 (8.7)	114 (61.0)	25 (6.5)	91 (21.6)	782 (35.7)
SEP							
Low (0-3)	273 (37.9)	0 (0.0)	166 (43.8)	67 (35.8)	161 (42.1)	249 (59.0)	916 (41.8)
Medium (4-6)	433 (60.1)	39 (39.4)	130 (34.3)	69 (36.9)	167 (43.7)	90 (21.3)	928 (42.4)
High (7-9)	14 (1.9)	60 (60.6)	83 (21.9)	51 (27.3)	54 (14.1)	83 (19.7)	345 (15.8)
Ever consumed alcohol?							
No	565 (78.5)	37 (37.4)	185 (48.8)	123 (65.8)	178 (46.6)	225 (53.3)	1313 (60)
Yes	155 (21.5)	62 (62.6)	194 (51.2)	64 (34.2)	204 (53.4)	197 (46.7)	876 (40)
Ever smoked?							
No	677 (94.0)	56 (56.6)	324 (85.5)	185 (98.9)	381 (99.7)	408 (96.7)	2031 (92.8)
Yes	43 (6.0)	43 (43.4)	55 (14.5)	2 (1.1)	1 (0.3)	14 (3.3)	158 (7.2)
Stage at diagnosis							

Stage I & II	347 (49.6)	77 (77.8)	139 (36.7)	60 (40.3)	88 (25.1)	142 (36.5)	853 (41.3)
Stage III `& IV	353 (50.4)	22 (22.2)	240 (63.3)	89 (59.7)	262 (74.9)	247 (63.5)	1213 (58.7)

Missing values for covariates were as follows: Stage at diagnosis (n=132); BMI (Body mass index), SEP (Socio-economic position), SD (standard deviation)

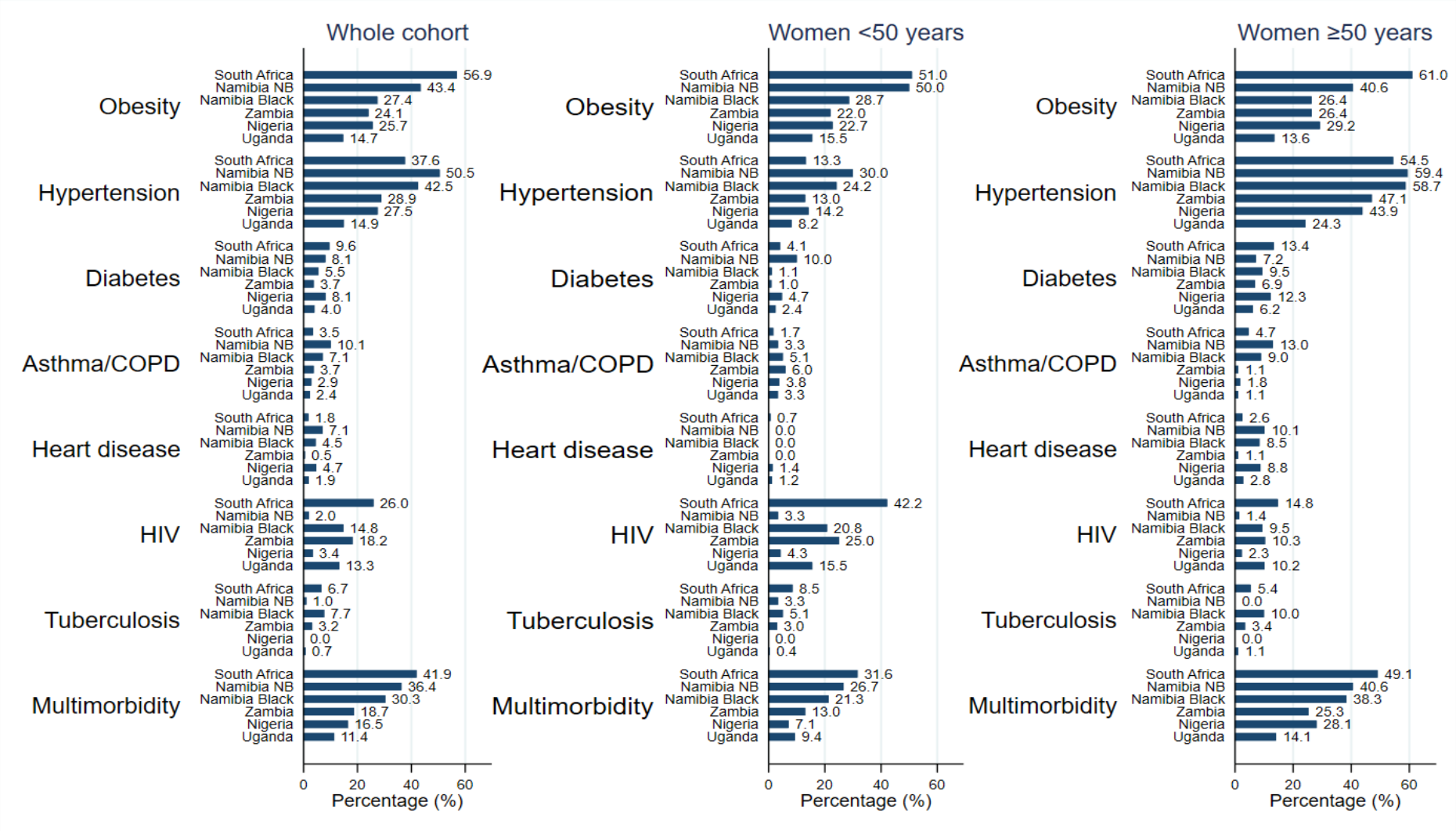
Table 5.2: Prevalence of pre-existing chronic conditions in women newly diagnosed with breast cancer in Sub-Saharan Africa, by country-site; ABC-DO study.

	Southern Africa (S.A.) Upper MICs			**S.A. Lower MIC**	**West Africa Lower MIC**	**East Africa LIC**	
	South Africa	**Namibia Non-Black**	**Namibia Black**	**Zambia**	**Nigeria**	**Uganda**	**Total**
Ranked chronic conditions	**N=720 (%)**	**N=99 (%)**	**N=379 (%)**	**N=187 (%)**	**N=382 (%)**	**N=422 (%)**	**N=2189 (%)**
Most common	Obesity (57)	Hypertension (51)	Hypertension (43)	Hypertension (29)	Hypertension (28)	Hypertension (15)	Obesity (35)
2nd most common	Hypertension (38)	Obesity (43)	Obesity (27)	Obesity (24)	Obesity (26)	Obesity (15)	Hypertension (32)
3rd most common	HIV (26)	Asthma/COPD (10)	HIV (15)	HIV (18)	Diabetes (8)	HIV (13)	HIV (16)
4th most common	Diabetes (10)	Diabetes (8)	Tuberculosis (8)	Diabetes (4)	Heart disease (5)	Diabetes (4)	Diabetes (7)
5th most common	Tuberculosis (7)	Heart disease (7)	Asthma/COPD (7)	Asthma/COPD (4)	HIV (3)	Asthma/COPD (2)	Asthma/COPD (4)
6th most common	Asthma/COPD (4)	HIV (2)	Diabetes (6)	Tuberculosis (3)	Asthma/COPD (3)	Heart disease (2)	Tuberculosis (4)
7th most common	Heart disease (2)	Tuberculosis (1)	Heart disease (5)	Heart disease (1)	Tuberculosis (0)	Tuberculosis (1)	Heart disease (3)
Chronic conditions	**N positive (% positive)**						

Obese	410 (56.9)	43 (43.4)	104 (27.4)	45 (24.1)	98 (25.7)	62 (14.7)	762 (34.8)
Hypertension	271 (37.6)	50 (50.5)	161 (42.5)	54 (28.9)	105 (27.5)	63 (14.9)	704 (32.2)
HIV	187 (26)	2 (2.0)	56 (14.8)	34 (18.2)	13 (3.4)	56 (13.3)	348 (15.9)
Diabetes	69 (9.6)	8 (8.1)	21 (5.5)	7 (3.7)	31 (8.1)	17 (4.0)	153 (7.0)
Asthma/COPD	25 (3.5)	10 (10.1)	27 (7.1)	7 (3.7)	11 (2.9)	10 (2.4)	90 (4.1)
Tuberculosis	48 (6.7)	1 (1.0)	29 (7.7)	6 (3.2)	0 (0.0)	3 (0.7)	87 (4.0)
Heart disease	13 (1.8)	7 (7.1)	17 (4.5)	1 (0.5)	18 (4.7)	8 (1.9)	64 (2.9)
Any chronic condition	617 (85.7)	73 (73.7)	256 (67.5)	114 (61)	193 (50.5)	163 (38.6)	1416 (64.7)
Number of pre-existing chronic conditions							
0	103 (14.3)	26 (26.3)	123 (32.5)	73 (39.0)	189 (49.5)	259 (61.4)	773 (35.3)
1	315 (43.8)	37 (37.4)	141 (37.2)	79 (42.2)	130 (34)	115 (27.3)	817 (37.3)
2	210 (29.2)	26 (26.3)	80 (21.1)	31 (16.6)	47 (12.3)	41 (9.7)	435 (19.9)
3	82 (11.4)	8 (8.1)	28 (7.4)	3 (1.6)	12 (3.1)	6 (1.4)	139 (6.3)
4+	10 (1.4)	2 (2.0)	7 (1.8)	1 (0.5)	4 (1.0)	1 (0.2)	25 (1.1)
Multimorbidity (≥2)	302 (41.9)	36 (36.4)	115 (30.3)	35 (18.7)	63 (16.5)	48 (11.4)	599 (27.4)
Legend	CD: HIV/Tuberculosis	NCDs					

- Countries ordered in terms of decreasing multimorbidity prevalence
- MICs (Middle income countries), LIC (Low income countries)
- COPD (Chronic obstructive pulmonary disease), CD (Communicable diseases), NCDs (Non-communicable diseases)
-

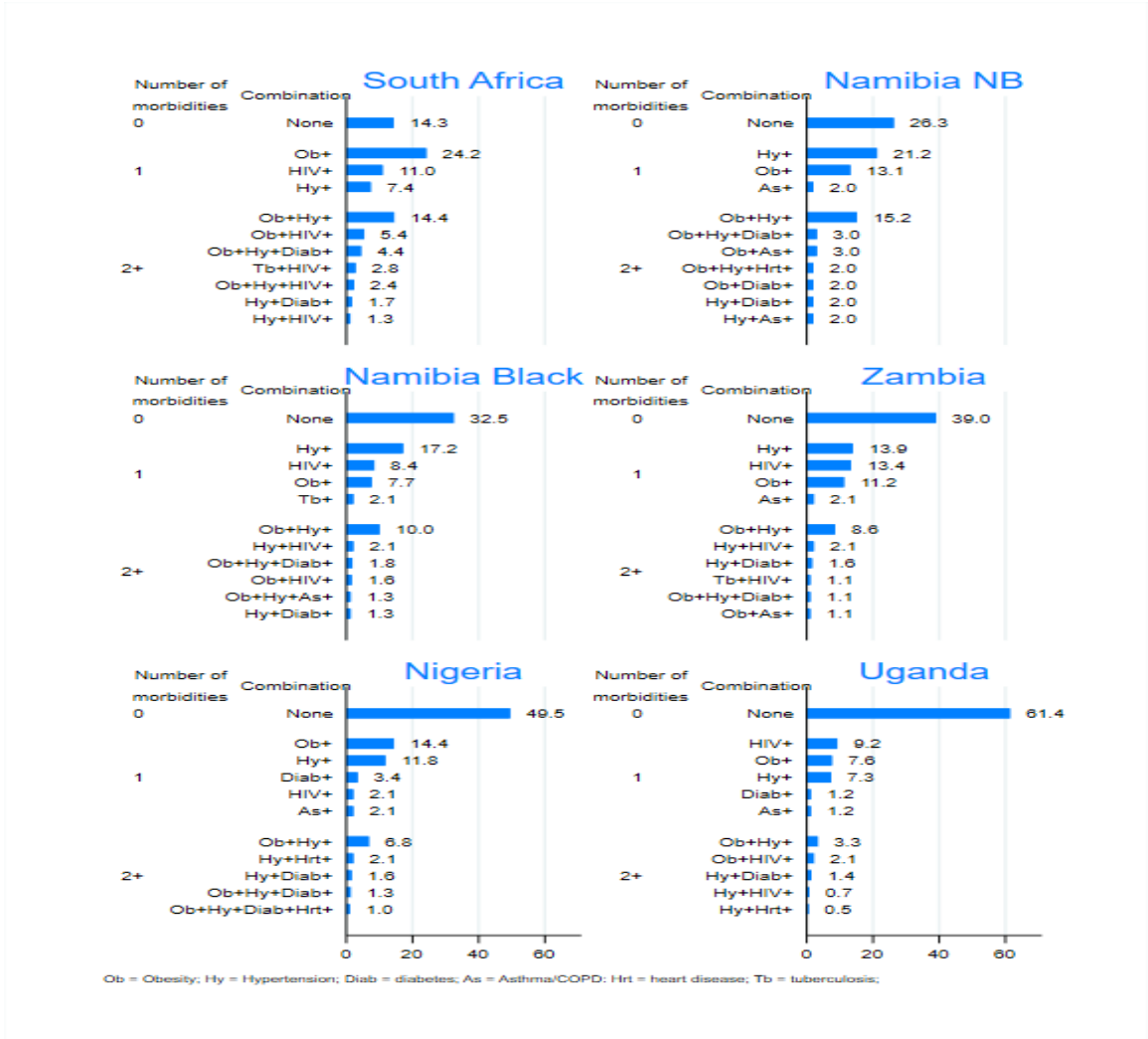
Figure 5.1: The prevalence of chronic conditions in women with breast cancer in the ABC-DO cohort by age group.



- NB (non-black)

With seven conditions included, of a possible 128 (2^7) morbidity combinations, 57 combinations were present among the 2189 women and only 16 combinations were present in at least 5 women. The profile and prevalence of these combinations for the 11 most common combinations in each population group is shown in Figure 5.2 (i.e. no pre-existing morbidities and ten combinations with at least one pre-existing morbidities). Where multimorbidity was present, obesity and hypertension was the dominant combination, affecting 15% of Namibian non-black and 14% of South African women. The only other combination affecting at least 5% of breast cancer patients in a given group was obesity and HIV in South Africa.

Figure 5.2: Profile of the combination of seven pre-existing morbidities amongst breast cancer patients in ABCDO study.



5.3.2. Determinants of chronic conditions

Associations of socio-demographic factors with each chronic condition are presented in table 5-3. In the mutually adjusted analysis of all countries combined, older women were significantly more likely to be obese, hypertensive, diabetic and have heart disease and less likely to be living with HIV. Of the three measures of socio-economic status, SEP was most frequently associated with the presence of a chronic condition. Women with higher SEP (7-9 (high) and 4-6 (medium)) were more likely to be obese and diabetic compared with women with low SEP (0-3). High SEP women were also more likely to have hypertension compared to those with low SEP (OR: 1.89, 95% CI 1.33-2.59). Associations of age and SEP with the two communicable diseases, tuberculosis and HIV, tended to be in the opposite direction to those for the aforementioned NCDs. Notably, women with medium SEP were less likely to have HIV compared to the women with low SEP. Those employed were more likely to be obese while level of education was not significantly associated with any chronic condition except in Nigeria where those with secondary education and above were more likely to have heart disease (result not shown).

Table 5.3: Associations of socio-demographic characteristics with each chronic conditions, among breast cancer patients in Sub-Saharan Africa, ABC-DO study. ORs are mutually adjusted.

	Non-communicable diseases					Communicable diseases		
Socio-demographic characteristics	**Obesity (BMI ≥ 30.0 kg/m2)**	**Hypertension**	**Diabetes**	**Asthma/COPD**	**Heart disease**	**HIV positive**	**Tuberculosis**	**NCDs combined**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (10 year increase)	1.09 (1.01-1.18)[a]	1.98 (1.81-2.17)[b]	1.51 (1.32-1.74)[b]	1.08 (0.91-1.29)	1.69 (1.37-2.09)[b]	0.64 (0.58-0.71)[b]	0.97 (0.81-1.15)	1.62 (1.50-1.76)[b]
Marital status								
Not married	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Married	1.25 (1.02-1.54)[a]	1.07 (0.87-1.33)	1.39 (0.97-2.00)	0.90 (0.57-1.42)	0.80 (0.45-1.43)	0.51 (0.39-0.67)[b]	0.62 (0.36-1.03)	1.02 (0.84-1.25)
Highest level of education								
Primary education and below	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Secondary education and above	1.01 (0.79-1.29)	1.05 (0.82-1.36)	0.77 (0.51-1.16)	1.03 (0.60-1.77)	1.06 (0.56-2.02)	1.18 (0.86-1.61)	1.13 (0.65-1.97)	1.04 (0.82-1.33)
Employment status								
Unemployed	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Employed	1.51 (1.17-1.97)[a]	0.98 (0.74-1.29)	1.11 (0.68-1.82)	1.16 (0.62-2.16)	0.71 (0.32-1.56)	0.88 (0.65-1.18)	0.90 (0.51-1.59)	1.22 (0.95-1.58)
SEP								
Low (0-3)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Medium (4-6)	1.93 (1.54-2.40)[b]	1.20 (0.95-1.51)	1.77 (1.16-2.69)[a]	1.85 (1.09-3.15)[a]	1.08 (0.58-1.99)	0.60 (0.46-0.79)[b]	1.35 (0.83-2.20)	1.76 (1.42-2.18)[b]
High (7-9)	3.05 (2.22-4.18)[b]	1.86 (1.33-2.59)[b]	3.25 (1.88-5.62)[b]	1.74 (0.86-3.51)	1.59 (0.72-3.52)	0.65 (0.41-1.02)	1.26 (0.55-2.86)	2.75 (2.02-3.75)[b]
Country								
Uganda	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Namibia Black	1.93 (1.34-2.78)[b]	3.76 (2.61-5.41)[b]	1.06 (0.54-2.09)	2.71 (1.28-5.76)[a]	1.84 (0.76-4.45)	1.27 (0.84-1.94)	10.61(3.18-35.46)[b]	2.60 (1.90-3.56)[b]
Namibia Non-Black	2.26 (1.35-3.77)[a]	2.98 (1.73-5.12)[b]	0.89 (0.35-2.27)	3.11 (1.17-8.29) [b]	2.30 (0.71-7.46)	0.25 (0.10-1.07)	1.30 (0.13-13.08)	2.94 (1.72-5.01)[b]
Nigeria	1.73 (1.19-2.51)[a]	2.26 (1.54-3.32)[b]	1.98 (1.04-3.76)[a]	1.09 (0.44-2.66)	2.82 (1.15-6.90)[a]	0.27 (0.14-0.50)[b]	Omitted	2.23 (1.62-3.08)[b]
South Africa	9.68 (6.65-14.07)[b]	2.67 (1.82-3.92)[b]	2.32 (1.19-4.55)[a]	1.29 (0.54-3.06)	0.53 (0.18-1.57)	2.72 (1.82-4.08)[b]	8.10 (2.33-28.12)[a]	6.13 (4.40-8.54)[b]
Zambia	1.77 (1.12-2.78)[a]	2.11 (1.33-3.33)[a]	0.76 (0.30-1.91)	1.49 (0.54-4.10)	0.22 (0.03-1.79)	1.75 (1.06-2.90)[a]	4.38 (1.06-18.15)[a]	1.93 (1.30-2.86)[a]

