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FACULTY OF HEALTH SCIENCES

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BREAST CANCER SURVIVAL TO 5 YEARS AMONG YOUNG (<40 YEARS) WOMEN IN THE SUB-SAHARAN AFRICAN BREAST CANCER-DISPARITIES IN OUTCOME (ABC-DO) COHORT STUDY

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A RESEARCH REPORT SUBMITTED TO THE FACULTY OF HEALTH SCIENCES, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN EPIDEMIOLOGY (EPIDEMIOLOGY AND BIOSTATISTICS).

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BREAST CANCER SURVIVAL TO 5 YEARS AMONG YOUNG (<40 YEARS) WOMEN IN THE SUB-SAHARAN AFRICAN BREAST CANCER-DISPARITIES IN OUTCOME (ABC-DO) COHORT STUDY

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DECLARATION

I, Dr. Oyepeju F. Abioye, declare that this report: "Breast Cancer Survival to 5 years among Young (<40 years) Women in the sub-Saharan African Breast Cancer – Disparities in Outcome (ABC-DO) Cohort Study" is my own unaided work and that every source used has been indicated by complete references. This report is being submitted for the Master of Science in Epidemiology degree at University of the Witwatersrand, Johannesburg, South Africa. It has never been submitted at this or another University for any degree.



SIGNATURE

18/02/2023

DATE

DEDICATION

To my loving husband, Ayooluwa T. Akintola, whose belief in my ability is completely unwavering and for gifting me with love that's enough to last for a lifetime; my bright-eyed son, Ayooluwa A. Akintola, for whom I am setting an example of diligence and excellence; and in memory of my tenacious father, Mr. L.O.S Abioye, without whom my dreams would have been mere dust. Every achievement is for you.

ABSTRACT

Introduction. Breast cancer remains a key global health challenge, accounting for most prevalent cause of cancer-related deaths worldwide. The impact of age at diagnosis on breast cancer survival has not been extensively investigated within the African context. Therefore, this study's objectives were to estimate the breast cancer survival time among women <40 years and investigate the factors associated with a 5-year survival differential between younger (<40 years) and older (>40 years) women in the ABC-DO Cohort Study in SSA.

Methods. Secondary data analysis of breast cancer patients from the multi-country ABC-DO Prospective Cohort Study of 5 African countries was carried out. Baseline characteristics of study participants were summarized using descriptive statistics. Kaplan Meier curves were generated to evaluate breast cancer survival time by age group "<40 years, 40-64 years, 65+ years". With the aid of Cox Multivariate Regression Modelling, factors correlated with a 5-year survival differential between younger and older women were investigated and Hazard Ratios were calculated adjusting for confounders.

Results. This study had a total number of 2158 participants, 462 (21.41%) were <40 years at diagnosis, 1314 were between 40-64years (60.89%), while 382 patients were 65 years and above (17.70%). A total of 1211 deaths were recorded at 5 years. The total time at risk and incidence rate at 5 years was 6086.73 person years and 33 per 100 women respectively. The lowest overall survival at 5 years was found among women <40 years (33.46%; CI = 0.28-0.38), followed by women aged 65 years+ (37.63%; CI = 0.32-0.42), and highest overall survival was among women in the 40-64 years age group (42.66%; CI=0.39-0.45). For each country, the 5-year probability of survival was higher among women aged 40-64 compared to women under 40. On Cox multivariate analysis, a 20% rise in mortality was reported among women < 40 years (aHR 1.20; 95% CI= 1.03-1.36) compared to women between 40-64 years in the final model, at $p<0.05$. The variables significantly associated with 5-year survival differential between younger and older women were: HIV status, Residence, and Stage at Diagnosis.

Conclusion. This study reports that breast cancer survival among women in sub-Saharan Africa is age-specific, with lower 5-year overall and country-specific survival among women < 40 years in comparison to older women. Factors associated with lower survival include stage at diagnosis, HIV status, and area of residence. Young women (<40 years) in SSA remain at risk of increased mortality from breast cancer, hence there is an urgent need for targeted strategies to achieve a more favorable stage at diagnosis and improved survival in this populace.

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"If I have seen any further, it is by standing on the shoulders of giants" – Sir Isaac Newton

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TABLE OF CONTENTS

DECLARATION i

DEDICATION ii

ABSTRACT iii

ACKNOWLEDGEMENTS iv

TABLE OF CONTENTS v

LIST OF FIGURES viii

LIST OF TABLES ix

LIST OF APPENDICES x

LIST OF ABBREVIATIONS AND ACRONYMS xi

CHAPTER ONE: INTRODUCTION 1

1.1 Background 1

1.1.1 Breast Cancer Burden in sub-Saharan Africa 1

1.1.2 Problem Statement 2

1.1.3 Justification 2

1.2 Research Question 2

1.3 Aim and Objectives 3

1.3.1 Study Aim 3

1.3.2 Specific Objectives 3

CHAPTER TWO: LITERATURE REVIEW 4

2.1 Introduction 4

2.2 Epidemiology of Breast Cancer 4

2.3 Understanding Breast Cancer Classification 5

2.4 Management of Breast Cancer 7

2.5 Breast Cancer Incidence and Mortality at the Population Level 5

2.6 Age as a Prognosticator of Breast Cancer Survival 7

2.7 Other Predictors of Breast Cancer Survival with a Focus on Evidence from sub-Saharan Africa....10
2.7.1 Stage at Diagnosis....10
2.7.2 Histological Markers....10
2.7.3 Ethnicity....11
2.7.4 Country's Human Development Index....12
2.7.5 Socio-Economic Predictors of Survival....12
2.8 Conceptual Framework on Predictors of Breast Cancer Survival....13
CHAPTER THREE: METHODOLOGY....15
3.1 Introduction....15
3.2 Description of Primary Study....15
3.3 Study Design....15
3.4 Study Site....15
3.5 Study Population....16
3.6 Data Collection....17
3.7 Data Management and Processing....18
3.7.1 Study Variables....18
3.7.1.1 *Outcome Variable*....18
3.7.1.2 *Explanatory Variables*....18
3.8 Data Analysis....20
3.8.1 Baseline Features of Study Participants....20
3.8.2 Survival Analysis....20
3.8.3 Cox Proportional Hazards Regression Analysis....21
3.9 Ethical Considerations....21
CHAPTER FOUR: RESULTS....23
4.1 Introduction....23
4.2 Study Participants' Baseline Characteristics....23
4.2.1 Baseline Characteristics of Study Participants by Age-Stage Distribution....26

4.2.2 Baseline Characteristics of Study Participants by Age-Subtype Distribution 27
4.3 Overall Breast Cancer Survival (by Age Group) of Study Participants.....27
4.3.1 Kaplan Meier Survival Curves by Age Group At 5 Years.....28
4.4 Breast Cancer Survival by Age Group of Study Participants Per Country.....29
4.4.1 Breast Cancer Survival by Age Group of Study Participants for South Africa 29
4.4.2 Breast Cancer Survival by Age Group of Study Participants for Zambia.....31
4.4.3 Breast Cancer Survival by Age Group of Study Participants for Namibia 32
4.4.4 Breast Cancer Survival by Age Group of Study Participants for Uganda 34
4.4.5 Breast Cancer Survival by Age Group of Study Participants for Nigeria.....35
4.5 Cox Proportional Hazards Regression Analysis 36
4.5.1 Testing Cox Proportional Hazard Assumption.....40
CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS.....41
5.1 Introduction.....41
5.2 Summary of Main Findings 41
5.3 Study Limitations.....42
5.4 Strengths of the Study.....43
5.6 Conclusion 43
5.7 Recommendations.....43
REFERENCES.....44
APPENDICES 50
APPENDIX I: PLAGIARISM DECLARATION FORM.....50
APPENDIX II: ABCDO DATA DICTIONARY 51
APPENDIX III: PERMISSION TO USE THE ABC-DO DATASET 53
APPENDIX IV: WITS HUMAN RESEARCH ETHICS COMMITTEE CLEARANCE CERTIFICATE 54
APPENDIX V: APPROVAL OF RESEARCH TITLE.....55
APPENDIX VI: TEST OF PROPORTIONAL HAZARDS ASSUMPTION.....56
APPENDIX VII: TURNITIN REPORT 57

LIST OF FIGURES

Figure 2.1 Conceptual Framework showing Predictors of Breast Cancer Survival

Figure 3.3: Map of sub-Saharan Africa Highlighting Countries Used in this Study

Figure 3.5: Flowchart showing recruitment and selection of study participants

Figure 4.1: Bar Chart Depicting Stage Distribution of Breast Cancer among participants by Age at diagnosis

Figure 4.2: Bar Chart Depicting Subtype Distribution of Breast Cancer among participants by Age at diagnosis

Figure 4.3: Kaplan-Meier Survival Curve showing time-to-death by Age Group

Figure 4.4: Kaplan-Meier Survival Curve showing time-to-death by Age Group for South Africa

Figure 4.5: Kaplan-Meier Survival Curve showing time-to-death by Age Group for Zambia

Figure 4.6: Kaplan-Meier Survival Curve showing time-to-death by Age Group for Namibia

Figure 4.7: Kaplan-Meier Survival Curve showing time-to-death by Age Group for Uganda

Figure 4.8: Kaplan-Meier Survival Curve showing time-to-death by Age Group for Nigeria

LIST OF TABLES

Table 2.5: Summary of Findings from Recent Studies Evaluating Breast Cancer Survival in Younger Women

Table 3.4: Study Sites Per Country for ABC-DO Data Collection

Table 4.1: Baseline Demographic Characteristics of Participants, by Age at diagnosis (N= 2158)

Table 4.2: Baseline Clinical Characteristics of Participants, by Age at diagnosis (N= 2158)

Table 4.3: Kaplan Meier Survivor Functions at 5 years by Age Group of Study Participants (N= 509)

Table 4.4: Kaplan Meier Survivor Functions at 5 years by Age Group of Study Participants for South Africa (N= 64)

Table 4.5: Kaplan Meier Survivor Functions at 5 years by Age Group of Study Participants for Zambia (N= 35)

Table 4.6: Kaplan Meier Survivor Functions at 5 years by Age Group of Study Participants for Namibia (N= 244)

Table 4.7: Kaplan Meier Survivor Functions at 5 years by Age Group of Study Participants for Uganda (N= 111)

Table 4.8: Kaplan Meier Survivor Functions at 5 years by Age group of Study Participants for Nigeria (N= 55)

Table 4.9: Cox Proportional Hazards Model depicting Unadjusted Hazard Ratios for Factors associated with 5-Year Survival Differential (Univariate analysis)

Table 4.10: Cox Proportional Hazards Model depicting Sequentially Adjusted Hazard Ratios for Factors associated with 5-Year Survival Differential (Multivariate analysis)

LIST OF APPENDICES

APPENDIX I: Plagiarism Declaration Form

APPENDIX II: ABC-DO Data Dictionary

APPENDIX III: Permission to Use the ABC-DO Dataset

APPENDIX IV: WITS Human Research Ethics Committee Clearance Certificate

APPENDIX V: Approval of Research Title

APPENDIX VI: Test of Proportional Hazards Assumption

APPENDIX VII: Turnitin Report

LIST OF ABBREVIATIONS AND ACRONYMS

ABC-DO African Breast Cancer- Disparities in Outcome

AJCC American Joint Committee on Cancer

ASR Age-standardized Rates

BC Breast Cancer

DFS Disease Free Survival

ER Estrogen Receptor

GLOBOCAN Global Cancer Observatory

HDI Human Development Index

HER2 Human Epidermal Growth Factor Receptor-2

IARC International Agency for Research on Cancer

KM Kaplan–Meier

LMIC Low- and-Middle-Income Countries

MeSH Medical Subject Headings

OS Overall Survival

POSH Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer

PR Progesterone Receptor

RS Relative Survival

SSA sub-Saharan Africa

TNBC Triple Negative Breast Cancer

TNM Tumour Node Metastasis

V Variables

CHAPTER ONE: INTRODUCTION

1.1 Background

Chapter One provides an overview of sub-Saharan Africa's breast cancer burden, this study's rationale, aim, and specific objectives.