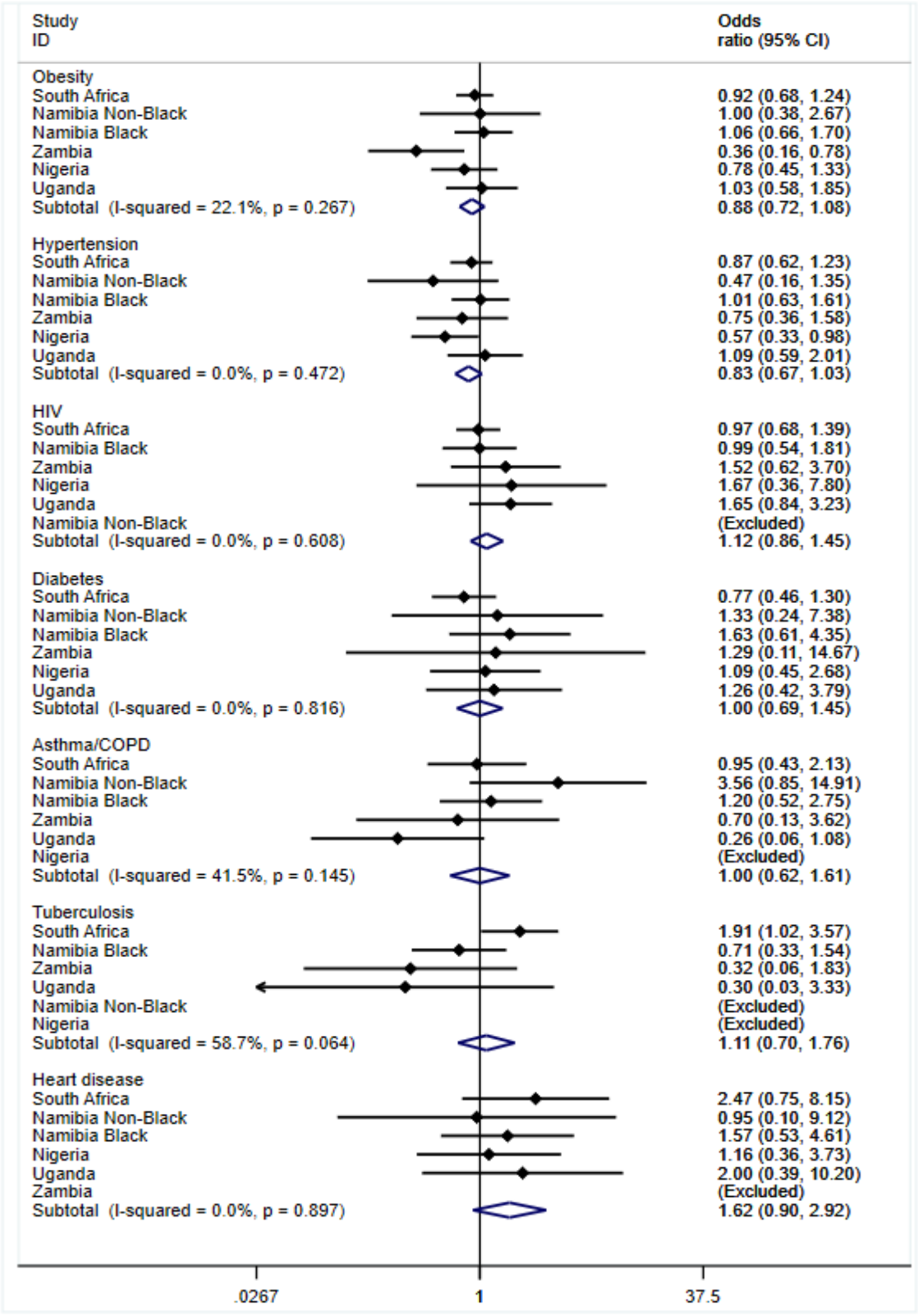
BMI (Body mass index), OR (Odds ratio), 95% CI (95% confidence interval), SEP (Socio-economic position), COPD (Chronic obstructive pulmonary disease), NCDs (Non-communicable diseases), NCDs (Obesity, hypertension, diabetes, asthma/COPD, heart disease), [a] Significant at $p<0.05$, [b] Significant at $p<0$.

Determinants of the presence of pre-existing multi-morbidities mirror the associations above, particularly for the NCDs, as the co-presence of obesity and hypertension was the most prevalent combinations. Adjusting for age and country site higher SEP compared to low SEP was associated with greater risk for multimorbidity at breast cancer diagnosis (Supplementary table 5.1).

5.3.3. Influence of pre-existing morbidities on stage at diagnosis

Among 2066 women with known stage at diagnosis, investigations of whether pre-existing morbidities affected stage at diagnosis are illustrated in Figure 5.3 for each site, and results of the ABC-DO wide pooled analysis are shown in Table 5.4. Most site-specific associations were not significant or suggestive, with the following exceptions. Adjusting for age at diagnosis, obese women from Zambia (OR: 0.36, 95% CI 0.16-0.78) and hypertensive women from Nigeria (OR: 0.57, 95% CI 0.33-0.98) were less likely to be diagnosed with advanced stage breast cancer compared to their country-counterparts without these conditions. In contrast, among South African women, those women who had tuberculosis were more likely to be diagnosed with advanced stage breast cancer than those without such a history (OR: 1.91, 95% CI 1.02-3.57). Nigeria, Zambian and Ugandan women who were HIV infected were more likely to be diagnosed with advanced stage breast cancer than their HIV-negative counterparts, though these associations were not significant and were not present in all settings (Figure 5.3). Thus meta-analytic estimates across all population groups suggested no association of tuberculosis, asthma/COPD, diabetes and HIV with stage at diagnosis, consistent with the pooled analyses in Table 5.4. However for hypertension, in meta-analyses, there was a suggestion of a 17% (-3% to 33%) relative reduction in advanced stage breast cancer associated with having this condition, which increased to a 35% (1 to 55%) reduction in pooled analyses adjusted for HIV.

Figure 5.3: Odds ratios of women being diagnosed with advanced stage breast cancer (stages III & IV) associated with each of the seven chronic conditions examined, by sub-Saharan Africa countries in the ABC-DO breast cancer cohort.



Similarly for obesity, the meta-analysis was suggestive of 12% (95% CI -8% to 28%) reduced odds of advanced stage at diagnosis, which became significant in pooled analyses (28% reduction (1 to 48%). Despite these individual conditions of obesity and hypertension being the most common multimorbidity combination, the overall effect of multimorbidity on advanced stage at cancer diagnosis was borderline suggestive of a positive association (OR: 1.34, 95% CI 0.95-1.89) (Table 5.4).

Table 5.4: Multiple logistic regression models of chronic conditions and presence of multimorbidity (≥2 chronic conditions) as predictors of advanced stage breast cancer (stages II & IV) in women newly diagnosed with breast cancer in Sub-Saharan Africa, ABC-DO breast cancer cohort.

Chronic conditions	**Odds ratio**	**95% CI**	**P value**
Obese			
No	1.00	Reference	**0.049**
Yes	0.72	**0.52-0.99**	
Hypertension			
No	1.00	Reference	**0.015**
Yes	0.65	**0.45-0.92**	
HIV			
Negative	1.00	Reference	0.331
Positive	0.85	0.58-1.22	
Any chronic condition			
No	1.00	Reference	0.120
Yes	1.30	0.92-1.84	
Multimorbidity			
< 2 chronic conditions	1.00	Reference	0.092
≥ 2 chronic conditions	1.34	0.95-1.89	

Multiple regression model (adjusted for age, country and HIV).
Obesity, hypertension, any chronic condition and multimorbidity were the only variables significant at p<0.01 on bivariate analysis and are evaluated in the multivariate analysis.

5.4. Discussion

5.4.1. Summary of findings

In this large cohort of breast cancer patients in five SSA countries, the prevalence of at least one of seven pre-existing chronic conditions (obesity, hypertension, diabetes, heart disease, asthma/COPD, HIV infection and tuberculosis) was high (65%) and 27% of women had at least two pre-existing chronic conditions (multimorbidity). Obesity and hypertension were the two most frequent conditions present, both individually and as a combination amongst women with multi-morbidities, particularly affecting older women and groups with higher socioeconomic status both at the intra-country individual level and, reflecting epidemiologic transitions, at national levels. HIV ranked 3rd in most countries except in non-black Namibian women and in West African Nigeria. The management of breast cancer in SSA thus needs to consider this high percentage of NCDs, alone or in combination with HIV. Nevertheless, none of the seven chronic conditions investigated were positively associated with having advanced stage breast cancer at diagnosis, with the exception of obesity and hypertension which were associated with having early stage breast cancer. The latter findings points to an opportunity to further increase early diagnosis, in an attempt to counterbalance any survival disadvantage among these women.

5.4.2. Major prevalent chronic conditions: in the population as risk factors for breast cancer and impact on prognosis

Multimorbidity prevalence closely tracked the wealth index of the countries under investigation and the socioeconomic position scores of the women under investigation. Women from higher MICs with more advanced westernized lifestyle transitions had the greater multimorbidity burden (South Africa (42%) followed by Namibia) than those from lower middle income Zambia and Nigeria and low income Uganda. These findings were in keeping with ranges of

14% to 68% reported from other studies (Ayeni et al., 2019a, Khanam et al., 2011, Nimako et al., 2013, Violan et al., 2014, Wang et al., 2015). With 27% of our patients presenting with multimorbidity (≥2 chronic conditions), SSA is facing a significant challenge of multimorbidity comprising both infectious diseases combined with the rapidly growing NCD prevalence as countries transition to westernized lifestyles. Hypertension ranked as the most common chronic condition in most countries except in South Africa where obesity ranked first, ranging from 15% in LIC Uganda to 51% amongst MIC non-black Namibian women. Hypertension is a public health challenge in Africa with 46% of its population aged 25 years and over living with hypertension (Dzudie et al., 2017, van de Vijver et al., 2013). Hypertension might be positively linked to risk of breast cancer especially in postmenopausal women (Chang et al., 2016, Han et al., 2017), hence its high prevalence among our women is particularly worrying. More critically, during the therapeutic phase, chemotherapy can worsen hypertension and cause cardiomyopathy (Fraeman et al., 2013, Izzedine et al., 2009).

Obesity, a known risk factor for breast cancer in postmenopausal women (Bhaskaran et al., 2014, Gravena et al., 2018), has also been associated with worse breast cancer outcomes for women of all ages (Kamineni et al., 2013, Lee et al., 2019). Obesity was commonly reported in this study though with high variation across countries in various stages of lifestyle transition. South Africa has the highest prevalence with 57% of the women obese while Uganda had the lowest prevalence (15%). The emerging prevalence of obesity in SSA has been largely attributed to the rising empowerment of women, sedentary lifestyles, economic development and urbanization (Biadgilign et al., 2017) ultimately leading to nutritional transition. Obesity at postmenopausal ages is a driver of increasing breast cancer incidence rates, thus in this instance the rising obesity rates are fuelling more cases with poorer prognosis. Diabetes with prevalence ranging from 4% in Uganda to 10% in South Africa is also a known risk factor for

breast cancer in postmenopausal women (Hardefeldt et al., 2012), it is also associated with worse survival with up to an increased risk of 52% in overall mortality (Gold et al., 2008, Zhao and Ren, 2016, Luo et al., 2015).

The high burden of HIV amongst particularly our southern African women in this study is of continued concern with HIV now regarded as a chronic infectious disease, though the general consensus is that there is no significant link between HIV and risk of breast cancer (Pantanowitz et al., 2011, Sarhan et al., 2010, Spano et al., 2012); however, studies have reported poorer prognosis in HIV positive patients with breast cancer (Coghill et al., 2015, McCormack et al., 2020).

5.4.3. Determinants of chronic conditions

As expected, most chronic conditions were more prevalent in older women, a finding consistent with previous studies in SSA (Alaba and Chola, 2013, Price et al., 2018, Ayeni et al., 2019b). We also found that women with higher SEP were more likely to present with obesity, hypertension and diabetes in contrast to findings from other mainly HIC studies where multimorbidity was more prevalent at lower SEP (Jackson et al., 2015, Violán et al., 2014, Jacobs et al., 2019, Pathirana and Jackson, 2018, Violan et al., 2014). However our findings were consistent with other studies from LMICs for multimorbidity (Khanam et al., 2011), overweight/obesity, hypertension and diabetes (Price et al., 2018). These findings perhaps reflects westernized lifestyle and dietary transitions first affecting higher SEP groups with the capital needed to purchase and live modern lifestyles (Jacobs et al., 2019).

5.4.4. Impact on stage

It is known that advanced cancer stage at diagnosis is affected by chronic conditions (Fleming et al., 2005, Griffiths et al., 2014, Gurney et al., 2015) however some studies have consistently demonstrated earlier stage at diagnosis with chronic conditions (Ayeni et al., 2019b, Ayoub et al., 2019, Vaeth et al., 2000). In this study we found no significant association between multimorbidity and advanced stage at breast cancer diagnosis. Women who had hypertension at diagnosis of breast cancer were more likely to have early stage breast cancer, perhaps due to their regular access to the health system facilities for other conditions (Jackson et al., 2015, Price et al., 2018). Our patients that were obese were less likely to present with advanced stage breast cancer, this is in contrast to studies suggesting that higher BMI is associated with a more advanced stage of breast cancer at diagnosis (Ayoub et al., 2019, Cui et al., 2002). Our finding could be attributable to reverse causality given the 59% of late stage tumour in the cohort.

5.4.5. Strengths and limitations

This study benefitted from a diversity of countries across SSA, a wide range of morbidities included, a strong SSA-perspective on the selection of morbidities, heterogeneity in socio-demographic factors, measured BMI, tested HIV in South Africa and a prospective design. However, the sample was tertiary hospital-based patients, and many breast cancer patients in SSA may never reach this level of the health system. Further limitations were noted: most of these chronic conditions were self-reported; hence we could have underestimated the prevalence of multimorbidity.

5.4.6. Implications on therapeutic management

The implication of multimorbidity in women with breast cancer is profound including the high cost of care (Picco et al., 2016, Rajpal et al., 2018) and poor quality of life (Fortin et al., 2004).

It may add complexity to cancer management by influencing prognosis and treatment decisions (Kimmick et al., 2014). Breast cancer patients with multimorbidity are less likely to receive surgery (Bates et al., 2014, Berglund et al., 2012), less likely to receive adjuvant chemotherapy (Lee et al., 2019, Van Leeuwen et al., 2011), more likely to receive a reduced dose and less likely to complete chemotherapy treatment when initiated (O'Connor et al., 2012), and less likely to initiate timely radiotherapy after surgical treatment (Hershman et al., 2006). Multimorbidity may cause higher rates of adverse effects of treatment (Sarfati et al., 2016, Ritchie et al., 2011) affecting overall goal of care. It has been associated with an increased risk of cardiotoxicity (Henry et al., 2018), immunosuppression during chemotherapy and radiotherapy for HIV positive women (Langenhoven et al., 2016, Ngidi et al., 2017). Further, at the health system level, the management of multimorbidity is much more complicated and demanding for the patients and the health system, requiring an integrated approach and long-term care (Cui et al., 2002). To effectively address these changing needs, countries in SSA require detailed surveillance on chronic condition trends to assist in developing models of care appropriate for LMICs.

5.5. Conclusion

There is a high prevalence of chronic conditions and multimorbidity in our breast cancer patients and socio-demographic factors play a major role in its determinants in SSA. With increasing life expectancy, the rapidly increasing multimorbidity burden in SSA is of great concern for its under resourced health care services. SSA studies of the impact of these morbidities on survival and therapeutic management are needed.

5.6. Supplementary Tables

Supplementary Table 5-1: Socio-demographic, geographical and behavioural factors associated with multimorbidity (at least 2 of obesity, hypertension, HIV, diabetes, asthma/COPD, heart disease, tuberculosis in addition to breast cancer) in women newly diagnosed with breast cancer in Sub-Saharan Africa, ABC-DO breast cancer cohort.

		Multimorbidity		
	Total	**No (< 2 chronic conditions)**	**Yes (≥ 2 chronic conditions)**	**Adjusted analysis**
	N=2189 (%)	N=1590 (%)	N=599 (%)	OR (95% CI)
Age in years, mean ± SD	51.6±13.9	49.9±14.0	56.4±12.2	**1.03 (1.02-1.04)[b]**
Marital status				
Married	1217 (55.6)	859 (54)	358 (59.8)	1.00 (Reference)
Not married	972 (44.4)	731 (46)	241 (40.2)	1.11 (0.90-1.37)
Highest level of education				
Primary education and below	827 (37.8)	608 (38.2)	219 (36.6)	1.00 (Reference)
Secondary education and above	1362 (62.2)	982 (61.8)	380 (63.4)	1.12 (0.88-1.42)
Employment status				
Unemployed	782 (35.7)	510 (32.1)	272 (45.4)	1.00 (Reference)
Employed	1407 (64.3)	1080 (67.9)	327 (54.6)	1.07 (0.82-1.40)
SEP				
Low (0-3)	916 (41.8)	725 (45.6)	191 (31.9)	1.00 (Reference)
Medium (4-6)	928 (42.4)	625 (39.3)	303 (50.6)	**1.45 (1.16-1.82)[b]**
High (7-9)	345 (15.8)	240 (15.1)	105 (17.5)	**2.15 (1.57-2.96)[b]**
Country				
Uganda	422 (19.3)	374 (23.5)	48 (8)	1.00 (Reference)
Namibia Black	379 (17.3)	264 (16.6)	115 (19.2)	**3.09 (2.11-4.50)[b]**
Namibia Non-Black	99 (4.5)	63 (4)	36 (6)	**3.62 (2.16-6.06)[b]**
Nigeria	382 (17.5)	319 (20.1)	63 (10.5)	**1.53 (1.02-2.31)[a]**
South Africa	720 (32.9)	418 (26.3)	302 (50.4)	**4.93 (3.52-6.92)[b]**
Zambia	187 (8.5)	152 (9.6)	35 (5.8)	**1.75 (1.08-2.82)[a]**
Ever consumed alcohol?				
No	1313 (60)	932 (58.6)	381 (63.6)	1.00 (Reference)

Yes	876 (40)	658 (41.4)	218 (36.4)	1.08 (0.87-1.34)
Ever smoked?				
No	2031 (92.8)	1490 (93.7)	541 (90.3)	1.00 (Reference)
Yes	158 (7.2)	100 (6.3)	58 (9.7)	1.03 (0.71-1.50)

OR (Odds ratio), 95% CI (95% confidence interval), SD (standard deviation), SEP (Socio-economic position), COPD (Chronic obstructive pulmonary disease, a Significant at p<0.05, b Significant at p<0.001. ORs adjusted for age and country.