1.1.1 Breast Cancer Burden in sub-Saharan Africa

Breast cancer currently constitutes a major global health challenge, accounting for the highest number of cancer diagnoses and cancer-related deaths worldwide, as reported by the 2018 Global Cancer Statistics (Bray *et al.*, 2018). In sub-Saharan African women, breast and cervical cancers alone made up close to 50% of new cancer diagnoses in 2018 (Bray *et al.*, 2018). Still, only few studies have estimated breast cancer survival rates in this region. Among conducted studies, 5-year survival estimates of women with cancer of the breast are under 50% in sub-Saharan Africa (SSA) (Joko-Fru *et al.*, 2020). Improving survival rates in this region, which are presently among the lowest in the world (Joko-Fru *et al.*, 2020), is a top objective for breast cancer control in Africa. Indeed, in 2021, WHO established a "Global Breast Cancer Initiative" to reduce inequities and enhance breast cancer survival among women in low- and middle-income countries (Anderson *et al.*, 2021).

Age is a notable predictor of breast cancer incidence and mortality (Zouzoulas *et al.*, 2020). The relatively higher preponderance of cases in women 40 years and older has resulted in breast cancer management being chiefly focused on women in this age group (Gabriel and Domchek, 2010). Sadly, while not as common, younger ages at diagnosis of breast cancer (<40 years) are associated with more aggressive subtypes (Rosenberg and Partridge, 2015), higher incidence of axillary lymph node infiltration, and consequently, significantly poorer prognoses (Zouzoulas *et al.*, 2020).

In addition, because women <40 years are within the child-bearing age-group and are often young mothers, there is a consequential impact of maternal orphans associated with younger deaths within this unique subgroup (Galukande *et al.*, 2021). In addition, they are within the economically productive age group, hence their morbidity and mortality from breast cancer impinges on overall societal productivity. As such, more research should be carried out to address these women, and emphasis should be placed on the provision of adequate preventive and curative medical intervention for women under age 40 with breast cancer.

1.1.2 Problem Statement

In sub-Saharan Africa (SSA), more than 400,000 women are estimated to die of breast cancer in the current decade (McCormack *et al.*, 2020). This is a very high death toll for a malignancy that is considered curable, if properly managed.

While survival has been found to be negatively impacted by clinical stage of disease (Jedy-Agba *et al.*, 2016) and HIV status (Chasimpha *et al.*, 2022), other patient's characteristics such as younger ages at diagnosis which may determine survival, have not been extensively studied in the African context. Women less than 40 years have not been actively considered for breast cancer screening; with the exception of women considered to be high-risk, such as those with family history of breast cancer (Anders *et al.*, 2009). Nonetheless, having breast cancer at younger ages increases the risk of aggressive tumours and subsequent death (Rosenberg and Partridge, 2015). Bearing this in mind, it is crucial to understand breast cancer mortality statistics among women under the age of 40.

1.1.3 Justification

Roughly 7% of breast cancer diagnoses in Western populations are made in women <40 years, yet survival rates among this sub-group of breast cancer patients are significantly worse than for women >40 years (Anders *et al.*, 2009). Even more alarming, in sub-Saharan Africa, there is insufficient research regarding factors associated with breast cancer survival, especially for women <40 years. This research gap constitutes a public health problem, and as such, there is a need to identify factors which impact survival among this sub-group of breast cancer patients, especially in SSA.

1.2 Research Question

What is the 5-year breast cancer survival time and its associated factors, among women less than 40 years in the ABC-DO Cohort Study in sub-Saharan Africa (SSA)?

1.3 Aim and Objectives

1.3.1 Study Aim

To determine the 5-year breast cancer survival and describe its associated factors among young women less than 40 years in the ABC-DO study in SSA.

1.3.2 Specific Objectives

Specific objectives of this study were to:

- Estimate breast cancer survival time among women <40 years in the ABC-DO Cohort Study in SSA.
- Investigate factors associated with a 5-year survival differential between younger (<40 years) and older women (>40 years) in the ABC-DO Cohort Study in SSA.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

For this study, comprehensive literature search was carried out on Google Scholar & PubMed for studies on the epidemiology, classification, management, survival, and predictors of survival from breast cancer. MeSH (medical subject headings) search terms on these electronic data bases included: “breast cancer” “survival” and “sub-Saharan Africa”, and publications used were from 2005 till date. Publications that reported prevalence, incidence, disease free survival, and overall survival were included. Search was restricted to the English Language. A manual search for relevant citations and references of included studies was also carried out.

2.2 Epidemiology of Breast Cancer

In 2018, roughly 2.1 million women were diagnosed with breast cancer, comprising almost 12% of cancer diagnosis worldwide (Bray *et al.*, 2018). Even more concerning, among women between the ages of 20-49, cancer of the breast is the most detected form of cancer (Anders *et al.*, 2009; Gentilini, Partridge and Pagani, 2020). In SSA, it is projected that over 400,000 women would die of breast cancer in this decade (McCormack *et al.*, 2020).

Age, as a risk factor of breast cancer incidence and survival, has notable epidemiological significance. The GRELL study, which investigated breast cancer incidence amongst women below 40 years in seven European countries discovered a 1.2% annual rise in breast cancer incidence among these young women over an 18-year period (1990 to 2008), with the highest increase between 15-34 years, when compared with older women (Leclère *et al.*, 2013). An American cancer epidemiological study also detected breast cancer survival to be distinctively lower among women <40 years, irrespective of the histological subtype and stage at diagnosis (Bleyer A *et al.*, 2006).

In Anders and colleagues’ 2009 study, it was astonishing to note breast cancer survival among women <40 years to be consistently lower than comparative survival in older women since 1975, further worsening breast cancer prognosis amongst younger women over the last four decades (Anders *et al.*, 2009). Therefore, this makes a solid case for the importance of studying breast cancer epidemiology and survival, especially in young women.

Other risk factors for increased breast cancer incidence include the presence of genetic mutations (BRCA1 mutation on Chromosome 17, BRCA2 mutation on Chromosome 13), early menarche, delayed pregnancies, previous history of breast cancer and non-cancerous breast

lesions, smoking, use of hormone replacement therapy and westernized lifestyles leading to an increased intake of processed foods and reduced physical activity (Łukasiewicz et al, 2021).

2.3 Breast Cancer Incidence and Mortality at the Population Level

Worldwide, breast cancer is most frequently diagnosed cancer in women, with 2.26 million cases in 2020 (Ferlay et al, 2021) and an annual projection of 2.7 million new diagnoses by 2030 (Łukasiewicz et al, 2021). At an age-standardized rate (ASR) of 13.6 per 100,000 women in 2020, almost 700,000 deaths were recorded globally due to breast cancer (Ferlay et al, 2020). Although breast cancer incidence rates were highest in developed regions, Africa and Asia represented over 60% of breast cancer mortality in 2020 (Ferlay et al, 2020).

Of all new cancers diagnosed in 2020 based on WHO's Global Cancer Observatory (GLOBOCAN) fact sheets, breast cancer incidences varied widely among women in sub-Saharan Africa, ranging from 12.4% in Zambia, 13.5% in Uganda, 27.1% in South Africa, 29.3% in Namibia, 38.4% in Mauritius to 38.7% in Nigeria (International Agency for Research on Cancer, 2020).

Amongst SSA countries in 2020, Mauritius had the highest age-standardized rate (ASR) at 66.2 per 100,000 women, while Namibia, South Africa and Nigeria followed at age-standardized rates of 57.6, 52.6 and 49.0 per 100,000 women respectively. Uganda and Zambia had much lower ASRs of 22.2 and 20.0 per 100,000 women respectively. When compared to what is obtainable in high-income regions like North America, with ASRs of 90.3 per 100,000 women in the United States and 82.1% in Canada, sub-Saharan African countries report significantly lower age-standardized breast cancer incidence rates (International Agency for Research on Cancer, 2020).

In spite of higher incidence rates in North America, breast cancer mortality rates are comparatively higher in SSA, with 12.4 deaths and 13.3 deaths /100,000 women in United States and Canada respectively, while 15.4-26.6 deaths per 100,000 women were recorded in Western, Middle and Eastern Africa in 2020 (International Agency for Research on Cancer, 2020).

Allemani and colleagues, in their 2018 study, discovered the breast cancer 5-year survival rate to be between 85-90% in the United States. This study however showed black women to have relatively lower survival i.e. 80%, compared to their white counterparts (Allemani *et al.*, 2018). This lends credence to the researchers' observation that breast cancer survival amongst

Africans and African Americans is relatively lower than for other races, and possible reasons for this finding should be further investigated (Allemani *et al.*, 2018).

Other researchers have studied breast cancer survival within the African context. In a prospective cohort study carried out in SSA, three-year crude overall breast cancer survival was found to be between 55-59% among South African and black Namibian women, with better survival outcomes (69-76%) observed among South African and mixed-race Namibian women (McCormack *et al.*, 2020). This study also reported an overall survival of 36% in Nigerian women, and 44-47% in Zambian and Ugandan women. Five-year survival, as noted by other researchers, ranged from <20% in The Gambia to 46% in Uganda (Sankaranarayanan *et al.*, 2010).

2.4 Understanding Breast Cancer Classification

Breast cancer is a heterogeneous disease with biologically unique subtypes that behave differently. Breast cancer characterization can be done based on TNM staging, histopathological grading, and molecular subtyping; all of which affect clinical progression, management, and outcomes (Li *et al.*, 2015).

Four histological markers; viz: human epidermal growth factor receptor-2 (HER2), estrogen receptor (ER), progesterone receptor (PR), and Ki-67, subdivide breast cancer into subtypes. The subtypes are: "Luminal A (ER-and/or PR-positive/HER2-negative /low Ki-67), Luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive Luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression), and triple-negative (ER and PR absent/HER2-negative)" (Li *et al.*, 2015).

The American Joint Committee on Cancer staging manual (7^{th} version) is utilized for TNM staging (Edge and Compton, 2010). With regards to tumour grading, breast cancer can be histologically graded as well, moderately, or poorly differentiated (Li *et al.*, 2015). Consequent upon the identification of these breast cancer subtypes and grading, researchers have better knowledge of the disease - which has been useful in individualizing treatment and predicting patient outcomes.

2.5 Management of Breast Cancer

While treatment varies across several hospitals in SSA, modalities of treatment offered to patients depends on the stage at diagnosis and histological markers expressed (Foerster *et al.*, 2019). Major treatment modalities include surgery, radiotherapy, hormonal therapy, and chemotherapy. Either single modality or combination therapy can be used in managing breast cancer. Breast cancer management is usually multidisciplinary, involving general surgeons, oncologists, radiotherapists, etc. In sub-Saharan Africa, oftentimes availability of treatment modality also affects what options patients are presenting with; which may not be the best for them amongst other setting-specific factors that may influence treatment options (Sutter *et al.*, 2017).

2.6 Age as a Prognosticator of Breast Cancer Survival

Age is a vital prognosticator of breast cancer survival. In a study conducted by Ohene-Yeboah and Adjei in Ghana, the peak age of breast cancer diagnosis was between ages 40-49 (Ohene-Yeboah and Adjei, 2012). Similarly, Gakwaya and colleagues' Ugandan study reported a peak age of diagnosis between ages 30-39 (Gakwaya *et al.*, 2008). Both studies suggest that younger ages of diagnosis are common in the sub-Saharan African populace, corroborating earlier findings observed by other researchers in this region (Gukas *et al.*, 2005; Clegg-lamptey and Hodasi, 2007).

With regards to the trend in relative survival (RS) by age; Joko-Fru et al (2020) observed that women less than 45 years had lower three-year survival estimates when compared to older women (between 55-64 years). McCormack et al. also observed a U-shaped survival pattern with younger women less than 30 years exhibiting lower survival rates when compared with women within the 40-49 years age bracket(McCormack *et al.*, 2020). These findings are suggestive of lower relative survival among younger women with breast cancer.