Supplementary Table 5-2: Association between individual chronic condition and multimorbidity (≥2 chronic conditions) with stage at diagnosis in women newly diagnosed with breast cancer in Sub-Saharan Africa, ABC-DO breast cancer cohort.

	Total	**Early stage (Stages I & II)**	**Advanced stage (Stages III & IV)**	**P value**
Chronic conditions	**N=2066 (%)**	**N=853 (%)**	**N=1213 (%)**	
Obese				
No	1334 (64.6)	512 (60.0)	822 (67.8)	**<0.001**
Yes	732 (35.4)	341 (40.0)	391 (32.2)	
Hypertension				
No	1394 (67.5)	535 (62.7)	859 (70.8)	**<0.001**
Yes	672 (32.5)	318 (37.3)	354 (29.2)	
HIV status				
Negative	1735 (84.0)	719 (84.3)	1016 (83.8)	0.746
Positive	331 (16.0)	134 (15.7)	197 (16.2)	
Diabetes				
No	1924 (93.1)	790 (92.6)	1134 (93.5)	0.440
Yes	142 (6.9)	63 (7.4)	79 (6.5)	
Tuberculosis				
No	1980 (95.8)	817 (95.8)	1163 (95.9)	0.912
Yes	86 (4.2)	36 (4.2)	50 (4.1)	
Asthma/COPD				
No	1978 (95.7)	816 (95.7)	1162 (95.8)	0.883
Yes	88 (4.3)	37 (4.3)	51 (4.2)	
Heart diseases				

No	2003 (97.0)	832 (97.5)	1171 (96.5)	0.193
Yes	63 (3.0)	21 (2.5)	42 (3.5)	
Any chronic condition				
No	714 (34.6)	260 (30.5)	454 (37.4)	**0.001**
Yes	1352 (65.4)	593 (69.5)	759 (62.6)	
Multimorbidity				
<2 chronic conditions	1491 (72.2)	588 (68.9)	903 (74.4)	**0.006**
≥2 chronic conditions	575 (27.8)	265 (31.1)	310 (25.6)	

***analysis limited to 2066 women with known stage at diagnosis. P value significant at <0.1 shown in bold face.
COPD (Chronic obstructive pulmonary disease),

PART THREE:INTEGRATED DISCUSSION AND CONCLUSION

"The doctor of the future will give no medicine, but will instruct his patients in care of the human frame, in diet, and in the cause and prevention of disease." – Thomas Edison, (1903)

6. CHAPTER SIX: INTEGRATED DISCUSSION AND CONCLUSION

This chapter presents a consolidated overview of this thesis. It focuses on summary of findings, main themes that emerged from the study with a particular focus on public health implications. Lastly, it discusses the recommendation for future research as well as the limitations of the study.

6.1. Key findings

This PhD thesis focused on multimorbidity and breast cancer, the most common female cancer worldwide with significant incidence projected for SSA in the next 20 years. A major contribution made to the literature has been to provide a better epidemiological understanding of the profile, pattern and prevalence of chronic conditions and multimorbidity and its determinants among breast cancer patients of SSA. Additionally, the multimorbidity and sociodemographic determinants of advanced stage at diagnosis in women with breast cancer and cancer treatment decisions in SSA have been described to provide insights on how lifestyle transitions are clustering to impact stage at presentation and breast cancer management. Table 6.1 summarizes the key findings of this thesis.

Table 6.1: Summary of research findings per study objectives

Thesis chapter	Study objective	Key findings
Chapter 3	To characterize and compare socioeconomic factors and chronic conditions among women with breast cancer from Soweto, South Africa with their age and neighbourhood matched controls. **Hypotheses:** Socioeconomic factors and chronic conditions are not predictors of stage at breast cancer diagnosis among women in Soweto, South Africa	• Majority (56%) of the women with breast cancer were obese, 84.0% had abdominal adiposity, 59% were hypertensive, 47% had impaired fasting plasma glucose, 17% were HIV infected, 8% had elevated total cholesterol, 78% had low HDL and 9% were assessed to be depressed. Ninety percent of the women with breast cancer had at least one metabolic disease. • Women without breast cancer were significantly more likely to have schooled beyond primary education, to have wider waist circumference and also more likely to be HIV infected than women with breast cancer. There were no significant differences in household SES, nutritional status (BMI), level of hypertension, fasting plasma glucose, dyslipidaemia or depression between women with and without breast cancer. • In women with breast cancer, higher household SES was significantly associated with early stage breast cancer at diagnosis, chronic conditions were not significantly associated with stage at breast cancer diagnosis. **Conclusion: The result highlights that the hypothesis tested is rejected because higher socioeconomic status was associated with early stage breast cancer although chronic conditions had no such influence in Soweto, South Africa.**

Chapter 4	To assess the multimorbidity burden of women newly diagnosed with breast cancer in 5 public hospitals in South Africa and the associations of these chronic conditions and multimorbidity with breast cancer stage at diagnosis and first breast cancer treatment received. **Hypothesis:** Multimorbidity is not a predictor of stage at breast cancer diagnosis and first breast cancer treatment received in South Africa women.	• The prevalence of multimorbidity was 44% in South African women with breast cancer. Individual chronic conditions were equally high: obesity (53%, hospital-specific range 48-56%), hypertension (41%, 34-49%), HIV (22%, 15-41%), diabetes (14%, 8-26%), tuberculosis (7%, 4-10%), asthma/COPD (5%, 4-9%), cerebrovascular disease (3%, 2-6%). • Overall, 56% of the women had advanced stage breast cancer (stages III & IV) ranging from 49% in Johannesburg Soweto hospital to 82% in KZN rural hospital. • The sociodemographic factors associated with multimorbidity were increasing age, enrolment at the KZN Durban and Pietermaritzburg hospitals and higher household SES. The Asians and whites were at reduced odds of multimorbidity compared to the black patients. • Self-reported hypertension was the only chronic condition significantly associated with stage at breast cancer diagnosis (Early stage), multimorbidity was not significantly associated with breast cancer stage at diagnosis. • In early stage breast cancer, women with multimorbidity were less likely to have surgery, less likely to receive chemotherapy and more likely to receive endocrine therapy than those with low multimorbidity burden. **Conclusion: Although multimorbidity had no influence on stage at breast cancer diagnosis, it was a predictor of first treatment received in women with early stage breast cancer in South Africa, I therefore reject this null hypothesis.**

Chapter 5	To determine profiles and patterns of multimorbidity in women newly diagnosed with breast cancer in 5 countries in SSA and their associations with stage at diagnosis. **Hypothesis:** Chronic conditions and multimorbidity have no effect on stage at diagnosis of breast cancer in SSA.	• Morbidity prevalence was highest for obesity (35%, country-specific range 15-57%), followed by hypertension (32%, 15-51%) and HIV (16%, 2-26%) then for diabetes (7%, 4-10%), asthma (4%, 2-10%), tuberculosis (4%, 0-8%) and heart disease (3%, 1-7%). Overall, 27% of women had multimorbidity ranging from 11% in Uganda to 42% in South Africa. • Older women were more likely to be obese, hypertensive, diabetic and have heart disease and less likely to be living with HIV than younger women. • Women with higher SES were more likely to be obese, hypertensive and diabetic compared with women with low SES. Older women and women with higher SES were also more likely to have multimorbidity. • Women who were obese and those who were hypertensive were significantly more likely to present with early stage breast cancer. • Multimorbidity was not significantly associated with stage at breast cancer diagnosis. **Conclusion: From these findings, i will also reject this hypothesis because chronic conditions (obesity and hypertension) were associated with early stage breast cancer, although multimorbidity was not associated with stage at breast cancer diagnosis in SSA.**

6.2. Emerging research themes from the findings

Overall, two main themes emerged from this findings: A methodological theme emerged through the series of study and analysis conducted and empirical themes arose during the course of this research.

6.2.1. Methodological theme

The multiple cohort approach was used in this study starting from a single centre study in objective 1/paper 1 to a multi-centre study in one country in objective 2/paper 2 to a multi-country study in objective 3/paper 3. This methodology provided the opportunity to test objectives and the same hypothesis in settings of steadily increasing context and environmental complexity for women with breast cancer, in order to identify unique and universal findings. Africa is the most diverse continent in the world and its diversity is centered around culture, ethnicity, gender, genetics and religion (Appiah et al., 2018). It provides the opportunity to identify determinants of multimorbidity and stage at diagnosis and account for women differences within and between different settings. It also helps to identify context-specific factors that can be targeted to most effectively decrease breast cancer stage at diagnosis and ultimately increase survival from common cancers in Africa. This methodology also enables comparisons of multimorbidity burden and stage at diagnosis in LMIC countries with varying income levels, patient and health system resources and stage in lifestyle transition. Several quantitative and qualitative studies have used cross-cultural, cross-national and multi-cohort longitudinal studies in answering research questions (Berrino et al., 2007, Coleman et al., 2011, Chapple and Ziebland, 2018, Walters et al., 2013).

An advantage of this methodological approach is that it provides the platform for tailoring specific research tools that speak to the local setting, while answering questions and knowledge gaps that universally exist within the South African and SSA settings. Hypotheses can be tested and compared in relatively smaller sample sizes in the single-centre study to larger sample sizes in the multi-center and

multi-country cohort. There is less personal bias across cohorts and the findings that are generalizable can be distinguished from those that are setting specific to assist with local and regional policies and interventions.

At times multi-cohort or multi-centric research introduces complexities alongside the benefits, for example, translating questionnaires can be a challenge, and heterogeneity in clinical practice among centres may also be a major confounding factor in interpreting the findings of these studies. Another limitation to this approach might be data quality across settings. Ensuring high data quality is a major concern in any multi-cohort or multi-centric study, however, in the 3 cohorts utilized for this study, standardized data collection procedures, strict quality control and close monitoring procedures were implemented throughout. Another limitation is the logistics involved in setting up such studies, especially where different health systems and languages are involved. Synchronizing staffing, project management, ensuring comparable methods and communication between research groups are challenging.

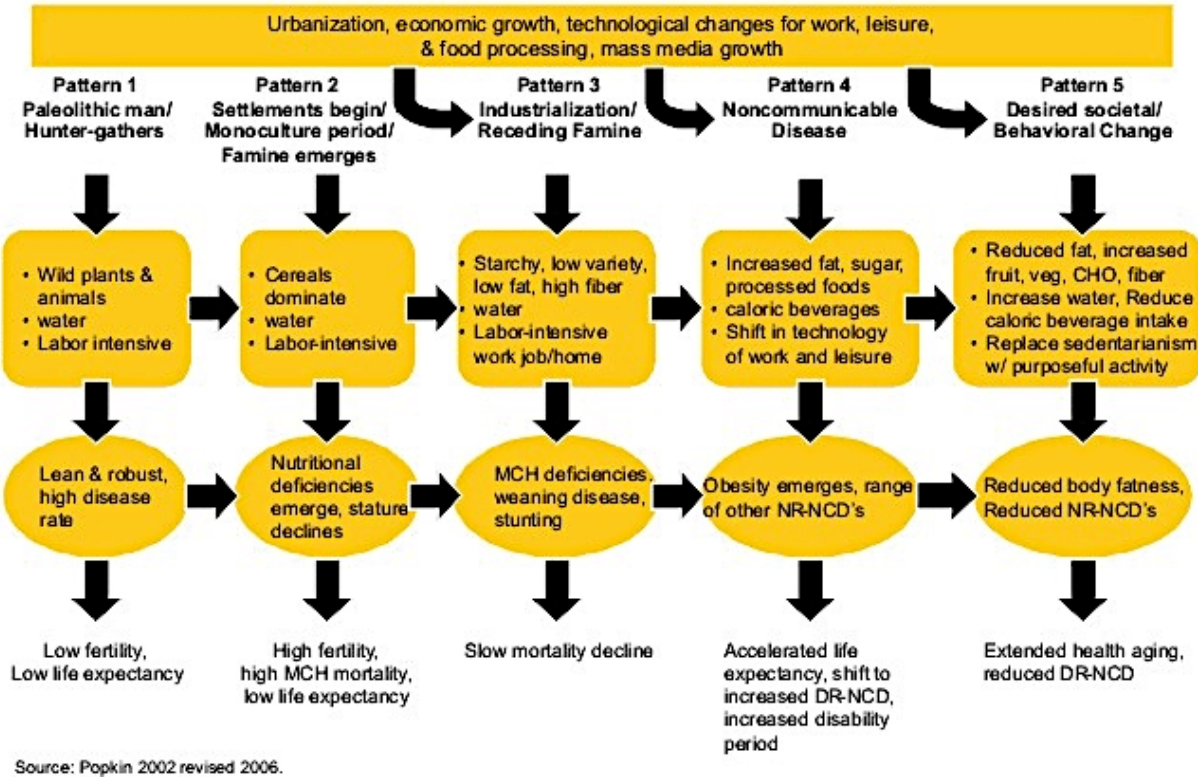
This is the first multiple cohort study to examine multimorbidity in women with breast cancer across settings in SSA. It identifies context-specific modifiable factors that need to be targeted to most effectively decrease the burden of multimorbidity, improve breast cancer stage at diagnosis and survival in Africa. The high prevalence of chronic conditions and multimorbidity across cohorts, the association of high SES with chronic conditions and multimorbidity, the association of hypertension with early stage breast cancer are some of the universal findings form this study. The association of obesity with early stage breast cancer is context specific in the multi-country cohort. These findings are contextualized below in the revisited conceptual model in figure 6.2. The findings from this approach has provided a most-needed evidence base from which to develop and evaluate setting-specific, and culturally-acceptable, interventions aimed at improving survival from breast cancer in SSA.

6.2.2. Empirical theme

In this study, higher socio-economic status was consistently associated with higher odds (risks) of NCDs and multimorbidity. This could be explained by the demographic, epidemiologic and nutritional transitions among different populations within different countries in SSA. During the last century wide-reaching changes in diet and nutritional status, disease patterns and life expectancy have occurred in SSA countries. These changes are thought to have occurred through three separate transitional processes. 1) The demographic transition 2) the epidemiological transition and 3) the nutritional transition.

1) The demographic transition refers to a change from a period of high fertility and mortality to a period of low fertility and mortality which is as a result of an increase in education, employment, income and longevity (Amuna and Zotor, 2008).
2) The epidemiological transition refers to a change from a period of high prevalence of communicable disease associated with famine, malnutrition and poor sanitation, to a period of increasing control of communicable diseases to a rapidly increasing prevalence of NCDs (Popkin, 2002a).
3) Nutritional transition is known as the change in diet and physical activity patterns in relation to agriculture development over a period of time. This transition is thought to have occurred simultaneously with the demographic and epidemiological transitions. Five evolutionary stages of human nutritional patterns and transition have been identified (Popkin, 1993, Abrahams et al., 2011) (Figure 6.1).

Figure 6.1: Five Stages of the Nutrition Transition



Stage 1 / pattern 1: Known as the hunter-gatherer stage, there is high consumption of carbohydrates and fibre and low consumption of saturated fat whilst obesity rates were low and physical activity levels were high.

Stage 2 / pattern 2: Known as the famine stage, low dietary diversity was noted. Dietary intake shifted towards cultivation and settlements while physical activity levels remained high.

Stage 3 / pattern 3: Period of receding famine. In this stage agriculture became more advanced. There was a decrease in carbohydrate consumption and increased fruit, vegetable and protein consumption whilst physical activity started to decrease. This is the period of development of more technically advanced and productive agriculture.

Stage 4 / pattern 4: This stage is associated with nutrition related NCDs and characterized by dietary intake high in sugar, fat, cholesterol and refined grains. This stage is further associated with low fibre consumptions and low levels of physical activity with increase in prevalence of obesity and NCDs.

Stage 5 / pattern 5: Stage of behavioral change. Changes in dietary intake will occur due to desired behavioural changes to delay or prevent degenerative diseases. There will be a shift towards an increase in complex carbohydrates, fruits and vegetables, whilst a decreased consumption of processed foods, fat, dietary products and high fat meat are promoted (Popkin, 1993).

These stages of transition differ in different countries in SSA, urban and rural areas in the same country may also be at different stages of the nutritional transition. While most HICs tend to be in final stage of the transition; most LMICs and SSA countries like South Africa, Namibia have not been immune to this nutritional transition (Abrahams et al., 2011, Bosu, 2015, Steyn and Mchiza, 2014). In fact the nutrition transition from stag 2-4 appears to be generally accelerating in SSA particularly among the middle income countries, where changes in dietary patterns are negatively affecting health outcomes in a large portion of the population. Most low-income countries are still in the early stages of nutritional transition. The overall result is that an increasing number of women are experiencing the double burden of underweight and obesity occurring simultaneously (Popkin, 2002b). Non-communicable diseases that used to be associated with old age in HICs are becoming more prevalent in SSA following the rapid increase in industrialization, economic development, urbanization and globalization (Popkin, 2015). Proliferation of fast-food outlets, restaurants and food vendors in cities have facilitated increased access to unhealthy diets, thereby transforming our urban settlements into obesogenic environments. It is important to identify those in the early stage of the nutritional transition as primordial prevention can still be introduced. For individuals of higher SES, with appropriate education and policy interventions, these transitions should offer improved access to nutritious foods since they can afford more healthy

foods. Yet our findings indicate that higher SES status is linked to higher obesity, hypertension, diabetes and multimorbidity among women of SSA. This is in contrast to HICs where overweight, obesity and multimorbidity is highest among the poor communities. This is a common finding for other LMICs (Steyn and Damasceno, 2006).

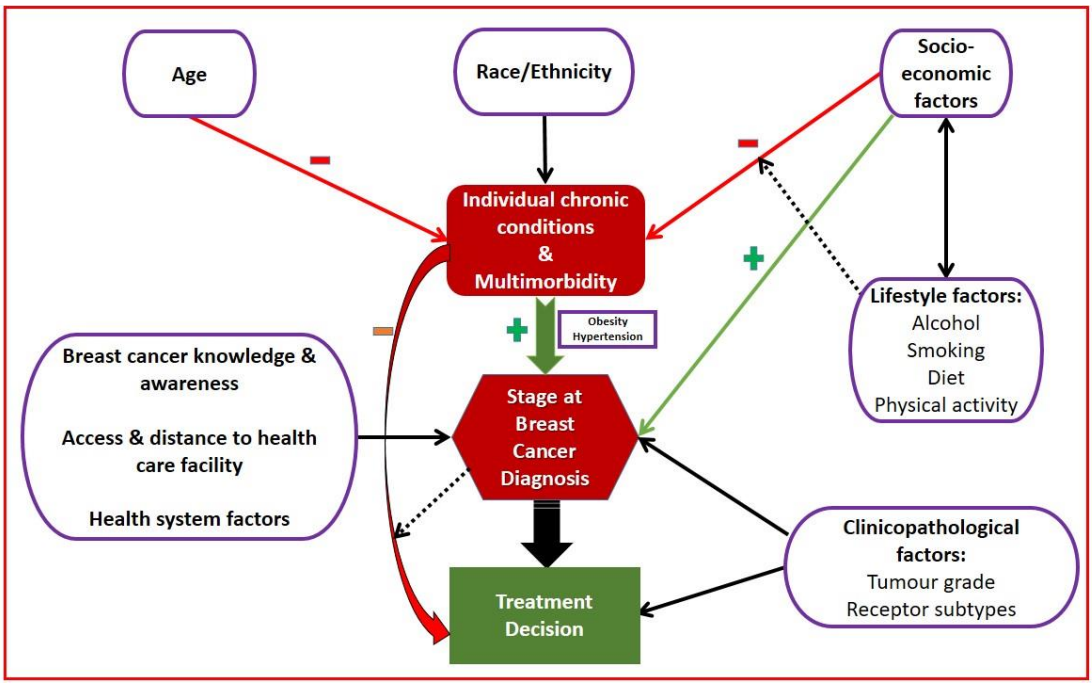
Sub-Saharan Africa is a LMIC continent, undergoing a rapid health transition resulting in double epidemics of communicable and non-communicable diseases in different stages of transition. Upper MICs have an exploding multimorbidity epidemic that may very well be mirrored in lower MICs and LICs as they develop which will be catastrophic for these countries whose health systems are least able to cope with the burden.