Some studies have evaluated breast cancer survival among younger women, with overall survival rates and survival trends reported in varying studies (Table 2.5).

In a 2011 Finland study by Liukkonen and colleagues, 212 women who were ≤ 35 years and diagnosed with breast cancer were observed over a median period of 78 months and had an overall survival (OS) of 80% (Liukkonen *et al.*, 2011). Similarly, a 2021 Portuguese study showed an overall survival of 86.5% among 207 women ≤ 35 over a 64.9 month median follow-up time (Eiriz *et al.*, 2021). Relative survival of 80% was also reported in a US study that showed 5-year relative survival by age group (Anders *et al.*, 2009).

While the overall survival in young women have been reported to be 80% and 86.5% respectively in some high-income countries (Liukkonen *et al.*, 2011; Eiriz *et al.*, 2021), there is a trend of lower survival among young women in SSA countries, with the need to compute specific relative/overall survival constituting a research gap in sub-Saharan Africa (Joko-Fru *et al.*, 2020; McCormack *et al.*, 2020).

Table 2.5: Summary of Findings from Recent Studies Evaluating Breast Cancer Survival in Younger Women

	Study Ref	Country	Calendar Period of BC Diagnosis	Definition of 'young' breast cancers	No. young women with breast cancer	Comparison group – definition & no of women	Outcome	Effect estimate
1	Liukkonen et al, 2011	Helsinki, Finland	Treated 1997-2007	<=35	212 (Median age at diagnosis=33)	No comparison group	All-cause mortality (Overall survival estimated)	80% OS at 5-years
2	Eiriz et al, 2021	Portugal	2008-2017	<=35	207 (Median age at diagnosis=31)	No comparison group	Overall survival, Disease free survival	86.5% OS at 5 years; DFS: 79.7% in non-metastatic population
3	Anders et al, 2016	United States, Taiwan, Netherlands, Sweden, Singapore	1980-2002	<=45	200	>=65yrs; 211	Disease free survival	Inferior Disease-free survival trends among younger women in cohort (HR=1.32; *P* = .094)
4	Anders et al, 2009	United States	2000-2005	---	---	Women in other age groups	Relative survival (RS)	5-year RS per age group 15-19y: 80% 20-24y: 75% 25-29y: 72% 30-34y: 76% 35-39y: 80% 45-80y: 84-86%
5	Hartley et al, 2006	South Carolina, USA	1998-2002	<40	78 (Mean age at diagnosis=35)	>=40yr old women used as controls; 228 controls (Mean age at diagnosis=59)	All-cause mortality Overall survival	Lower overall survival for women <40 years on KM curves

2.7 Other Predictors of Breast Cancer Survival with a Focus on Evidence from sub-Saharan Africa

2.7.1 Stage at Diagnosis

Stage at diagnosis is a well-recognized prognostic marker for breast cancer, with up to 77% of its diagnosis in SSA being late-stage (i.e. stage 3 or 4) (Jedy-Agba *et al.*, 2016). This factor is believed to be a major contributor to the lower survival rates seen in this region (Jedy-Agba *et al.*, 2016).

Joko-Fru and colleagues corroborated this in their study, showing stage at diagnosis as a prognosticator of survival, after confounders such as age at diagnosis and country had been adjusted for. These researchers observed that late-stage diagnosis can be linked to age at diagnosis, as the delays in accessing health care in this region could lead to older ages at presentation. However, there was no significant association between both possible predictors of survival. Late-stage diagnosis did not also correlate with tumour grade but there was correlation with tumour size; which was anticipated, as tumour size is a determinant of cancer stage (Joko-Fru *et al.*, 2020).

Outside SSA, stage at diagnosis is also an important prognosticator. For instance, a 2021 Portuguese study (Eiriz *et al.*, 2021) on breast cancer in women under 35 years revealed Disease Free Survival (DFS), explained as the timespan between cancer diagnosis and its recurrence, disease progression or death, to be significantly higher (79.7% and 73.3% at 5 and 10 years respectively) among the non-metastatic cancer populace. For patients with metastatic cancer, a 51.8% 5-year overall survival (OS) since metastatic disease diagnosis was observed. In this study, non-metastatic and metastatic cancer patients were followed up for an average of 64.6 and 72.7 months respectively.

Other factors found to be responsible for late-stage diagnosis are: low community awareness of breast cancer and distance barrier to accessing healthcare among the general population (Pruitt *et al.*, 2015; Tetteh and Faulkner, 2016).

2.7.2 Histological Markers

The impact of lifestyle and environmental factors on cancer is typically accumulated and discovered several years along the line, and as such, might not be as significant to breast cancer occurrence in young women. Genetic and histological attributes, however, are very important in this sub-population (Eiriz *et al.*, 2021).

There is constant agreement in literature that triple-negative breast cancer (i.e. ER, PR, and HER2 negative) which is the most aggressive subtype, compromise survival chances among

patients (Bae *et al.*, 2015; Gnanamuttupulle *et al.*, 2021). In the context of young age, a 2021 study on young women with breast cancer found 5-year overall survival in TNBC patients to be 75.3%, about 8% lower than 5-year overall survival of 83.3% among Hormone receptor negative/HER2-positive patients, and more than 15% lower than 5-year overall survival of 91.9% among Hormone receptor positive/HER-2 negative patients. This corroborates the findings of increased mortality among TNBC patients especially among young women (Eiriz *et al.*, 2021).

Furthermore, HER2-positive tumours are reported to be more widespread among younger women, in comparison to older patients (Gentilini, Partridge and Pagani, 2020). This is important, as increased recurrence and mortality are associated with HER2-positivity (Patel, Unni and Peng, 2020).

Histological markers have also been correlated with breast cancer metastasis. In fact, 5-year survival of patients with metastatic disease differed with varying histological pictures in a 2021 study, with a 60% survival rate observed among those with HR-positive/HER2-negative tumours, and significantly lower survival rate of 23.4% among those with TNBC (Eiriz *et al.*, 2021).

In view of the above, it is very concerning to note the possible correlation between CNS metastasis in breast cancer and immunohistochemical markers. While an association has been noted in literature between CNS metastasis and ER-receptor negativity in patients (Palmieri *et al.*, 2006), another study alludes to overall better prognosis with estrogen receptor-positive cancers when compared with estrogen-negative cancers across sub-Saharan Africa (McCormack *et al.*, 2020). HER2-positivity and TNBC have also been linked to CNS metastasis, contributing to high mortality rates from breast cancer (Eiriz *et al.*, 2021).

2.7.3 Ethnicity

Ethnicity has significant impact on survival from breast cancer. For instance, black women have increased breast cancer incidence before 45, with higher mortality rates in every US state when compared to non-Hispanic Whites (American Cancer Society, 2015). Factors seemingly responsible for this disparity include health care access - which is typically lower among ethnic minorities such as black and Hispanic women, and late-stage presentation to the hospital (American Cancer Society, 2015).

Howbeit, findings from the POSH study, carried out in the United Kingdom on women 40 years and younger with breast cancer also identified black ethnicity as an independent risk

factor for lower survival, in spite of similar access to health care with White and Asian women (Copson *et al.*, 2014).

Some studies ascribe poorer outcomes in Black women to higher grade (Yedjou *et al.*, 2019) and more aggressive tumour subtypes such as triple-negative tumours (Allicock *et al.*, 2013). Nonetheless, the impact of ethnicity as an independent prognosticator of breast cancer deserves more extensive research focus.

2.7.4 Country's Human Development Index

Human development index (HDI) has been cited as a factor that may affect breast survival rates across countries/regions. Joko-Fru et al. found that survival was better among nations with high HDI when contrasted with low HDI nations. HDI may also impact age at diagnosis, indirectly affecting survival, as this study observed that although mean age at diagnosis in high HDI countries (56.5years) was higher than in low HDI countries (48 years), survival experience was still better in high HDI countries, where 5-year relative survival among patients diagnosed early was as high as 84.7%, compared to an almost 20% reduction of 67.1% in lower HDI countries (Joko-Fru *et al.*, 2020).

2.7.5 Socio-Economic Predictors of Survival

Socio-economic indices are viable breast cancer survival predictors. Some socio-economic indicators were analyzed by McCormack et al. and they include level of education, breast cancer awareness, rural or urban residency. This study observed higher mortality among women with lower level of education, women without the knowledge that breast cancer could be cured, and those living in rural areas. The effect of treatment types on survival rate has not been studied significantly, however higher mortality has been found among those who were not treated at all and those who had systemic therapy only when compared to those who had both systemic therapy and surgery(McCormack *et al.*, 2020). This could impact outcomes in SSA as not all health facilities across the region offer all the modes of therapy for breast cancer. Radiotherapy facilities are not as common as they should be, and in countries where they are available, they are located very distantly away from other urban places and rural areas (Edge *et al.*, 2014).

Lack of access to adequate therapy, tumour aggressiveness, late stage at diagnosis, and comorbidities are contributing factors to poor breast cancer survival in Africa. Treatment choices are also influenced by accessibility, cost, and adherence, in the context of additional comorbidities as well as alternative medicine use by patients in this region. However, prognostic and predictive factors investigated have been confined to a small number of clinical and treatment parameters. While outcomes in survival may be largely influenced by these

clinical and treatment parameters, there is need for a more complete assessment of the whole journey in women under 40 years who have breast cancer. Adequate follow up from when symptoms are first noticed through post-diagnostic therapy, subsequent disease cure, recurrence or spread may reveal other factors that may be associated with the disparities in outcomes.

2.8 Conceptual Framework on Predictors of Breast Cancer Survival

This study's conceptual framework is an adaptation of the Health Belief Model (Champion and Skinner, 2008) which emphasizes the importance of certain factors on the overall health outcome i.e., breast cancer survival in this study.

These factors include the: perceived susceptibility to a disease (in this case, breast cancer), perceived seriousness and threat of death from the condition, perceived benefits of actions taken for overall risk mitigation (e.g., breast cancer screening or treatment), as well as individual modifying factors.

In an Ethiopian study, the practice of breast self-examination (BSE), which is correlated with early detection of breast cancer was higher among young women with high perceived susceptibility to, and severity of breast cancer (Assfa Mossa, 2022). Another Iranian study found that women with high perceived benefits of screening were more likely to engage in breast self-examination and mammography, thus improving survival indices (Darvishpour, Vajari and Noroozi, 2018).

Individual modifying factors like age at diagnosis, race and socio-economic indices are important predictors of breast cancer survival, with studies showing higher breast cancer mortality among younger women in SSA (Joko-Fru et al, 2020), Black women (Yedjou et al, 2019), women with lower level of education, those who live in rural areas, and who have low awareness of breast cancer (McCormack et al, 2020).

Using this conceptual framework, the predictors of breast cancer survival are summarized in Figure 2.1 below.