6.3. Conceptual framework

This section reflects upon the conceptual framework utilized in this study. The conceptual framework of the thesis combined adaptations of the classic bio-psychosocial theoretical model (Engel, 1981) and Andersen model of total patient delay (Andersen et al., 1995) and its applications in cancer diagnosis (Walter et al., 2012) (Figure 6.2). This conceptual framework highlights the various factors such as patient factors, their existing chronic conditions and multimorbidity, and breast cancer clinical factors as well as health system factors that may contribute to stage at breast cancer diagnosis and treatment decisions. The bio-psychosocial model construes human health as a product of the reciprocal influences of biological, interpersonal, psychological, and macrosystem contextual dynamics that unfold over historical and personal time. The relative importance of these different influences vary within a person over time.

In applying this framework, we see that our results contribute to confirming the continued use with a little modification of the conceptual framework as a guide for determining the patient and health system factors, chronic condition and multimorbidity influencing stage at breast cancer diagnosis and treatment decisions. I suggest the positive association observed between higher SES and multimorbidity requires individual chronic conditions and multimorbidity to remain in the model. With the finding of higher multimorbidity in higher socio-economic groups which is the reverse of what is evident from studies in HICs and with the possible explanations being demographic, epidemiological and nutritional transitions occurring in SSA, there is need to investigate the effect of behavioral/lifestyle factors in relation to SES and its effect on multimorbidity, and requires including diet, physical activity, alcohol intake and smoking as a possible effect modifier for the association (See dashed arrow Figure 6.2). In addition the magnitude of the effect of multimorbidity on treatment decisions differs depending on the stage at diagnosis which has been highlighted in the model (See dashed arrow, Figure 6.2).

Figure 6.2: Revised conceptual framework for the associations of multimorbidity with stage at diagnosis and treatment decision in women with breast cancer.



Solid arrows indicate associations between variables, with + (blue) and – (red) symbols depicting positive and negative associations respectively. Dashed arrows represent effect modification of the identified association.

In SSA, breast cancer and indeed most other cancers are generally diagnosed at late stages with limited treatment options and dismal 5-year survival outcomes. The various studies conducted for this body of work have limited capacity to confirm the causes of differing stages at breast cancer diagnosis in the different settings. However, significant positive associations did emerge for SES and individual chronic conditions (obesity and hypertension) with early stage breast cancer at diagnosis. This adds weight to the continued relevance of this conceptual framework as a guide for determining the factors influencing stage at breast cancer diagnosis with emphasis on the direction of the effect of these factors.

In this study, breast cancer knowledge and awareness among patients and cancer care providers and other health system factors associated with stage at breast cancer diagnosis were not investigated. Prior studies from HICs and LMICs, including our own have revealed a myriad of patient and health system factors that appear to affect the stage at breast cancer diagnosis (Pace and Shulman, 2016, Akuoko et al., 2017, Krok-Schoen et al., 2016, Joffe et al., 2018). We found that greater breast cancer knowledge and awareness was associated with earlier stage at breast cancer diagnosis, and women who underwent ≥ 2

health system visits within the referral network prior to diagnostic investigations at the tertiary CHBAH compared to women who had only 0-1 hospital visits before being referred for diagnostic workup were more likely to present with advanced stage breast cancer at diagnosis. Patient pathways to presentation to health care facilities and timely recognition of disease symptoms and appropriate management in primary and secondary hospitals are key determinants of outcomes in cancer. Reducing diagnostic delays may increase the proportion of early stage cancers identified and improve prognosis. Overall, this model confirms the importance of chronic conditions and multimorbidity along with other patient sociodemographic and environmental, clinical and health system factors in determining stage at breast cancer diagnosis and treatment decisions. In addition, it enables us to include the component for addressing lifestyle factors associated with increasing SES that might be beneficial in reducing the burden of multimorbidity in SSA.

6.4. Implications

- The findings from this study are first of their kind in women newly diagnosed with breast cancer in SSA. This thesis has laid the foundation for understanding the profiles, patterns and burden of chronic conditions and multimorbidity in women with breast cancer in SSA. The findings reveal the need for an effective integrated and comprehensive array of health service interventions to deal with the increasing multimorbidity burden among breast cancer patients spanning primary to tertiary levels of care. While previous studies have investigated the factors associated with multimorbidity in different cohorts of patients with different underlying medical conditions, this is the first that investigated these associations in multi-centre and multi-country settings in SSA. This approached confirmed our universal alarming finding of increasing SES associated with multimorbidity in SSA countries; the reverse of trends observed in HICs.

- Close relationships exist in course, cause and outcome between communicable diseases, maternal and perinatal conditions, nutritional conditions and NCDs. They all have common underlying social conditions such as unhealthy environments and poverty, commonalities across disease groups in co-morbidity, causation, and care needs. Both communicable diseases and NCDs frequently co-exist in the same individual, and one can increase the impact or risk of the other. Interventions to improve maternal and child health – such as reducing malnutrition are also integral components of a continuum of preventive measures for NCDs.
- The concept of syndemics cannot be overlooked. A syndemic is the clustering of two or more diseases within a population that arise from, and contributes to, persistent economic and social inequalities (Singer, 2000). Patients experience morbidity through a combination of complex social and medical conditions that impact quality of life and survival outcomes. This clustering of social and health problems is often overlooked in models of epidemiological transition investigations. In SSA, it is imperative to recognize the different clusters of SES and multimorbidity in our women with breast cancer and how they interact with each other and affect health outcomes. This would frame new models of investigations that integrate more than just disease specific models, incorporating economic and social conditions that exacerbate the effects of disease clusters. Moreover, it is important to incorporate syndemic considerations into disease prevention and management of health system approaches. Screening for common morbidities like hypertension, diabetes, HIV, depression, alcoholism and algorithms for understanding and accommodating socioeconomic circumstances for treatment plans should be routinely introduced for single clinic visits in primary care. This should be followed by sustained, cost-effective community interventions to foster healthier lifestyle among the majority socioeconomically

disadvantaged communities and to address their social problems holistically (Mendenhall et al, 2017).

- Implementation of UN sustainable development goals including those for education and NCDs is essential. Action against NCDs in SSA is needed now, and must take place alongside continued efforts to address communicable diseases and healthcare education among patients and health care providers. Nevertheless, there are opportunities to take advantage of the common risk factors between these disease groups and build on existing work. For instance, leveraging the experience, resources and models of existing HIV/AIDS programs could benefit the management of NCDs; and a greater emphasis on strengthening health systems through stronger primary health care, universal coverage and integrated chronic care delivery is likely to be valuable for any condition. It is important to recognize and address the potential risks of setting up yet another vertical program for control of NCDs in resource-limited SSA countries – and to promote resource-sharing and integration where feasible.
- There is also need to place a primary focus on prevention of the most common NCDs like obesity, cardiovascular diseases and cancer. Measures to reduce alcohol and tobacco use, such as increased taxation are already in place in many countries, but efforts to support sustained tobacco cessation and alcohol abuse programmes need to be emphasized. The high obesity and hypertension burden policy interventions (e.g. sugar tax and salt content regulations introduced in South Africa) need to be expanded to dissuade the consumption of ultra-processed, energy-dense, nutrition-poor drink and food. Sustained interventions and incentives to promote physical activity are also essential.
- For the majority of African countries cancer population screening programmes are unaffordable. There is thus an urgent need to focus on secondary prevention and implementation science

methodologies for cost-effective early detection interventions that most countries have defined in the cancer control programmes. These are particularly relevant for good prognosis cancers if detected early such as breast, cervical and prostate cancers.

- There is also a need to find cost-effective treatment and care solutions. For those diagnosed with metastatic breast and other cancers, improvement in quality of life can be achieved by improving access to pain management and supportive care through palliative and home-based care programs, these programs are already in place for HIV/AIDS and are transferrable to other conditions.
- Adherence to treatment is a key component of multimorbidity management to minimize their impact, prevent further disability, improve health outcomes, and reduce healthcare costs (Bodenheimer et al., 2002). Poor adherence to treatment regimens particularly in a situation of polypharmacy for chronic conditions, has long been recognized as a substantial barrier to achieving better outcomes for patients as it negatively impacts their quality of life and health outcomes and increases healthcare costs. Studies have shown that only half of patients with multimorbidity take their medications as prescribed (Brown et al., 2011, Sabaté 2013, von Buedingen et al., 2018). The reasons behind poor adherence are complex and multi-factorial. Ensuring adherence to treatments in multimorbid patients requires a multi-stakeholder, patient-centred approach in which the different stakeholders may provide different services but are integrated with one another (Costa et al., 2015). Practical ways of improving adherence involve behavioural change at the patient level, patient and caregiver empowerment through educational programs, optimization of drug prescription duration and simplifying complex drug regimens by the physician, enhancing communication between physician and patient, easy access to medications and regularly assessing adherence (Marengoni et al., 2016).Health system

strengthening is also essential in tackling the menace of NCDs in SSA. The severe shortage of trained health workers is not just an obstacle to tackling NCDs but also to the delivery of quality services as a whole. There is need for a universal health coverage that ensures everyone has access to effective health services when needed, without any form of financial hardship.

- It has been shown that mortality from causes other than breast cancer as a percentage of all-cause mortality is smallest for women in their forties and fifties (Rosenberg 2006). NCDs are known to increase with age and patients who present with breast cancer at an average age of around 55 years will also present with high burdens of other NCDs. Given the good prognosis of early-stage BC, the long-term benefit of breast cancer treatment, particularly in the elderly population, depends also on the optimum treatment of their co-existing multimorbidities, particularly hypertension, obesity and diabetes. Thus, optimum treatment of breast cancer and common multimorbidities among African women is required to optimise their survival.

6.5. Future research

This study focused on the effect of chronic conditions and multimorbidity on breast cancer stage at diagnosis and its effect on breast cancer treatment decisions among women from SSA. Shortcomings include our suboptimal understanding on the early stage diagnosis of breast cancer observed among obese and hypertensive women, and also our lack of understanding of the effect of these individual chronic conditions and multimorbidity on treatment efficacy and tolerance, including potentially harmful drug-drug interactions, quality of life (QOL) and survival in women with breast cancer in SSA. Given these shortcomings, these are the 2 studies I would like pursue to fill the identified research gaps, and particularly building on our findings in the following ways:

1) Explore the association of obesity and hypertension with early stage breast cancer with emphasis on qualitative research such as focused group discussion or in-depth one-on-one interviews to be able to seek in-depth understanding of this finding through open ended exploratory questions.
2) The overall relative 3 and 5 years survival of women with breast cancer in SSA is estimated at 65.8% (63.5–68.1) and 59.0% (56.3–61.6) respectively (Joko-Fru et al., 2020); this is very poor compared to findings from HICs. In our SABCHO and ABC-DO studies in South Africa and SSA respectively, we are collecting information on the entire breast cancer journey of our breast cancer patients, and factors hypothesized to have direct impacts on survival. These include lifestyle factors, clinical cancer characteristics and stage at diagnosis, treatments prescribed and received and morbidity factors. The impact (if any) of individual chronic conditions and multimorbidity on the survival of women with breast cancer in SSA is of course required. This is another focus of my future research where I will be able to quantitatively determine and compare the incremental effects of multimorbidity and other factors on survival.

6.6 Limitations

This section addresses the limitation of this thesis as a whole. The study design used in this thesis was purely quantitative, a mixed-method approach would have enabled qualitative approaches to explore findings in more depth. For example the associations of obesity and hypertension with early stage diagnosis might have been further explored to understand patient and health system factors at play. In addition the finding on higher SES and multimorbidity could have also been explored for causality. Another limitation is that this study was based mainly on secondary data analysis and hence limited by the data available from different studies. The initial cohort studies were not designed specifically to address the impact of multimorbidity on stage at breast cancer diagnosis and treatment, hence the limited number of chronic conditions evaluated. Lastly, for objectives 2 and 3, the individual chronic conditions

were self-reported to a large extent and this could have led to underestimation of the prevalence of these chronic conditions and multimorbidity in the study.

6.7 Conclusion

In conclusion, multimorbidity and breast cancer stage at diagnosis, treatment decisions and treatment adherence need to be addressed if we are to reduce morbidity, improve quality of life and survival among women with breast cancer in SSA.

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APPENDICES

APPENDIX ONE: PLAGIARISM DECLARATION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Oluwatosin Adetayo Ayeni (Student number: 966440) am a student registered for the degree of PHD in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 12th Feb 2021

APPENDIX TWO: ETHICS CLEARANCE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Oluwatosin Ayeni

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180326

NAME: (Principal Investigator)	Dr Oluwatosin Ayeni
DEPARTMENT:	Paediatrics MRC/Wits Developmental Pathways for Health Research Unit Chris Hani Bragwanath Academic Hospital, Johannesburg Charlotte Maxeke Johannesburg Academic Hospital Inkosi Albert Luthuli/Grey's/Ngwelezana Hopitals
PROJECT TITLE:	Barriers to Early Stage Presentation of Breast Cancer Patients in South Africa
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Shane Norris and Dr Maureen Joffe
APPROVED BY:	CB Penny Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/08/2018

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX THREE: APPROVAL OF STUDY TITLE

UNIVERSITY OF THE
WITWATERSRAND,
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Reference: Mrs Sandra Benn
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03 January 2020
Person No: 966440
PAG

Dr OA Ayeni
E01, Houghton Village
6 Boundry Road
2198
South Africa

Dear Dr Oluwatosin Ayeni

Doctor of Philosophy: Approval of Title

We have pleasure in advising that your proposal entitled *Factors influencing breast cancer presentation time and a Delphi process to identify solutions for earlier presentation in South African women* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX FOUR: PAPER ONE

Prevalence of comorbidities in women with and without breast cancer in Soweto, South Africa: Results from the SABC study

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Background. Comorbidities occurring concurrently in breast cancer patients can be burdensome, as they may negatively influence time and stage of presentation.
Objectives. To describe the comorbid health conditions among South African (SA) black women with and without breast cancer and to determine factors associated with advanced-stage presentation of breast cancer.
Methods. A population-based case-control study on breast cancer was conducted in black women in Soweto, SA, the SABC (South Africa Breast Cancer) study. Lifestyle information and blood samples were collected from 399 women with histologically confirmed new cases of invasive primary breast cancer, recruited prior to any therapy, and 399 age- and neighbourhood-matched controls without breast cancer. We compared self-reported metabolic diseases, depression, anthropometric measurements, blood pressure, HIV status and point-of-care lipid and glucose levels between patients with breast cancer and the control group.
Results. In the whole population, the mean (standard deviation) age was 54.6 (12.9) years, the majority (81.2%) of the participants were overweight or obese, 85.3% had abdominal adiposity, 61.3% were hypertensive, 47.1% had impaired fasting plasma glucose, 8.4% had elevated total cholesterol, 74.8% had low high-density lipoprotein and 10.9% were assessed to be depressed. Ninety-one percent of the whole cohort had at least one metabolic disease. In the breast cancer group, 72.2% had one or more metabolic diseases only (HIV-negative and no evidence of depression), compared with 64.7% of the control group. From a multivariate logistic regression adjusted model, higher household socioeconomic status conferred a 19% reduction in the odds of having advanced-stage breast cancer at diagnosis, while hypertension, dyslipidaemia and HIV were not significantly associated with stage at breast cancer diagnosis in the adjusted model.
Conclusions. A large proportion of women experience several comorbidities, highlighting the need to address the chronic non-communicable disease epidemic in SA and to co-ordinate multidisciplinary primary-, secondary- and tertiary-level care in the country's complex healthcare system for better outcome.

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Globally, ~41 million people die from non-communicable diseases (NCDs) each year, with >85% of deaths occurring in low- and middle-income countries (LMICs), including South Africa (SA).[1] In SA, 39% of total deaths in 2010 were due to NCDs, with the number of deaths similar to deaths from the combination of HIV and tuberculosis.[2] It is projected that in LMICs the number of deaths from NCDs will be five times higher than the number of deaths from communicable diseases by the year 2030.[3] Most deaths occur in the productive years, compromising the developmental goals defined by the World Health Organization (WHO), which include economic stability, poverty reduction and health equity.[4] The major NCD burden in LMICs is made up of hypertension, cardiovascular diseases, chronic lung diseases, type 2 diabetes, cancer and depression, all of which increase with age.[5] Risk factors such as alcohol consumption, smoking, dietary factors, lack of exercise and excess weight are responsible for a large share of the global disease burden, mediated directly or through conditions such as increased weight/body mass index (BMI), high blood pressure (BP), and elevated cholesterol and blood glucose levels.[6] It is worrisome that in SA this rapidly increasing NCD burden is occurring at the same time as the large number of HIV-positive individuals well managed on antiretroviral treatment is ageing.[7,8]

Cancer is one of the major causes of morbidity and mortality globally, with an estimated 14.9 million incident cases and ~8.2 million cancer deaths in 2013 making cancer among the leading causes of death globally.[9] According to the WHO, cancer is the second leading cause of NCD deaths, accounting for 21% of all NCD deaths.[10] Breast cancer remains the most common cancer among women worldwide and is a major contributor to women's cancer deaths. In LMICs the mortality-to-incidence ratios are comparatively high, mainly owing to advanced stage at diagnosis and suboptimal management.[11] Countries in sub-Saharan Africa, including SA, have

yet to identify cancer as a priority, allocating limited resources mainly to HIV, tuberculosis and other infectious disease management,[12-17] although the burden of cancer and NCDs in this region is increasing rapidly.[18]

Existing lifestyle risk factors and the metabolic syndrome (high blood glucose, high BP, abnormal cholesterol levels and excess fat around the waist) have been associated with increased breast cancer risk, especially in postmenopausal women.[19-22] Studies in LMICs have shown that the prevalence of the metabolic syndrome in breast cancer patients can be as high as 40%.[21] It has also been reported that about a third of women with breast cancer are likely to experience psychological distress.[23] Studies have shown that the prevalence of anxiety and depression ranges from 1.5% to 50% among women with breast cancer, depending on definitions and methods of assessment of psychological disorders.[24,25]

There have been conflicting reports on the association of education with breast cancer. Older studies have shown that women with higher education are at an increased risk of developing breast cancer compared with those with low education.[26-28] However, studies conducted in LMICs have reported the reverse.[29,30]

Studies have shown that stage at cancer diagnosis is affected by other health conditions, but the direction and magnitude of this effect are highly inconsistent.[31] Several competing mechanisms such as the surveillance hypothesis, psychological hypothesis, competing-demand hypothesis and death-from-other-cause hypothesis may affect stage at diagnosis.[32]

The interplay between metabolic diseases, depression, HIV and breast cancer influences cancer treatment decisions and patients' tolerance of and adherence to treatment.[33,34] Furthermore, the presence of metabolic diseases, depression and HIV has also been reported to negatively influence survival in breast cancer patients.[34-37] Metabolic diseases are largely preventable by eliminating risk factors such as harmful alcohol use, tobacco use, physical inactivity and an unhealthy diet. Better understanding of the prevalence of metabolic diseases, depression and HIV in SA populations is needed to improve health policies and service integration.[38]

Objectives

We conducted a population-based case-control study primarily to describe and compare the burden of metabolic diseases, HIV infection and depression in women with and without breast cancer. However, because the covariates analysed could possibly be associated with stage at breast cancer diagnosis, we analysed these covariates further to determine their effect on stage at diagnosis. The objectives of this study were to describe and compare the burden of metabolic diseases, depression and HIV among women newly diagnosed with invasive breast cancer at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, SA, with that in age- and residential neighbourhood-matched controls, and to determine factors associated with advanced-stage breast cancer diagnosis.

Methods

Study design and setting

The SABC (South Africa Breast Cancer) study is a population-based case-control study set up in Soweto, home to a high-density urban population, to study the aetiology of breast cancer in SA black women. The SABC study is co-ordinated by the International Agency for Research on Cancer in collaboration with the University of the Witwatersrand, CHBAH, North-West University and the University of Southampton.

Women were recruited at the Breast Unit of CHBAH between December 2014 and June 2017. CHBAH is the largest public hospital in SA with >90% of patients being black, and it boasts an infrastructure with pathology laboratory services and professional skills that are not easily available in other African settings. Approximately 85% of patients presenting to CHBAH are referred from public sector primary- and secondary-care facilities within a 30 - 60 km radius, and the rest are either self-referred or referred from private general practitioners. Controls were recruited from the same communities as the cases.

Recruitment of cases and controls

Eligibility criteria

Cases. Women aged ≥18 years with histologically confirmed newly diagnosed breast cancer who provided written consent and met all the inclusion and exclusion criteria were enrolled. Exclusion criteria were pregnancy or breastfeeding, chronic renal disease, a previous cancer diagnosis or inability to answer questions.

Controls. Women aged ≥18 years who matched the cases for age (±5 years) and area of residence were selected from the Soweto population. Controls were recruited by community volunteers at churches and community centres.

For all subjects, fasting blood samples were collected prior to the start of any treatment (for cases), fractionated into serum, plasma, red blood cells and buffy coats, and stored at –80°C. At the same time, spot urine samples were collected from all subjects, aliquoted and stored at –80°C.

Procedures

Interviews

Investigators and trained study staff conducted face-to-face interviews. We collected detailed information on socioeconomic status (SES) during infancy and early childhood, health and reproductive history (number of births, age at each birth, age at menarche, and duration of breastfeeding for each birth), history of benign breast disease, use of exogenous hormones, smoking habits, alcohol intake, maximum attained body weight, body silhouette at different ages, physical activity (household and recreational) and hours per day spent sedentary (e.g. watching television), diet, occupation, environmental exposures, ethnicity, and family history of cancer. In particular, self-reported demographics, comorbidities (hypertension, diabetes, cardiovascular disease, tuberculosis, hypercholesterolaemia and depression) and socioeconomic indicators (education level, household socioeconomic score determined from motor vehicle ownership and household possessions (refrigerator, microwave, cell phone and landline telephone, washing machine, bed, cooking facilities), with the score calculated as described in a footnote to Table 1) were collected. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression and other major depressive symptoms. Its validity has been tested in studies in SA and a similar study in Mexican women.[39-41] Only seven of the nine questions from the PHQ were used. The two questions 'Feeling down, depressed or hopeless' and 'Moving or speaking so slowly that other people could have noticed' were omitted because they did not perform well on test-retest reliability assessments.[41]

Anthropometric data and other measurements

Body weight, standing and sitting height, and waist and hip circumferences were measured. Pulse and BP were measured according to the American Heart Association recommendations.[42] Participants were seated, and three consecutive readings were taken.

Table 1. Sociodemographic profile and disease risk in women from the SABC study with and without breast cancer

Variables	Total (*N*=798)	Participants: Breast cancer (*N*=399)	Participants: Controls (*N*=399)	*p*-value
Age (years), mean (SD)	54.6 (12.9)	54.6 (12.8)	54.7 (12.9)	0.939
Level of education, *n* (%)				
Completion of primary education and below	167 (20.9)	97 (24.3)	70 (17.5)	0.023*†
Completion of secondary education	617 (77.3)	298 (74.7)	319 (80.0)	
Some tertiary education	14 (1.8)	4 (1.0)	10 (2.5)	
Household SES (assets score, 0 - 8‡), mean (SD)	5.4 (1.3)	5.4 (1.3)	5.5 (1.3)	0.182
BMI (kg/m²), *n* (%)				
Underweight§ and normal (<24.9)	150 (18.8)	82 (20.5)	68 (17.0)	0.649
Overweight (25.0 - 29.9)	192 (24.1)	93 (23.3)	99 (24.8)	
Obese (30.0 - 39.9)	215 (26.9)	105 (26.3)	110 (27.6)	
Morbidly obese (≥40)	241 (30.2)	119 (29.8)	122 (30.6)	
Waist circumference (cm), mean (SD)	94.6 (13.8)	93.4 (13.8)	95.9 (13.7)	0.009*
Abdominal adiposity (waist circumference in cm), *n* (%)				
<80	117 (14.7)	64 (16.0)	53 (13.3)	0.271
≥80	681 (85.3)	335 (84.0)	346 (86.7)	
Dyslipidaemia (TC and HDL in mmol/L), *n* (%)				
TC ≤6.21	731 (91.6)	368 (92.2)	363 (91.0)	0.523
TC >6.21	67 (8.4)	31 (7.8)	36 (9.0)	
HDL ≤1.3	597 (74.8)	310 (77.7)	287 (71.9)	0.061
HDL >1.3	201 (25.2)	89 (22.3)	112 (28.1)	
Hypertension (BP reading alone in mmHg, patients hypertensive on medications excluded), *n* (%)				
Normal BP (<120/<80)	167 (36.5)	84 (36.4)	83 (36.7)	0.323
Category 1 (120 - 139/80 - 89)	142 (31.1)	79 (34.2)	63 (27.9)	
Category 2 (140 - 159/90 - 99)	99 (21.7)	43 (18.6)	56 (24.8)	
Category 3 (≥160/≥100)	49 (10.7)	25 (10.8)	24 (10.6)	
Hypertension (using either BP reading or medication use), *n* (%)				
No	309 (38.7)	163 (40.8)	146 (36.6)	0.217
Yes	489 (61.3)	236 (59.2)	253 (63.4)	
Fasting glucose (mmol/L), *n* (%)				
≤5.5	422 (52.9)	212 (53.4)	210 (52.6)	0.828
>5.5	376 (47.1)	185 (46.6)	189 (47.4)	
Missing	2	2	0	
Risk of depression (using either PHQ-9 score or self-reported depression), *n* (%)				
No	711 (89.1)	364 (91.2)	347 (87.0)	0.053
Yes	87 (10.9)	35 (8.8)	52 (13.0)	
HIV status, *n* (%)				
Negative	642 (80.5)	333 (83.5)	309 (77.4)	0.032*
Positive	156 (19.5)	66 (16.5)	90 (22.6)	

SABC = South Africa Breast Cancer; SD = standard deviation; SES = socioeconomic status; BMI = body mass index; TC = total cholesterol; HDL = high-density lipoprotein; BP = blood pressure; PHQ-9 = Patient Health Questionnaire-9.
*Significant at p<0.05.
†Fisher's exact test.
‡Household SES (assets) score determined from: motor vehicle = 1, refrigerator = 1, microwave = 1, land telephone = 1, washing machine = 1, cell phone = 1, bed = 1, gas/electric stove = 1 (1 for yes, 0 for no).
§19 women were underweight.

Blood measurements

Fasting plasma glucose and lipids (total cholesterol (TC) and high-density lipoprotein (HDL)) were measured enzymatically with a glucose oxidase method and cholesterol oxidase method, respectively, using the RX Daytona Plus (Randox, UK) automated clinical chemistry analyser method. The coefficient of variation for the laboratory technician was <2% for the assays. Cases and controls were measured in the same batch. HIV status was measured by either the HIV 1-2 rapid test (Alere Inc., USA) for the controls or an enzyme-linked immunosorbent assay (ELISA) through the National Health Laboratory Service for the cases, because the cases were enrolled through the clinic.

Comorbidity measurements and classifications

The main comorbidities measured were obesity, hyperlipidaemia, hyperglycaemia, hypertension, depression and HIV infection. Obesity was determined by calculating the BMI from the height and weight using the WHO obesity cut-offs. A BMI of <18.5 kg/m² was categorised as underweight, 18.5 - 24.9 kg/m² as normal, 25 - 29.9 kg/m² as

overweight, 30 - 39.9 kg/m² as obese, and ≥40 kg/m² as morbidly obese.[43] Dyslipidaemia was defined as a TC level of >6.21 mmol/L or an HDL level of <1.19 mmol/L, while a fasting glucose level of >5.5 mmol/L was considered to indicate impaired fasting glucose.[44,45] BP was calculated using the average between the second and third BP readings. Hypertension was defined using BP readings alone and categorised as normal blood pressure (systolic <120 mmHg and diastolic <80 mmHg), category 1 (systolic 120 - 139 mmHg or diastolic 80 - 89 mmHg), category 2 (systolic 140 - 159 mmHg or diastolic 90 - 99 mmHg) or category 3 (systolic ≥160 mmHg or diastolic ≥100 mmHg).[46] It was further defined as 'No' or 'Yes' (mean systolic BP of ≥140 mmHg or mean diastolic BP ≥90 mmHg, or normal BP with self-reported hypertensive medication use).

Outcome measurement

The primary outcome measurement was stage at breast cancer presentation to the CHBAH Breast Unit (early stage I and II v. advanced stage III and IV), which was extracted from the Breast Unit database. Stage was assessed clinically at diagnosis. It was primarily coded according to the tumour-node-metastasis (TNM) classification and then converted to Manchester staging.

Statistical analysis

Differences in demographics, socioeconomic factors, metabolic diseases, depression and HIV between the breast cancer and control groups were described and reported using Pearson's χ^2 and Fisher's exact tests for categorical variables. Means and standard deviations (SDs) were computed for continuous variables using Student's *t*-test to report differences between groups. Frequencies of metabolic diseases in the cohort were analysed and reported, and frequencies of metabolic diseases, depression and HIV in breast cancer patients were also analysed with stage at breast cancer diagnosis as the outcome variable. To examine associations with advanced-stage breast cancer, we used multivariable logistic regression models. Variables for which *p*-values were <0.1 in bivariate analysis were included in our multivariate models. Odds ratios (ORs) were examined in three models in our multivariate analysis, with r^2 values (coefficient of determination) reported as explained variation. We added in a stepwise fashion sociodemographic factors (age and household SES), dyslipidaemia, hypertension and HIV to examine the association between these factors and advanced presentation of breast cancer. Analysis was performed using Stata version 14 (StataCorp, USA).

Ethical considerations

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (ref. no. M140980) and the International Agency for Research on Cancer Ethics Committee (ref. no. IEC 12-38).

Results

A total of 798 women (399 cases and 399 controls) were correctly matched for both neighbourhood and age to within 5 years. In the first year of recruitment, controls were enrolled independently of case matching in accordance with a predictive recruitment algorithm developed from analysis of patients enrolled in a previous study.[47] The characteristics of the cohort are summarised in Table 1. The overall mean age (SD) was 54.6 (12.9) years. Educational level, HIV status and waist circumference differed significantly between the two groups. Women in the control group were more likely than the breast cancer patients to have schooling beyond primary education (p=0.023). Over a fifth (22.6%) of the women in the control group were HIV-positive, while the figure for the breast cancer group was 16.5% (p=0.032). The mean (SD) waist circumference in the control group was 95.9 (13.7) cm while that in the breast cancer group was 93.4 (13.7) cm (p=0.009). There were no significant differences in household SES, nutritional status (BMI), level of hypertension, dyslipidaemia, fasting plasma glucose or assessment of depression between the two groups. In the total cohort, the majority (81.2%) of the participants were overweight or obese, 85.3% (n=681) had abdominal adiposity, 8.4% (n=102) had elevated TC, 74.8% (n=597) had low HDL, 47.1% (376) had impaired fasting plasma glucose, 61.3% (n=489) were hypertensive, with 43.2% (n=341) on treatment, and 10.9% (n=87) were assessed to be depressed (Table 1).

In determining the number of metabolic diseases reported in the whole cohort, only 9% (n=72) of the women had no metabolic disease; 24.1% (n=192) had one metabolic disease, 38.1% (n=304) had two metabolic diseases, 24.7% (n=197) had three metabolic diseases and 4.1% (n=33) had four metabolic diseases (Table 2). There were no significant differences in the number of metabolic diseases between the cases and their controls (p=0.285).

When combining at least one metabolic disease, depression and HIV, 2.9% (n=23) of the women presented with these three diseases in the whole cohort, and this proportion was almost doubled in the control group (3.8%, n=15) compared with the breast cancer group (2.0%, n=8). The majority (72.2%, n=285) of the women in the breast cancer group and 64.7% (n=257) of those in the control group presented with metabolic diseases alone (HIV-negative and no evidence of depression).

Women with no metabolic disease, depression or HIV comprised 5.8% (n=23) and 4.0% (n=16) of the breast cancer group and the control group, respectively. The distribution of metabolic diseases, depression and HIV was significantly different between the breast cancer and control groups (p=0.036) (Table 3).

In bivariate analysis, among women from the breast cancer group (Table 4) there was a 21% reduction in the odds of presenting with advanced-stage breast cancer for every unit increase in household

Table 2. Frequency of metabolic diseases* in women from the SABC study, overall and by case/control status

Metabolic diseases, *n*	Total (*N*=798), *n* (%)	Breast cancer (*N*=399), *n* (%)	Controls (*N*=399), *n* (%)	*p*-value
0	72 (9.0)	42 (10.5)	30 (7.5)	0.285
1	192 (24.1)	101 (25.3)	91 (22.8)	
2	304 (38.1)	139 (34.9)	165 (41.3)	
3	197 (24.7)	99 (24.8)	98 (24.6)	
4	33 (4.1)	18 (4.5)	15 (3.8)	
Total	798 (100)	399 (100)	399 (100)	

SABC = South Africa Breast Cancer.
*Defined as obesity (body mass index ≥30 kg/m²), dyslipidaemia (total cholesterol >6.21 mmol/L), hypertension (blood pressure ≥140/≥90 mmHg or medication use) and hyperglycaemia (fasting glucose >5.5 mmol/L).

Table 3. Frequency of at least one metabolic disease,* depression and HIV in women from the SABC study, overall and by case/control status

At least one MD, D, HIV	Total (*N*=798), *n* (%)	Breast cancer (*N*=399), *n* (%)	Controls (*N*=399), *n* (%)	*p*-value
MD+, D–, HIV–	542 (68.4)	285 (72.2)	257 (64.7)	0.036
MD+, D–, HIV+	103 (13.0)	41 (10.4)	62 (15.6)	
MD+, D+, HIV–	58 (7.3)	23 (5.8)	35 (8.8)	
MD–, D–, HIV+	27 (3.4)	15 (3.8)	12 (3.0)	
MD+, D+, HIV+	23 (2.9)	8 (2.0)	15 (3.8)	
MD–, D–, HIV–	39 (4.9)	23 (5.8)	16 (4.0)	
Total	792 (100)	395 (100)	397 (100)	
Not shown†	6	4	2	

SABC = South Africa Breast Cancer; MD = metabolic disease; D = depression.
*Obesity, hyperlipidaemia, hypertension or hyperglycaemia.
†D+, MD–, HIV– and D+, HIV+, MD– combinations.

Table 4. Bivariate analysis of variables associated with advanced-stage presentation (stages III and IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa

	Bivariate analysis	
Variables	OR (95% CI)	*p*-value
Age (years)	0.99 (0.97 - 1.00)	0.162
Level of education		
Completion of primary education and below	3.47 (0.35 - 34.51)	0.384
Completion of secondary education	2.77 (0.28 - 26.90)	
Some tertiary education	Reference	
Household SES (asset score)	0.79 (0.67 - 0.92)	0.002*
BMI (kg/m^2)		
Underweight and normal (<24.9)	Reference	0.343
Overweight (25.0 - 29.9)	0.80 (0.4 4 - 1.45)	
Obese (30.0 - 39.9)	0.59 (0.33 - 1.05)	
Morbidly obese (≥40)	0.74 (0.42 - 1.31)	
Waist circumference	0.99 (0.98 - 1.00)	0.167
Abdominal adiposity (waist circumference in cm)		
<80	1.41 (0.82 - 2.41)	0.212
≥80	Reference	
Dyslipidaemia (TC and HDL in mmol/L)		
TC ≤6.21	2.53 (1.13 - 5.63)	0.018*
TC >6.21	Reference	
HDL ≤1.3	1.77 (1.09 - 2.87)	0.019*
HDL >1.3	Reference	
Hypertension (BP reading alone in mmHg, patients hypertensive on medications excluded)		
Normal (<120/<80)	Reference	0.516
Category 1 (120 - 139/80 - 89)	1.15 (0.62 - 2.14)	
Category 2 (140 - 159/90 - 99)	0.65 (0.31 - 1.37)	
Category 3 (≥160/≥100)	0.89 (0.37 - 2.19)	
Hypertension (using either BP reading or medication use)		
No	1.64 (1.09 - 2.46)	0.015*
Yes	Reference	
Impaired fasting glucose (mmol/L)		
≤5.5	Reference	0.217
>5.5	1.28 (0.86 - 1.90)	
Risk of depression (using either PHQ-9 score or self-reported depression)		
No	1.31 (0.65 - 2.66)	0.437
Yes	Reference	
HIV status		
Negative	Reference	0.041*
Positive	1.75 (1.01 - 2.99)	

OR = odds ratio; CI = confidence interval; BMI = body mass index; TC = total cholesterol; HDL = high-density lipoprotein; BP = blood pressure; PHQ-9 = Patient Health Questionnaire-9.
*Significant at $p<0.05$.