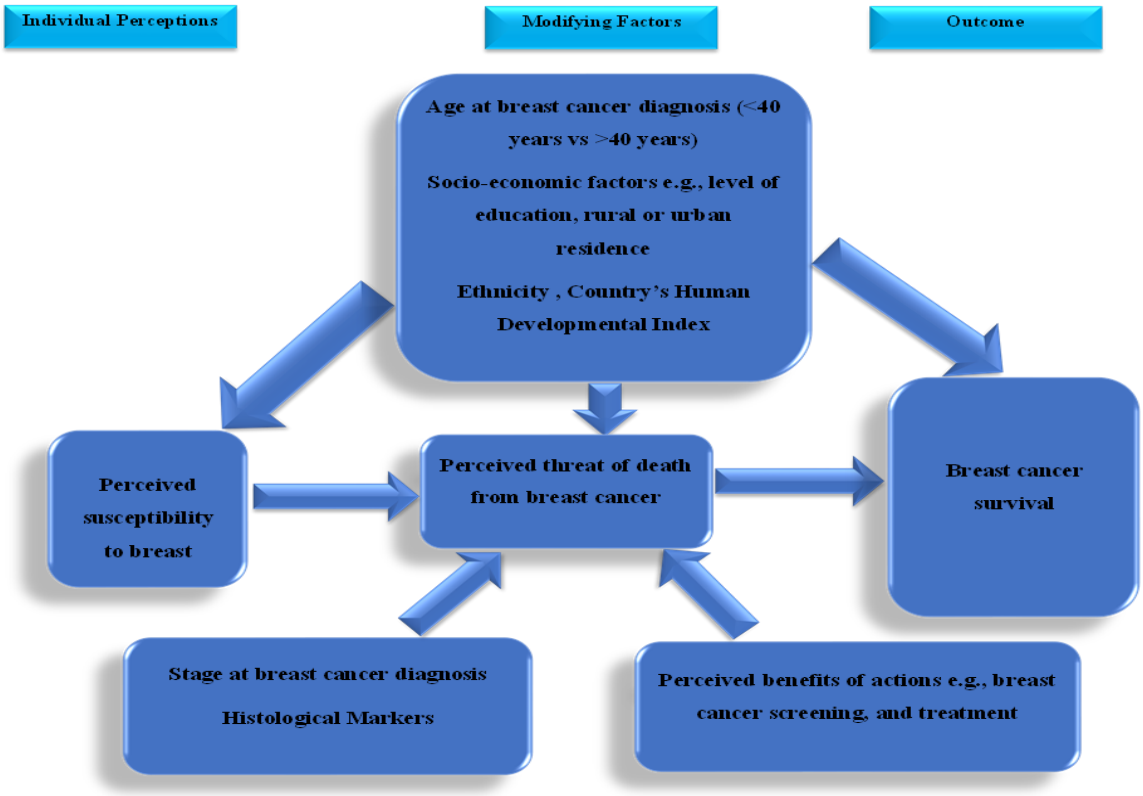


Figure 2.1: Conceptual Framework showing Predictors of Breast Cancer Survival

CHAPTER THREE: METHODOLOGY

3.1 Introduction

In Chapter Three, a thorough description of the primary study, study design, site, and population are presented. A comprehensive overview on data collection, management, analysis as well as ethical considerations is also provided. Data analysis carried out includes descriptive statistics, survival analysis using crude Kaplan-Meier estimates and Cox Regression.

3.2 Description of Primary Study

The African Breast Cancer – Disparities in Outcomes (ABC-DO) study was a hospital-based prospective cohort study which recruited over 2000 women, 18 years and older, who presented to 8 facilities in 5 SSA countries; namely: Uganda, Namibia, South Africa, Nigeria and Zambia) between September 2014 – December 2017, and followed them up till: 5 years from point of diagnosis, date of participant's death or when she was last known to be alive (McKenzie *et al.*, 2016).

Eligibility criteria included: histological and/or clinical breast cancer diagnosis in women presenting to participating facilities. A questionnaire was used to collect detailed data on sociodemographic factors, HIV status (tested for in South Africa but self-reported in the remaining 4 nations); clinical data on breast cancer stage (and receptor subtype if available). Data on treatment modalities were obtained from medical records.

Telephone calls were placed to participants or their next of kin once every three months. Contact details as well as information obtained were managed using a mobile health application (mHealth app) designed for this study.

3.3 Study Site

The primary data was collected from 8 hospitals in 5 SSA countries (South Africa, Uganda, Nigeria, Namibia, and Zambia). Table 3.4 provides a list of the study sites, while the countries understudied are highlighted on the SSA map in Figure 3.4.

Table 3.4: Study Sites Per Country for ABC-DO Data Collection

Country	Hospital(s)
South Africa	Chris Hani Baragwanath Academic Hospital (Batho Pele Breast Clinic), Soweto

Nigeria	Abia State University Hospital, Aba
	Federal Medical Centre, Owerri
	Maranatha Clinic
Namibia	Windhoek Central Hospital
Uganda	Mulago Hospital Complex, Kampala
Zambia	University Teaching Hospital, Lusaka
	Kabwe General Hospital



Figure 3.3: Map of sub-Saharan Africa showing the countries used in this study

3.4 Study Design

An analysis of existing/secondary data from the prospective ABC-DO Breast Cancer Cohort Study. This data was collected by the International Agency for Research on Cancer (IARC).

Study participants were followed up three-monthly via telephone calls to either the participants or when unavailable, the next of kin. For this analysis, data was retrieved for participants followed up until 5 years from the point of diagnosis, death of participant or date when she was last known to be alive.

3.5 Study Population

Women who were 18 years and older, with a histological and/or clinical breast cancer diagnosis in any of the 8 hospitals were recruited in 5 SSA countries: South Africa, Uganda, Nigeria, Namibia, and Zambia, between Sept 2014 – Dec. 2017.

From 2014 through 2017, 2313 women were recruited into the study, with 85 women excluded (as they did not have either clinical or histological diagnosis of breast cancer). Of the remaining 2228 women, 70 were excluded due to prior treatment, recurrence or being a part of a very small racial/ethnic group. 2158 women with breast cancer were captured within the ABC-DO database, followed up as study participants for 7 years (data analysis for this study was conducted up till 5 years), and they all met the inclusion criteria to be analyzed for this study.