SES asset score (OR 0.79, 95% confidence interval (CI) 0.67 - 0.92). Women with a TC level ≤6.21 mmol/L and an HDL level ≤1.3 mmol/L had a higher risk of advanced-stage disease (OR 2.53, 95% CI 1.13 - 5.63 and OR 1.77, 95% CI 1.09 - 2.87, respectively). Women who were HIV-positive but not hypertensive were also more likely to present with advanced-stage disease (OR 1.64, 95% CI 1.09 - 2.46 and OR 1.75, 95% CI 1.01 - 2.99, respectively). Variables significant in the bivariate analysis were further explored in individual and combined logistic regression models controlling for age (Table 5).

Sociodemographic factors (model 1) independently explained 2.9% of the variance, and household SES was shown to partially influence the likelihood of advanced stage at diagnosis. Comorbid factors (model 2) explained 3.3% of the variance, with patients with no dyslipidaemia and patients with no hypertension having greater odds of advanced-stage presentation. In the final model with all factors included (model 3), 4.9% of the variance was explained. The associations of advanced-stage breast cancer with household SES were slightly attenuated on adjustment (OR 0.81, 95% CI 0.69 - 0.95), whereas associations with hypertension, dyslipidaemia and HIV were no longer significant in mutually adjusted models (Table 5).

Discussion

We found that there was a high burden of metabolic diseases, depression and HIV in women with and without breast cancer in Soweto. About two-thirds of the whole cohort had two or more metabolic diseases and 10.2% had at least one metabolic disease and depression. The prevalence of metabolic diseases and depression was comparable in women with breast cancer and those without.

Women with breast cancer had lower levels of education compared with their controls. There was a significant difference in waist circumference and HIV status between the two groups, while levels of obesity, hyperlipidaemia, hypertension, hyperglycaemia and depression were similar. The combination of at least one metabolic disease, depression and HIV differed between the breast cancer group and the control group. A higher household socioeconomic asset score was protective against advanced-stage breast cancer at presentation, while hypertension, dyslipidaemia and HIV had no significant influence on stage at presentation.

The study demonstrated that women with breast cancer were significantly less educated than their controls, supporting literature reports that showed less-educated women and women with low SES to be at increased risk of breast cancer.[29,30] The increased risk of breast cancer in less educated women is partly due to changes in reproductive factors and lifestyle modification. We reported a high prevalence of comorbidity among Soweto women in general, corroborating findings from previous studies in SA from various settings.[48,49] About one-fifth of our whole cohort were HIV-positive, while almost 14% of breast cancer patients with at least one metabolic disease and depression were also positive for HIV. This finding further supports the fact that our population is carrying a double burden involving an epidemiological overlap of NCDs and infectious diseases.

Studies have reported an association between metabolic diseases and risk of breast cancer, especially in postmenopausal women.[22,50] There was no significant difference in our study with regard to individual metabolic disease components (obesity, dyslipidaemia, hypertension and hyperglycaemia) or in the number of metabolic diseases with which women with and without breast cancer presented; however, the proportion of women presenting with metabolic diseases was so high in both groups that significant differences were difficult to detect. Several factors, such as physical activity, dietary intake, smoking and alcohol intake, could explain the high prevalence of metabolic diseases in our study, and these lifestyle behaviours will be the focus of a future article.

Women with higher SES tended to present with early-stage breast cancer disease. It has been reported that intention to seek medical care is not entirely dependent on education and SES but on complex personal and social factors and previous healthcare-seeking habits.[51] Appropriate targeted interventions to address inequalities evident in stage at breast cancer diagnosis may help in improving stage at diagnosis.

The cost of care of breast cancer patients with metabolic diseases, depression and HIV places a big burden on the limited

Table 5. Multiple logistic regression models of factors influencing advanced-stage presentation (stages III and IV) among women diagnosed with breast cancer at the Chris Hani Baragwanath Academic Hospital Breast Clinic in Soweto, South Africa

Variables	Bivariate analysis OR (95% CI)	Model 1, sociodemographic OR (95% CI)	Model 2, comorbidities OR (95% CI)	Model 3, sociodemographic + comorbidities OR (95% CI)
Sociodemographic				
Age in years	0.99 (0.97 - 1.00)	0.99 (0.97 - 1.00)		0.99 (0.98 - 1.02)
Household socioeconomic status (asset score)	0.79 (0.67 - 0.92)*	0.79 (0.67 - 0.92)*		0.81 (0.69 - 0.95)*
Comorbidities				
Dyslipidaemia (TC in mmol/L)				
≤6.21	2.53 (1.13 - 5.63)*		2.46 (1.10 - 5.54)*	2.18 (0.96 - 4.96)
>6.21	Reference		Reference	Reference
Hypertension (using either BP reading or medication use)				
No	1.64 (1.09 - 2.46)*		1.56 (1.04 - 2.35)*	1.50 (0.96 - 2.35)
Yes	Reference		Reference	Reference
HIV status				
Negative	Reference		Reference	Reference
Positive	1.75 (1.01 - 2.99)*		1.60 (0.93 - 2.77)	1.44 (0.80 - 2.57)
r^2		0.0286*	0.0335*	0.0486*

OR = odds ratio; CI = confidence interval; TC = total cholesterol; BP = blood pressure.
*Significant at $p<0.05$.

healthcare resources in SA public hospitals. Controlling cost of care and significant patient out-of-pocket costs should be of great concern among public and private managers and policymakers. The integrated chronic disease management (ICDM) model was introduced as a response to the dual burden of HIV/AIDS and NCDs in SA. However, the aim for which the ICDM model was initiated, i.e. to use the HIV programme as leverage for scaling up services for NCDs, is yet to be achieved.[52] The majority of patients experiencing multiple comorbidities visit healthcare facilities frequently. Navigation and co-ordination of care in these patients can be very difficult, and ultimately they are vulnerable to suboptimal quality of care. Our results highlight the necessity for health system integration of services and continuity of care.[53] The management of breast cancer patients also burdened with metabolic diseases, depression and HIV may result in further fragmentation of care, as cancer treatment is complex and multidisciplinary in nature. It is therefore essential for patient management to extend beyond the cancer domain and include the high burden of other communicable and non-communicable diseases. Co-ordination and integration of care for cancer and other comorbid conditions is fundamental to cost-effective healthcare delivery for patients and health systems alike, as previously identified.[54,55] Shared hospital appointments, community-based cancer care and collaboration with primary healthcare services may all be helpful in improving co-ordination of care for breast cancer patients and may improve survival outcomes in these patients.

Poor quality of life and survival among women with breast cancer may be exacerbated by multiple comorbidities.[56] Other factors that may adversely affect outcome include large out-of-pocket expenses such as transport costs and loss of wages and employment that may result in poor adherence to multiple treatments and adverse drug interactions that may affect cancer treatment efficacy and tolerance. Breast cancer patients with comorbidities are more likely than those without to experience adverse outcomes as a result of non-completion of radiation therapy and are less likely to initiate and complete chemotherapy.[57,58]

Study limitations

The limitations to this study include the fact that it was conducted in Soweto, which means that our findings may not be generalisable to the whole population of SA. Some bias is possible in our recruitment and exposure assessment, but our participation rate was high (91.3%) and women were not aware of our research hypothesis. Any misclassification is therefore probably random. Simultaneous testing of several hypotheses was carried out in our analysis to assess differences in sociodemographic factors and metabolic diseases, depression and HIV across stage at breast cancer presentation. This could reduce the significance value to very precise levels and increases the chances of a false-negative error (type 2 error);[59] however, our focus was more on the actual effect size than the level of significance, and our analysts was focused on a single primary endpoint. Despite these limitations, knowledge gained from this study on the prevalence of metabolic diseases, depression and HIV in women from Soweto with and without breast cancer and our finding on the importance of the household socioeconomic asset score in relation to stage at breast cancer diagnosis highlight the need for better community awareness and screening for metabolic diseases, depression, HIV and other chronic disease, for further research on treatment compliance in patients with breast cancer, treatment tolerance and efficacy and survival outcomes, and for integration of care for multi-comorbidities.

Conclusions

Many SA women with breast cancer from socioeconomically disadvantaged communities are burdened with metabolic diseases, depression and HIV. There is a need for research on treatment efficacy and tolerance, and co-ordination of care for easier navigation in SA's complex healthcare system.

Declaration. This publication was a requirement for OA's PhD degree.

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APPENDIX FIVE: PAPER TWO

The multimorbidity profile of South African women newly diagnosed with breast cancer

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Cancer Epidemiology

Multimorbidity in women with breast cancer may delay presentation, affect treatment decisions and outcomes. We described the multimorbidity profile of women with breast cancer, its determinants, associations with stage at diagnosis and treatments received. We collected self-reported data on five chronic conditions (hypertension, diabetes, cerebrovascular diseases, asthma/chronic obstructive pulmonary disease, tuberculosis), determined obesity using body mass index (BMI) and tested HIV status, in women newly diagnosed with breast cancer between January 2016 and April 2018 in five public hospitals in South Africa. We identified determinants of ≥2 of the seven above-mentioned conditions (defined as multimorbidity), multimorbidity itself with stage at diagnosis (advanced [III–IV] *vs.* early [0–II]) and multimorbidity with treatment modalities received. Among 2,281 women, 1,001 (44%) presented with multimorbidity. Obesity (52.8%), hypertension (41.3%), HIV (22.0%) and diabetes (13.7%) were the chronic conditions that occurred most frequently. Multimorbidity was more common

Additional Supporting Information may be found in the online version of this article.
Key words: breast cancer, chronic conditions, multimorbidity, stage at diagnosis and South African women
Abbreviations: BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HIV: human immunodeficiency virus; HSES: household socioeconomic status; IQR: interquartile range; KZN: KwaZulu-Natal; OR: odds ratio; SABCH: South African Breast Cancer and HIV Outcomes study; SD: standard deviation; SSA: sub-Saharan Africa
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with older age (OR = 1.02; 95% CI 1.01–1.03) and higher household socioeconomic status (HSES) (OR = 1.06; 95% CI 1.00–1.13). Multimorbidity was not associated with advanced-stage breast cancer at diagnosis, but for self-reported hypertension there was less likelihood of being diagnosed with advanced-stage disease in the adjusted model (OR 0.80; 95% CI 0.64–0.98). Multimorbidity was associated with first treatment received in those with early-stage disease, $p = 0.003$. The prevalence of multimorbidity is high among patients with breast cancer. Our findings suggest that multimorbidity had a significant impact on treatment received in those with early-stage disease. There is need to understand the impact of multimorbidity on breast cancer outcomes.

What's new?

Multimorbidity in women with breast cancer increases with age and may influence treatment decisions and outcome. The authors find that in South Africa 44%, of women newly diagnosed with breast cancer also suffered from other chronic conditions, most prevalently obesity, hypertension, HIV and diabetes. Asian and white women were less likely to present with multimorbidity when compared to black women, but multimorbidity was more common in women with higher socioeconomic status. The authors propose to evaluate the effect of multimorbidity on the South African health system and its impact on scarce health care resources.

Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, accounting for 6.6% of all cancer deaths.[1] In South Africa, it is also the most common cancer among women, accounting for 20.8% of all female cancers. Age-standardised annual incidence rates are 18 per 100,000 in black women, 49 in women of mixed ancestral, 57 in the Asian women and 88 in white South African women.[2]

The strongest determinant of breast cancer survival is stage at diagnosis[3–5] and over 50% of women in South Africa have advanced-stage disease at diagnosis.[6] A similar situation exists across sub-Saharan Africa (SSA), attributable in part to modifiable factors which include lack of early diagnosis strategies at the primary care level,[7] inadequate knowledge and awareness of breast cancer, inadequate access to care, socioeconomic factors,[5,6,8] as well as tumour biology.[9]

In addition to late diagnosis, another challenge to breast cancer control in South Africa may be the presence of chronic conditions at the time of breast cancer diagnosis. Multimorbidity has been defined as the presence of two or more chronic conditions in the same individual.[10] In South Africa, the effective treatment of infectious diseases, such as human immunodeficiency virus (HIV), has extended life expectancy, leading to increases in the prevalence of age-related chronic conditions. The number of people with two or more chronic conditions, such as cancer, hypertension, diabetes, obesity, HIV and tuberculosis is also growing rapidly and the burden is worse in poor communities.[11] Patients with multimorbidity are at higher risk for inadequate disease management due to independent management of each disease within overburdened health systems, significant out of pocket costs and poor adherence for the patients who are likely to have to take more medications, adverse drug reactions and potential drug–drug, drug–enzyme and drug–gene interactions affecting treatment efficacy.[10,12] Furthermore, patients with multimorbidity may be at additional risk of substandard care due to a high possibility of obtaining conflicting advice on care and treatment.[13,14] The burden of multimorbidity, its determinants and impact on healthcare is well established in high-income countries,[15,16] but there are few studies in low- and middle-income countries.[17,18] Many women with breast cancer have other chronic diseases at the time of their breast cancer diagnosis, and these conditions may affect the stage at diagnosis of breast cancer, treatment modality and prognosis.[19–22] It has been demonstrated that patients with cancer and other chronic diseases have reduced quality of life and survival.[22–24]

In our previous work describing the prevalence of multimorbid health conditions among 798 black South African women with and without breast cancer, although multimorbidity prevalence in cases was not higher than in the age-matched general population, the prevalence in cases were themselves high: 79.5% were overweight or obese, 59.2% were hypertensive, 46.6% had impaired fasting plasma glucose, 16.5% were HIV positive and 64.2% had ≥2 chronic conditions.[25] Other South African studies reported that the prevalence of multimorbidity increases with age[26] and is associated with higher household income.[17]

The prevalence and patterns of multimorbidity in a given cancer patient population have important implications for targeted patient-oriented prevention, diagnosis, treatment, disease control and improved outcome strategies.[27] The aim of our study is fourfold: (*i*) to describe the prevalence and patterns of multimorbidity in women newly diagnosed with breast cancer in five public hospitals in South Africa; (*ii*) to determine sociodemographic factors associated with different chronic conditions; (*iii*) to determine the factors associated with

multimorbidity; and (*iv*) to assess whether multimorbidity is associated with breast cancer stage at diagnosis and first treatment received.

Methods

We used data from a cohort of women enrolled in the ongoing South African Breast Cancer and HIV Outcomes study (SABCHO) collected between January 2016 and April 2018.[28] Five public hospital breast centres across Gauteng and KwaZulu-Natal provinces served as recruitment sites: Chris Hani Baragwanath Academic Hospital (Soweto Hospital, Johannesburg), Charlotte Maxeke Johannesburg Academic Hospital (Central Johannesburg Hospital), Addington Hospital and Inkosi Albert Luthuli Central Hospital in Durban (KwaZulu-Natal [KZN] Durban hospitals), Grey's Hospital, Pietermaritzburg (KZN Pietermaritzburg hospital) and Ngwelezane Hospital (KZN rural Hospital). The tertiary hospitals where all patients were enrolled in the study and received their treatments are located in city centres. The Central Johannesburg, KZN Durban hospitals and KZN Pietermaritzburg hospital all provide diagnostic services, surgery, chemotherapy, radiation therapy and endocrine treatments. The Soweto hospital, Johannesburg provides diagnostic, surgical and endocrine treatment services and patients have to travel to the Central Johannesburg hospital for chemotherapy and radiation treatments. The KZN rural hospital provides only diagnostic services, endocrine treatments and follow-up surveillance of patients following surgical, chemotherapy and radiation therapy treatments at KZN Durban hospitals located more than 200 km away. In the KwaZulu-Natal province, most patients undergo diagnostic procedures in the district referral hospitals and surgery is performed either at district hospitals or at the tertiary hospital centres. Some Patients have to bare out of pocket transport costs to access their treatment while others travel using hospital transport. The women differ in education and socioeconomic status with the more rural communities accessing the KZN Pietermaritzburg and KZN rural hospitals generally less educated and more impoverished than urban communities. The patient referral demographics for each participating hospital are shown in Table 1.

Our study was approved by the University of the Witwatersrand Human Research Ethics Committee (Approval Number: M150351, dated: May 6, 2015), and the Institutional Review Board of Columbia University (protocol number AAAQ1359, dated January 1, 2016). Our study was performed in accordance with the Declaration of Helsinki.

Recruitment of participants

Women who were newly diagnosed with invasive breast cancer were ≥18 years of age and had resided in South Africa for ≥5 years were eligible for enrolment in the SABCHO study. Patients who had a previous cancer diagnosis (excluding non-melanoma skin cancer or noninvasive cervical cancer), had previously received >1 month of radiotherapy or chemotherapy, had previously received any endocrine therapy, or were unable to give informed consent, were excluded.

Study procedures

Women were enrolled on the day of the diagnostic visit following voluntary written informed consent. Participants

Table 1. Characteristics of the hospital sites

	Soweto hospital, Johannesburg[1]	Central Johannesburg hospital[2]	KZN Durban hospitals[3]	KZN Pietermaritzburg hospital[4]	KZN rural hospital[5]
Location	Johannesburg (Gauteng province)	Johannesburg (Gauteng province)	Durban (KwaZulu-Natal Province)	Pietermaritz-burg (KwaZulu-Natal Province)	Empageni (KwaZulu-Natal Province)
Main population catchment area (N)	Soweto (3 million)	Johannesburg, East and Central (1.5 million)	Durban metropolitan (3.5 million)	Western KwaZulu-Natal and distant rural communities (3.5 million)	Uthungulu, Umkhanyakude, Zululand (3 million)
Surgery	Surgery performed at this hospital	Surgery performed at this hospital	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital
Oncology capacity (Chemotherapy and radiotherapy)	None. Patients are referred to Central Johannesburg hospital	Full oncology capacity	Full oncology capacity	Full oncology capacity	None. Patients are referred to KZN Durban hospitals.

[1]Chris Hani Baragwanath Academic Hospital, Soweto Johannesburg.
[2]Charlotte Maxeke Johannesburg Academic Hospital.
[3]Addington Hospital and Inkosi Albert Luthuli Central Hospital, Durban, KwaZulu-Natal.
[4]Grey's Hospital, Pietermaritzburg, KwaZulu-Natal.
[5]Ngwelezane Hospital, KwaZulu-Natal.

Table 2. Sociodemographic characteristics, prevalence of chronic conditions and stage at breast cancer diagnosis in women newly diagnosed with breast cancer in South Africa, by study-site

	Soweto, Johannesburg hospital (n = 795)	Central Johannesburg hospital (n = 511)	KZN Durban hospitals (n = 436)	KZN Pietermaritzburg hospital (n = 462)	KZN rural hospital (n = 77)	Total (n = 2,281)	p-value
Age in years, mean ± SD	55.1 ± 14.3	55.3 ± 14.2	58.1 ± 13.6	57.3 ± 14.7	55.6 ± 14.8	56.2 ± 14.3	0.002
Ethnicity							
Asian	7 (0.9%)	18 (3.5%)	172 (39.4%)	63 (13.6%)	1 (1.3%)	261 (11.4%)	<0.001
Black	734 (92.3%)	378 (74.0%)	203 (46.6%)	364 (78.8%)	75 (97.4%)	1,754 (76.9%)	
Mixed	42 (5.3%)	28 (5.5%)	17 (3.9%)	18 (3.9%)	0 (0.0%)	105 (4.6%)	
White	12 (1.5%)	87 (17.0%)	44 (10.1%)	17 (3.7%)	1 (1.3%)	161 (7.1%)	
Marital status							
Married/cohabiting	329 (41.5%)	212 (41.5%)	156 (36.1%)	140 (30.5%)	24 (31.2%)	861 (37.9%)	0.001
Unmarried	464 (58.5%)	299 (58.5%)	276 (63.9%)	319 (69.5%)	53 (68.8%)	1,411(62.1%)	
Highest level of education							
Completion of informal/primary education	192 (24.2%)	90 (17.8%)	127 (29.7%)	180 (39.2%)	38 (52.1%)	627 (27.7%)	<0.001
Completion of high school/any tertiary education	602 (75.8%)	416 (82.2%)	301 (70.3%)	279 (60.8%)	35 (47.9%)	1,633 (72.3%)	
Employment status							
Unemployed	583 (73.3%)	335 (65.6%)	342 (78.4%)	373 (80.7%)	63 (81.8%)	1,696 (74.4%)	<0.001
Employed	212 (26.7%)	176 (34.4%)	94 (21.6%)	89 (19.3%)	14 (18.2%)	585 (25.6%)	
Household socioeconomic status (score 0–6), median(IQR)[1]	4 (2–5)	4 (3–5)	4 (2–4)	2 (1–4)	1 (1–2)	2 (3–5)	<0.001
Residential distance from hospital site (km), median (IQR)	12.8 (6.8–27.2)	19.7 (8.7–34.7)	20.4 (16.0–56.1)	84.1 (8.3–155.6)	58.9 (29.1–144.2)	20.6 (8.9–42.9)	<0.001
Have you ever consumed alcohol?							
No	616 (77.5%)	407 (79.7%)	359 (82.3%)	382 (82.7%)	68 (88.3%)	1,832 (80.3%)	0.039
Yes	179 (22.5%)	104 (20.3%)	77 (17.7%)	80 (17.3%)	9 (11.7%)	449 (19.7%)	
Have you ever smoked?							
No	718 (90.3%)	427 (83.6%)	367 (84.2%)	413 (89.4%)	74 (96.1%)	1,999 (87.6%)	<0.001[3]
Yes	77 (9.7%)	84 (16.4%)	69 (15.8%)	49 (10.6%)	3 (3.9%)	282 (12.4%)	
Stage at diagnosis							
Early stage (0–II)	402 (50.6%)	196 (38.4%)	172 (40.0%)	181 (39.2%)	14 (18.4%)	965 (43.9%)	<0.001
Advanced stage (III and IV)	393 (49.4%)	315 (61.6%)	258 (60.0%)	281 (60.8%)	62 (81.6%)	1,309 (56.1%)	
Receptor subtype							
Luminal A	111 (14.1%)	123 (24.6%)	152 (35.0%)	71 (15.4%)	19 (24.7%)	476 (21.1%)	<0.001
Luminal B	467 (59.5%)	232 (46.4%)	172 (39.7%)	255 (55.3%)	30 (38.9%)	1,156 (51.2%)	
HER2 enriched	94 (12.0%)	69 (13.8%)	50 (11.5%)	58 (12.6%)	14 (18.2%)	285 (12.6%)	

(Continues)

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Table 2. Sociodemographic characteristics, prevalence of chronic conditions and stage at breast cancer diagnosis in women newly diagnosed with breast cancer in South Africa, by study-site (Continued)

	Soweto, Johannesburg hospital (n = 795)	Central Johannesburg hospital (n = 511)	KZN Durban hospitals (n = 436)	KZN Pietermaritzburg hospital (n = 462)	KZN rural hospital (n = 77)	Total (n = 2,281)	p-value
Triple negative	113 (14.4%)	76 (15.2%)	60 (13.8%)	77 (16.7%)	14 (18.2%)	340 (15.1%)	
Chronic conditions considered							
Nutritional status (BMI)							
Underweight[2] and normal (≤24.9 kg/m^2)	160 (21.8%)	98 (20.6%)	96 (23.4%)	109 (24.4%)	19 (24.7%)	482 (22.5%)	0.094
Overweight (25–29.9 kg/m^2)	160 (21.8%)	133 (28.0%)	117 (28.5%)	103 (23.1%)	17 (22.1%)	530 (24.7%)	
Obese (≥30.0 kg/m^2)	415 (56.4%)	244 (51.4%)	197 (48.1%)	234 (52.5%)	41 (53.2%)	1,131 (52.8%)	
Self-reported hypertension							
No	487 (61.3%)	322 (63.0%)	224 (51.4%)	254 (55.0%)	51 (66.2%)	1,338 (58.7%)	<0.001
Yes	308 (38.7%)	189 (37.0%)	212 (48.6%)	208 (45.0%)	26 (33.8%)	943 (41.3%)	
HIV status							
Negative	564 (74.7%)	401 (82.5%)	342 (85.3%)	343 (75.4%)	45 (59.2%)	1,695 (78.0%)	<0.001
Positive	191 (25.3%)	85 (17.5%)	59 (14.7%)	112 (24.6%)	31 (40.8%)	478 (22.0%)	
Self-reported diabetes							
No	720 (90.6%)	465 (91.0%)	324 (74.3%)	388 (84.0%)	71 (92.2%)	1,968 (86.3%)	<0.001
Yes	75 (9.4%)	46 (9.0%)	112 (25.7%)	74 (16.0%)	6 (7.8%)	313 (13.7%)	
Self-reported prior tuberculosis							
No	742 (93.3%)	491 (96.1%)	394 (90.4%)	417 (90.3%)	70 (90.9%)	2,114 (92.7%)	0.002
Yes	53 (6.7%)	20 (3.9%)	42 (9.6%)	45 (9.7%)	7 (9.1%)	167 (7.3%)	
Self-reported asthma/COPD							
No	763 (96.0%)	482 (94.3%)	399 (91.5%)	444 (96.1%)	71 (92.2%)	2,159 (94.7%)	0.007
Yes	32 (4.0%)	29 (5.7%)	37 (8.5%)	18 (3.9%)	6 (7.8%)	122 (5.3%)	
Self-reported cerebrovascular disease							
No	773 (97.2%)	503 (98.4%)	412 (94.5%)	453 (98.1%)	74 (96.1%)	2,215 (97.1%)	0.005[3]
Yes	22 (2.8%)	8 (1.6%)	24 (5.5%)	9 (1.9%)	3 (3.9%)	66 (2.9%)	

Missing values for covariates were as follows: marital status (n = 9), the highest level of education (n = 21), BMI (n = 138), HIV status unknown (n = 108) and stage at diagnosis (n = 7).
[1]HSES: Household socioeconomic status (possessions) score determined from homeownership = 1, motor vehicle = 1, microwave = 1, washing machine = 1, flush toilet = 1, indoor running water = 1; Denominator = 6 (1 for Yes, 0 for No).
[2]54 women were underweight.
[3]p-value (Fisher's exact test).
Abbreviation: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; km, kilometres; KZN, KwaZulu-Natal; SD, standard deviation.

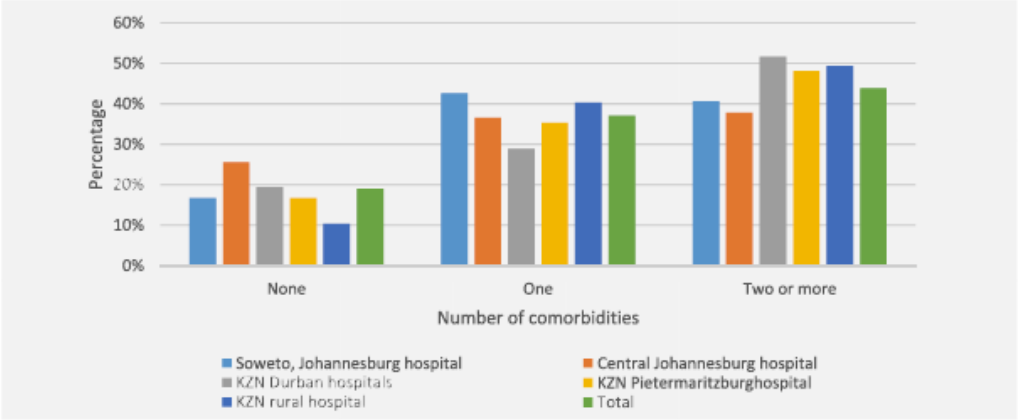


Figure 1. Percentage of women newly diagnosed with breast cancer from each hospital site in South Africa, with none, one, two or more of obesity, self-reported hypertension, self-reported diabetes, self-reported cerebrovascular disease, self-reported asthma/COPD, HIV and self-reported prior tuberculosis. [Color figure can be viewed at wileyonlinelibrary.com]

consented to HIV testing. Those who tested positive were referred for ART initiation prior to commencement of cancer treatment. Those who refused HIV testing were still included in the study and HIV status was recorded as unknown.

Sociodemographic and anthropometric measures

Trained study staff collected detailed sociodemographic information (age, self-identified ethnicity, marital status, employment status, highest level of education completed, residential address); reproductive history (number of full-term pregnancies, age at first full-term pregnancy, use of oral and injectable contraceptives, use of hormone replacement therapy) and behavioural factors (alcohol consumption, smoking). Tumour American Joint Committee on Cancer (7th edition) stage, grade, receptor status and first treatment received data were extracted from medical records.[29] Participants were grouped by stage at diagnosis as early (I–II) or advanced (III–IV).

Household socioeconomic scores were determined using self-reported homeownership, car ownership, possession of a washing machine or microwave, presence of a flush toilet inside the home and presence of indoor running water. We assigned a score of 1 for each of these items and the scores were added out of a total of six. We documented the residential address of each participant at enrolment and computed the shortest straight-line distance to the enrolling hospital in kilometres (km).

We assessed seven chronic conditions: obesity, hypertension, diabetes, cerebrovascular disease, asthma/COPD, HIV infection and tuberculosis. HIV status was tested using the enzyme-linked immunosorbent assay through the National Health Laboratory Services. Bodyweight and height measurements were measured at enrolment, and obesity was defined as a body mass index (BMI) ≥30.0 kg/m^2. Patients were asked if they were ever treated for tuberculosis and whether they had ever been diagnosed and treated for the other four conditions (hypertension, diabetes, cerebrovascular disease and asthma/COPD). We defined multimorbidity as having ≥2 of these seven chronic conditions.

Statistical analysis

Determinants of each chronic condition and multimorbidity (≥2 chronic conditions) were examined in a multisite-pooled analysis using bivariate and multivariate logistic regression. Odds ratios (OR) for multimorbidity were examined in three models by adding potentially associated factors in a stepwise fashion. In Model 1, we examined all sociodemographic factors (age, ethnicity, marital status, the highest level of education, employment status and household socioeconomic status). Model 2 included sociodemographic and geographical factors (hospital site and residential distance from the hospital) and Model 3 included sociodemographic, geographical factors and behavioural factors (alcohol intake and smoking). Finally, multivariable logistic regression models were used to examine whether chronic conditions and multimorbidity were associated with advanced-stage breast cancer (Stage III–IV). We included in the multivariate models variables for which p values were <0.1 in bivariate analysis with advanced-stage breast cancer. ORs were examined in two models (Model A [unadjusted] and Model B (which was adjusted for age, ethnic, highest level of education and hospital site). We further examined the associations between multimorbidity and first treatment received (primary surgery, neoadjuvant chemotherapy or neoadjuvant endocrine therapy) by their stage at diagnosis using Pearson's Chi-squared test. Analysis was performed using Stata version 15 (StataCorp Ltd, College Station, TX).

Data availability

Data for our study contain confidential patient information. Data supporting the results reported in this article may be requested from the corresponding author.

Table 3. Pooled multivariate logistic regression model of sociodemographic characteristics and association with chronic conditions in women newly diagnosed with breast cancer in South Africa

Sociodemographic characteristics	Obesity (BMI ≥ 30.0 kg/m2)	Hypertension	Diabetes	Cerebrovascular disease	Asthma/COPD	HIV positive	Tuberculosis
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age in years	1.00 (0.99–1.00)	1.08 (1.07–1.09) [1]	1.04 (1.03–1.05)[1]	1.04 (1.02–1.06)[1]	0.99 (0.98–1.01)	0.94 (0.93–0.95)[1]	0.97 (0.95–0.98)[1]
Ethnic							
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Asian	0.8 (0.6–1.3)	3.3 (2.1–5.3)[1]	9.4 (4.5–19.6) [1]	1.1 (0.4–3.1)	1.0 (0.5–2.1)	0.3 (0.1–3.6)	0.8 (0.2–3.0)
Black	2.1 (1.4–2.9) [1]	2.4 (1.6–3.5) [1]	2.8 (1.4–5.8) [1]	0.6 (0.2–1.6)	0.5 (0.3–0.9) [2]	16.4 (4.0–67.2)[1]	2.5 (0.9–6.9)
Mixed	1.5 (0.9–2.6)	2.8 (1.6–5.0) [1]	4.4 (1.9–10.3) [1]	0.5 (0.1–2.8)	0.7 (0.3–1.8)	5.2 (1.1–25.7)[2]	2.0 (0.5–7.2)
Highest level of education							
Primary education and below	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Secondary and above	1.2 (0.9–1.5)	1.0 (0.8–1.2)	0.9 (0.6–1.2)	0.8 (0.4–1.4)	0.8 (0.4–1.2)	1.2 (0.9–1.6)	0.7 (0.5–1.1)
Employment status							
Unemployed	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Employed	1.2 (0.9–1.4)	0.8 (0.6–1.0)	0.7 (0.5–0.9)[2]	0.7 (0.3–1.6)	0.7 (0.4–1.2)	1.2 (0.9–1.5)	0.8 (0.6–1.2)
Household socioeconomic status (score 0–6)	1.2 (1.1–1.2) [1]	1.1 (1.0–1.1)[2]	1.1 (1.0–1.2) [2]	0.9 (0.8–1.1)	1.2 (1.0–1.3) [2]	0.8 (0.8–0.9) [1]	0.9 (0.8–1.0)
R2	0.02	0.19	0.11	0.06	0.02	0.22	0.04

HSES, Household socioeconomic status (possessions) score determined from (homeownership = 1, motor vehicle = 1, microwave = 1, washing machine = 1, flush toilet = 1, indoor running water = 1) Denominator = 6 (1 for Yes, 0 for No).
[1]Significant at $p < 0.001$.
[2]Significant at $p < 0.05$.
Abbreviations: 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; HSES, Household socioeconomic status.

Table 4. Pooled associations between sociodemographic, geographical and behavioural factors with chronic conditions (≥2 (multimorbidity) *vs.* <2) in women newly diagnosed with breast cancer

Characteristics	<2 chronic conditions (n = 1,280)	≥2 chronic conditions (multimorbidity) (n = 1,001)	Bivariate analysis OR (95% CI)	p-value
Age in years, mean ± SD	54.4 ± 15.0	58.4 ± 13.0	1.02 (1.01–1.03)	<0.001[1]
Ethnicity (%)				
Black	976 (76.2%)	778 (77.7%)	1.00 (Referent)	
Asian	130 (10.2%)	131 (13.1%)	1.26 (0.97–1.64)	<0.001[1]
Mixed	56 (4.4%)	49 (4.9%)	1.10 (0.74–1.63)	
White	118 (9.2%)	43 (4.3%)	0.46 (0.32–0.66)	
Marital status (%)				
Married/co-habiting	513 (40.2%)	348 (34.9%)	1.00 (Ref)	0.010[1]
Unmarried	763 (59.8%)	648 (65.1%)	1.25 (1.05–1.49)	
Highest level of education (%)				
Primary education and below	324 (24.4%)	303 (30.7%)	1.00 (Referent)	0.006[1]
Secondary education and above	949 (74.6%)	684 (69.3%)	0.77 (0.64–0.93)	
Employment status (%)				
Unemployed	921 (71.9%)	775 (77.4%)	1.00 (Referent)	0.003[1]
Employed	359 (28.1%)	226 (22.6%)	0.75 (0.62–0.91)	
Household socioeconomic status (score 0–6), median (IQR)	3 (2–5)	4 (2–5)	1.02 (0.97–1.07)	0.488
Hospital site (%)				
Soweto, Johannesburg	472 (36.9%)	323 (32.3%)	1.00 (Referent)	<0.001[1]
Central Johannesburg	318 (24.8%)	193 (19.3%)	0.89 (0.71–1.11)	
KZN Durban	211 (16.5%)	225 (22.5%)	1.56 (1.23–1.97)	
KZN Pietermaritzburg	240 (18.8%)	222 (22.2%)	1.35 (1.07–1.70)	
KZN rural	39 (3.1%)	38 (3.8%)	1.42 (0.89–2.28)	
Residential distance from hospital site (km), median (IQR)	19.9 (8.7–39.5)	21.8 (9.1–48.1)	1.00 (1.00–1.01)	0.033[1]
Have you ever consumed alcohol? (%)				
No	1,004 (78.4%)	828 (82.7%)	1.00 (Ref)	0.011[1]
Yes	276 (21.6%)	173 (17.3%)	0.76 (0.62–0.94)	
Have you ever smoked? (%)				0.044[1]
No	1,106 (86.4%)	893 (89.2%)	1.00 (Ref)	
Yes	174 (13.6%)	108 (10.8%)	0.77 (0.60–0.99)	

OR, odds ratio = odds of reporting ≥2 chronic conditions compared to <2 chronic conditions. HSES: Household socioeconomic status (possessions) score determined from (homeownership = 1, motor vehicle = 1, microwave = 1, washing machine = 1, flush toilet = 1, indoor running water = 1) Denominator = 6 (1 for Yes, 0 for No); KZN, KwaZulu-Natal; SD, standard deviation; IQR, interquartile range; km, kilometres.
[1]Variables significant at $p < 0.05$.

Results

A total of 2,281 women were included in the study: 795 (34.9%) from Soweto, Johannesburg hospital, 511 (22.4%) from Central Johannesburg hospital, 435 (19.1%) from KZN Durban hospitals, 462 (20.2%) from KZN Pietermaritzburg hospital and 77 (3.4%) from KZN rural hospital (Table 2). The mean age at diagnosis was 56.2 ± 14.3 years; women from the two Johannesburg hospitals compared to the KZN cities hospitals (Durban and Pietermaritzburg) were significantly younger and more likely to be married. In the combined sample, the majority (76.9%) of women were black Africans while KZN Durban hospitals had the highest

Table 5. Pooled multiple logistic regression model of sociodemographic, geographical and behavioural factors associated with ≥2 chronic conditions (multimorbidity) in women newly diagnosed with breast cancer

Characteristics	Model 1 (Sociodemographic factors) OR (95% CI)	Model 2 (Sociodemographic and geographical factors) OR (95% CI)	Model 3 (Sociodemographic, geographical and behavioural factors) OR (95% CI)
Age in years	1.02 (1.01–1.03)[1]	1.02 (1.01–1.03)[1]	1.02 (1.01–1.03[1]
Ethnicity			
Black	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Asian	1.05 (0.79–1.38)	0.70 (0.50–0.97)[2]	0.70 (0.50–0.97)[2]
Mixed	0.99 (0.66–1.50)	0.93 (0.61–1.40)	0.97 (0.63–1.49)
White	0.39 (0.27–0.58)[1]	0.34 (0.23–0.51)[1]	0.36 (0.24–0.54)[1]
Marital status			
Married/cohabiting	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Unmarried	1.09 (0.90–1.30)	1.06 (0.89–1.28)	1.07 (0.89–1.29)
Highest level of education			
Primary education and below	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Secondary education and above	1.04 (0.84–1.29)	1.08 (0.87–1.35)	1.08 (0.87–1.35)
Employment status			
Unemployed	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Employed	0.93 (0.75–1.14)	0.93 (0.75–1.15)	0.93 (0.75–1.15)
Household socioeconomic status (score 0–6)	1.01 (0.96–1.07)	1.06 (0.99–1.13)	1.06 (1.00–1.13)[1]
Hospital site			
Soweto, Johannesburg		1.00 (Ref)	1.00 (Ref)
Central Johannesburg		1.03 (0.81–1.31)	1.02 (0.80–1.30)
KZN Durban		1.90 (1.43–2.53)[1]	1.89 (1.42–2.51)[1]
KZN Pietermaritzburg		1.49 (1.13–1.98)[2]	1.49 (1.12–1.97)[2]
KZN rural		1.57 (0.94–2.63)	1.54 (0.92–2.57)
Residential distance from hospital site (km)		1.00 (0.99–1.00)	1.00 (0.99–1.00)
Have you ever consumed alcohol?			
No			1.00 (Ref)
Yes			0.85 (0.67–1.07)
Have you ever smoked?			
No			1.00 (Ref)
Yes			0.96 (0.71–1.29)
R^2	0.028	0.031	0.033

OR, odds ratio = odds of reporting ≥2 chronic conditions compared to <2 chronic conditions.
[1]Significant at $p < 0.001$.
[2]Significant at $p < 0.05$.

percentage of Asians (39.4%) compared to other sites, and central Johannesburg hospital had the highest number of white women (17.0%).

In the combined sample, most of the women had at least a high school education (72.3%), but there was a significant difference between the sites as 52.1% of women attending KZN rural hospital had only completed primary education. Overall >50% of women were unemployed; women from the Johannesburg hospitals and KZN Durban hospitals had higher HSES than women from KZN Pietermaritzburg and KZN rural hospitals. Participants from KZN Pietermaritzburg hospital had the furthest distance to travel and women from Soweto, Johannesburg hospital travelled the shortest distance (84.1 *vs.* 12.8 km; Table 2). There was a significant difference between the sites for smoking and alcohol consumption, with the KZN rural hospital reporting the least for both compared to the other sites. Overall, 56.1% of the women presented with advanced-stage breast cancer. Soweto, Johannesburg hospital was the only site where more

Table 6. Pooled bivariate analyses of the association between chronic conditions and advanced-stage disease among women newly diagnosed with breast cancer

Characteristics	Bivariate analysis OR (95% CI)	*p*-value
Obese	0.84 (0.70–0.99)	0.041[1]
Self-reported hypertension	0.74 (0.62–0.87)	<0.001[1]
Self-reported diabetes	0.80 (0.63–1.01)	0.064
Self-reported cerebrovascular disease	1.00 (0.61–1.64)	0.998
Self-reported asthma/COPD	0.82 (0.57–1.18)	0.286
HIV positive	1.52 (1.23–1.87)	<0.001[1]
Self-reported prior tuberculosis	1.49 (1.07–2.08)	0.019[1]
Multimorbidity	0.88 (0.68–1.10)	0.138

[1]Significant at $p < 0.05$.
Abbreviation: COPD, Chronic obstructive pulmonary disease.

than half (50.6%) presented at an early (Stage I–II). Most (72.3%) of the women had oestrogen and progesterone receptor-positive (Luminal A and B) breast cancer (Table 2).

Prevalence of chronic conditions

At enrolment, 19.0% of the women reported no chronic conditions (hypertension, diabetes, cerebrovascular diseases, asthma/chronic obstructive pulmonary disease, tuberculosis, HIV and obesity) ranging from 10.4% in KZN rural hospital to 25.6% at Central Johannesburg hospital (Fig. 1 and Supporting Information Table S1). In the combined sample, 52.8% of women were obese. The second most common chronic condition was hypertension (41%), which ranged from 34% at the KZN rural hospital to 48.6% at KZN Durban hospitals. HIV was the third most prevalent chronic condition (22.0%) but with considerable variation, highest (40.8%) at the KZN rural hospital and lowest at the KZN Durban hospitals (14.7%). Diabetes ranked as the fourth most prevalent chronic condition affecting 14% of women, with <10% at the two Johannesburg hospitals. Finally ranking fifth, sixth and seventh were tuberculosis, COPD/asthma and cerebrovascular disease, respectively, with each present in <10% of breast cancer patients at each site. Overall, 43.9% of breast cancer patients met our definition of multimorbidity (presence of ≥2 additional chronic conditions) and KZN Durban hospitals had the highest proportion (51.6%; Fig. 1 and Supporting Information Table S1).

Bivariate and multivariable logistic regression models of associations between sociodemographic variables and each chronic condition are presented in Supporting Information Table S3 and Table 3, respectively. In the multivariate analysis, with every 1-year increase in age, there was an 8% increase in the odds of hypertension, 4% increase in the odds of having diabetes, 4% increase in the odds of cerebrovascular disease, 6% reduced odds of HIV and 3% reduced odds of tuberculosis. When compared to the black women, white women had reduced odds of all the chronic conditions except asthma and the Asian women had increased odds of hypertension, diabetes and asthma/COPD. Of the three measures of socioeconomic status, HSES was most frequently associated with the presence of a chronic condition. Women with higher HSES were more likely to be obese, hypertensive, diabetic, report asthma/COPD and were less likely to be living with HIV (Table 3). The variance in the different chronic conditions that could be explained by age, ethnic and socioeconomic status ranged from 2% for obesity to 22% for HIV infection.

In Table 4, bivariate logistic regression showed positive associations between multimorbidity and age, marital status, hospital sites and negative associations with ethnicity, the highest level of education, employment status, alcohol consumption and smoking. These significant associations at the bivariate level were further explored in multivariate logistic regressions in three models (Table 5). In Model 1 (sociodemographic variables only), age contributed independently to an increased odds of multimorbidity and being white was associated with a decreased odds of multimorbidity. In Model 2 (sociodemographic and geographical factors) age and white ethnicity remained significant and being Asian was associated with a lower odds of multimorbidity. Women from KZN Durban hospitals (OR = 1.90, 95% CI 1.43–2.53) and KZN Pietermaritzburg hospital (OR 1.49, 95% CI 1.13–1.98) had an increased odds of having multimorbidity and the factors in Model 2 were able to explain 3.1% of the variance in multimorbidity. In Model 3 (sociodemographic, geographical and behavioural variables), age, white and Asian ethnicity, enrolment at KZN Durban hospitals and KZN Pietermaritzburg hospital remained significant, although higher HSES was now associated with an increased odds of multimorbidity (OR = 1.06, 95% CI 1.00–1.13), none of the behavioural factors were significant in the model (Table 5).

Table 7. Pooled multivariate logistic regression models of chronic conditions associated with advanced-stage disease (Stages III–IV) in women newly diagnosed with breast cancer

Characteristics	Model A OR (95% CI)	*p*-value	Model B OR (95% CI)	*p*-value
Obese	0.92 (0.77–1.09)	0.340	0.85 (0.71–1.03)	0.098
Self-reported hypertension	0.77 (0.64–0.92)	0.005[1]	0.80 (0.64–0.98)	0.036[1]
HIV positive	1.36 (1.09–1.71)	0.008[1]	1.07 (0.83–1.38)	0.582
Self-reported prior tuberculosis	1.32 (0.93–1.88)	0.123	1.22 (0.84–1.78)	0.286
R^2	0.013		0.040	

[1]Significant at $p < 0.05$, Model A (unadjusted), Model B (adjusted for age on presentation, ethnic, highest level of education and hospital site).

Table 8. Association between multimorbidity and first treatment received by stage at diagnosis in women newly diagnosed with breast cancer

	Stages 0–II (early stage)				Stages III and IV (advanced stage)			
Multimorbidity	Primary surgery (n = 662 (%))	Neoadjuvant chemotherapy (n = 141 (%))	Neoadjuvant endocrine therapy (n = 131 (%))	p-value	Primary surgery (n = 125 (%))	Neoadjuvant chemotherapy (n = 881 (%))	Neoadjuvant endocrine therapy (n = 206 (%))	p-value
No (<2 chronic conditions)	372 (73.7)	80 (15.8)	53 (10.5)		67 (9.6)	520 (74.7)	109 (15.7)	0.184
Yes (≥2 chronic conditions)	290 (67.6)	61 (14.2)	78 (18.2)		58 (11.2)	361 (70.0)	97 (18.8)	
Total[1]	662 (70.9)	141 (15.1)	131 (14.0)	0.003	125 (10.3)	881 (72.7)	206 (17.0)	

Row percentages are shown.
[1]Total for Stages 0–II (early stage) = 934, the total for Stages III and IV (advanced stage) = 1,212. Some 135 women had missing treatment information.

Bivariate and multivariate logistic regression models of chronic conditions and multimorbidity associated with advanced-stage breast cancer disease at diagnosis are presented in Tables 6 and 7, respectively. In the bivariate analysis (Table 6), obesity and hypertension were negatively associated with advanced-stage breast cancer at diagnosis. Women who were HIV positive and women who reported prior tuberculosis had positive associations with advanced-stage breast cancer at diagnosis. There was no significant association between multimorbidity and advanced-stage breast cancer at diagnosis (OR = 0.88, 95% CI 0.74–1.04; Table 6). The significant variables at $p < 0.1$ were further explored in the multivariate model (Table 7). In Model A, women who reported having hypertension had lower odds of advanced-stage breast cancer and women who were HIV positive had higher odds of advanced-stage breast cancer at diagnosis than those women without the disease. In Model B, adjusting for age, ethnic, highest level of education and hospital site, self-reported hypertension (OR = 0.80, 95% CI 0.64–0.98) was the only chronic condition associated with advanced-stage breast cancer disease (Table 7).

In women with early-stage (Stages 0–II) breast cancer, there was a significantly higher proportion of women with multimorbidity who received neoadjuvant endocrine therapy (18.2%) compared to those without multimorbidity who received neoadjuvant endocrine treatment (10.5%, p = 0.003; Table 8).

Discussion

In our study, we found that among women newly diagnosed with breast cancer from five public hospitals across South Africa, more than 80% reported at least one chronic condition and 43.9% had two or more chronic conditions. Older women, higher HSES and women enrolled at the KZN Durban and Pietermaritzburg hospitals, had higher odds of multimorbidity, while the Asian and white women were less likely to present with multimorbidity when compared to black women. Hypertensive women were less likely to have advanced-stage breast cancer at diagnosis, while multimorbidity was not associated with advanced-stage breast cancer at diagnosis.

The burden of multimorbidity in our cohort was high with 43.9% of the whole sample reporting two or more chronic conditions. Multimorbidity is of increasing concern in South Africa and this high prevalence of noncommunicable and communicable multimorbidity has significant implications for the mode of health care delivery and the health system. Severe chronic conditions narrow treatment choices and are associated with poor quality of life and survival, especially in postmenopausal women.[24,30] In South Africa chronic disease management is meant to be delivered using the integrated chronic disease management approach;[31] however, this is yet to be achieved as people with multimorbidity receive fragmented and inefficient health care delivery.[32,33] There is a need for an effective integrated and comprehensive array of health services spanning from primary to tertiary levels.

The most common chronic condition reported in this sample of women with breast cancer was obesity (52.8%), which was much higher than report from the recent South African national survey with obesity prevalence of 41.7% in adult women (ranging from 30.6% among the white women to 49.2% among the Asian women).[34]

Our results indicate that multimorbidity in women with breast cancer is associated with sociodemographic characteristics (age, ethnic and HSES) and hospital site where they are seeking health care. It is well accepted that multimorbidity is associated with increasing age, due to age-related chronic health conditions.[35] The Asians in South Africa have been reported to have a high burden of chronic conditions,[17] which is in keeping with our findings for individual chronic conditions in this population group. This is primarily the result of high prevalence of hypertension and diabetes in the Asian group; HIV prevalence was low. A study conducted among Asian South Africans living in Durban also reported a high burden of hypertension (47.5%), diabetes (20.1%) and obesity (32.4%).[36] Despite this high finding of the prevalence of individual chronic conditions in Asian women in our cohort, they were still less likely to present with multimorbidity (OR = 0.70, 95% CI 0.50–0.97) compared to the black African women. This may be due to the higher prevalence of obesity in the black women,[37] and equally high burden of hypertension. South Africa has the highest

burden of hypertension in people >50 years of age in SSA,[27,38] HIV-infection and tuberculosis were almost exclusive to the black African women in our cohort. This double burden of communicable and noncommunicable diseases in women with breast cancer is of concern and can ultimately impact on treatment, quality of life and survival.

We found that women with higher HSES were more likely to present with multimorbidity, independent of ethnicity. There is a dearth of knowledge on the association between socioeconomic status and multimorbidity in South Africa; however, our finding is in contrast to other South African studies that reported that poorer women and those socioeconomically deprived bear a greater burden of multimorbidity.[39,40] Women socioeconomically deprived had 50% increased odds of having multimorbidity compared to those not socioeconomically deprived.[40] This may be due to different definitions and mode of measurement of socioeconomic status in the studies.

Patients also experience varying delays within the referral network, as reflected in significant differences in the proportions of advanced stage (Stages III and IV) at presentation of patients at the different sites (ranging from 50% [lowest] at the Soweto, Johannesburg hospital and 73% [highest] at the KZN Pietermaritzburg and KZN rural hospital). These challenges are compounded for patients with high multimorbidity who have to visit other clinics for their chronic medications apart for their breast cancer treatments.

Some of our findings on the association between individual chronic conditions, multimorbidity and stage of breast cancer diagnosis are consistent with previous work in South Africa and SSA. Although obesity was associated with a reduced risk of being diagnosed with advanced-stage breast cancer in the bivariate analysis, when included in the multivariable analysis with other chronic conditions this was no longer significant. This is in keeping with studies from Africa and high-income countries[41–43] where obesity did not emerge as being associated with advanced-stage disease at breast cancer diagnosis. Obesity is a risk factor for luminal type breast cancers, which tend to be slower growing and less likely to be diagnosed at advanced stage.[44,45] Obesity is not a comorbidity that has been shown to increase contact with health services in our setting; we therefore cannot imply its protective effect from regular contact with the health facilities.

Women who reported being hypertensive were less likely to have advanced stage of breast cancer at diagnosis, before and after adjusting for potential covariates. This may imply regular contact with the health systems that may result in patient breast cancer education by the health services or a surveillance effect leading to earlier stage at diagnosis.[19] This may also be related to tumour biology because breast cancer in younger women (with less hypertension prevalence) tend to be the more aggressive subtypes.[46–48] HIV infection, prior tuberculosis, diabetes, asthma/COPD, cerebrovascular disease and multimorbidity was not associated with advanced-stage breast cancer at diagnosis.

Our findings show that multimorbidity was significantly associated with first treatment received in women with early-stage breast cancer. Among women with multimorbidity with early-stage breast cancer, a large proportion was placed on less aggressive neoadjuvant endocrine therapy. Older women with multimorbidity are more likely to have poor Eastern Cooperative Oncology Group (ECOG) performance status and not able to withstand the stress of surgery or chemotherapy and are therefore not likely to be placed on standard more aggressive treatments.[49]

Some limitations need to be noted. As the data on the various chronic conditions was self-reported the prevalence of these conditions may be higher than reported. The list of chronic conditions was not comprehensive, and therefore certain health conditions may not have been detected and may result in potential confounding. We had to rely on patient self-reports of their diagnosed comorbidities and that they were on treatment. In South Africa, hospital records are not electronically centralised and patient records from different clinics are not readily accessible for diagnostic and treatment details. Another limitation was that in the interview we did not specify if the patient had a current history of tuberculosis or previous history, while not ideal, it was not a common prior condition so did not affect overall results, as seen in Supporting Information Table S2 where the tuberculosis rows and columns are all relatively small. Despite these limitations, the strength of this study includes the uniquely large sample of South African women with breast cancer and inclusion of hospitals in different geographical regions. We described the burden and pattern of multimorbidity, and the difference in chronic conditions between different hospital settings and have also measured factors associated with individual chronic conditions as well as multimorbidity. Furthermore, our study provides data on the association between these chronic conditions and multimorbidity, and advanced-stage breast cancer at diagnosis, in South Africa women.

Our findings give important insight into demographic and socioeconomic factors associated with multimorbidity in women with breast cancer in South Africa. There is need for policymakers to evaluate the effect of multimorbidity on the health system and its impact on the limited health care resources.

In conclusion, we have demonstrated a high prevalence of multimorbidity in women newly diagnosed with breast cancer from different public hospital settings in South Africa, with many of these chronic conditions being associated with sociodemographic factors. Women that were hypertensive were less likely to be diagnosed with advanced-stage breast cancer. Our findings contribute to the literature in understanding sociodemographic factors associated with multimorbidity in South Africa. There is need to understand how multimorbidity may impact breast cancer outcomes.

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Informed consent

All participants provided written informed consent.

Disclaimer

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APPENDIX SIX: PAPER THREE

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CANCER EPIDEMIOLOGY

Preexisting morbidity profile of women newly diagnosed with breast cancer in sub-Saharan Africa: African Breast Cancer—Disparities in Outcomes study

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Abstract

The presence of preexisting morbidities poses a challenge to cancer patient care. There is little information on the profile and prevalence of multi-morbidities in breast cancer patients across middle income countries (MIC) to lower income countries (LIC) in sub-Saharan Africa (SSA). The African Breast Cancer–Disparities in Outcomes (ABC-DO) breast cancer cohort spans upper MICs South Africa and Namibia, lower MICs Zambia and Nigeria and LIC Uganda. At cancer diagnosis, seven morbidities were assessed: obesity, hypertension, diabetes, asthma/chronic obstructive pulmonary disease, heart disease, tuberculosis and HIV. Logistic regression models were used to assess determinants of morbidities and the influence of morbidities on advanced stage (stage III/IV) breast cancer diagnosis. Among 2189 women, morbidity

Abbreviations: ABC-DO, Africa Breast Cancer—Disparities in Outcomes; BMI, body mass index; CD, communicable diseases; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ELISA, enzyme-linked immunosorbent assay; HICs, high-income countries; HIV, human immunodeficiency virus; LMICs, low and middle income countries; NCDs, non-communicable diseases; OR, odds ratio; SEP, socioeconomic position; SSA, Sub-Saharan Africa; TNM, tumour, node, metastasis classification.

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