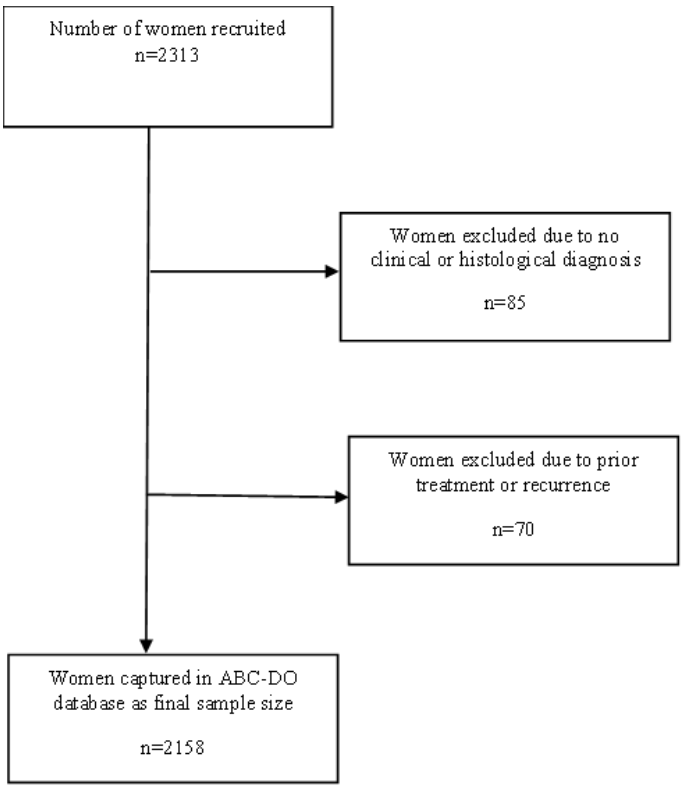


Figure 3.5: Flowchart showing recruitment and selection of study participants

3.6 Data Collection

Data source was the completed ABC-DO interviewer-administered questionnaire, after which clinical data and follow-up outcomes were extracted from participants' case files. The survey gathered extensive information on sociodemographic characteristics such as level of education, site-specific socioeconomic status, number of children, pregnancy history, age, presence of

comorbidities (e.g., HIV) and reproductive history of participants. Clinical data comprised of breast cancer stage, grade, and receptor subtype. Within 12 months from the diagnosis, information on life-prolonging interventions such as surgical excision, chemotherapy, or radiotherapy was also gathered.

3.7 Data Management and Processing

ABC-DO data was accessed on approval from the study's Principal Investigator and captured into STATA as *"ABCDO Oyepeju".* Data was extracted from the primary study according to age status at the point of diagnosis. A new variable for age status was generated, which subdivided the study participants into three groups (<40 years, 40-65years and >65years). Censored data was excluded from the analysis. Data was cleaned and examined for duplicate records and consistency. Confidentiality of study participants was ensured by using only anonymized data (unique ID codes were generated for each participant).

3.7.1 Study Variables

3.7.1.1 *Outcome Variable*

The outcome variable of interest was time-to-death from date of diagnosis by age at diagnosis.

3.7.1.2 *Explanatory Variables*

Socio-demographic variables (age, year of diagnosis, country, ethnicity, educational level), stage at diagnosis, Human Epidermal Growth Factor Receptor 2 (HER2) status, Hormone receptor status (ER & PR), HIV status.

These variables (v) are described below:

a) Age
   - v '1' = <40 years
   - v '2' = 40-64 years
   - v '3' = 65 years++

b) Year of Diagnosis
   - v '1' = 2014
   - v '2' = 2015
   - v '3' = 2016
   - v '4' = 2017

c) Country

- ‘1’ = South Africa
- ‘2’ = Namibia
- ‘3’ = Nigeria
- ‘4’ = Uganda
- ‘5’ = Zambia

d) Ethnicity

- ‘1’ = Black
- ‘2’ = White
- ‘3’ = Mixed

e) Educational level

- ‘1’ = None
- ‘2’ = Primary
- ‘3’ = Secondary
- ‘4’ = Technical
- ‘5’ = University

f) Stage at Diagnosis

- ‘1’ = Stages 1 & 2
- ‘2’ = Stage 3
- ‘3’ = Stage 4

g) Subtype

- ‘1’ = LumA
- ‘2’ = LumB
- ‘3’ = HER2 positive (HER2+)
- ‘4’ = Triple Negative

h) Hormone Receptor Status

ER status: Binary variable with two outcomes:

- ‘0’ = ER negative (ER^-)
- ‘1’ = ER positive (ER+)

PR status: Binary variable with two outcomes:

- v '0' = PR negative (PR^-)
- v '1' = PR positive (PR+)

i) HER2 Status: A binary variable with two outcomes:
- v '0' = HER2 negative ($HER2^-$)
- v '1' = HER2 positive ($HER2^+$)

j) HIV: A binary variable with two outcomes:
- v '0' = Uninfected (HIV^-)
- v '1' = Infected (HIV^+)

k) Residence:
- v 1 = "Urban"
- v 2 = "Rural"

A comprehensive ABC-DO Data Dictionary is provided in Appendix II.

3.8 Data Analysis

STATA/SE 17 for Windows was used for statistical analyses.

3.8.1 Baseline Features of Study Participants

Baseline features (demographic and clinical) of study participants were presented using Descriptive Tables showing age at breast cancer diagnosis by year of diagnosis, country, ethnicity, educational level, stage at diagnosis, breast cancer subtype, estrogen and progesterone receptor status, and HIV status. All variables of interest were categorical variables, and as such, were described using percentages.

These baseline characteristics were compared among three groups of women by age group: women <40 years, 40-64 years and >65years; with a research focus on women <40 years. Women >65years were grouped separately to account for excess mortality in this age group due to other factors that may cause death in older people in general. Frequencies between age groups were compared using Pearson's chi-square test with p-values reported.

3.8.2 Survival Analysis

Survival analysis was carried out to determine the time-to-death from point of diagnosis of study participants. Survival was defined as the probability of being alive over a 5-year period from the date of diagnosis, while incidence rate was defined as the ratio of number of participants who died from breast cancer to the person-time at risk over a 5-year period. Study participants for whom the time-to-death was not observed at the 5-year mark were censored.

The analysis time was measured in years, with the time scale set to 365.25. Person-time at risk, incidence rate, number of deaths and number of censored participants were subsequently calculated up till the 5-year period.

Not all study participants were recruited on the exact date of their breast cancer diagnosis, some entered the study at the time of baseline interview (after diagnosis). As such, the origin of follow-up (time zero) was not the entry time for all women, and this was reflected in the Kaplan Meier survival curves, with number of women at risk not being equal to overall number of women in the study at time zero (time=0).

Survival time (time-to-death over a 5-year period from the point of diagnosis**),** overall survival probability by age group and survival probability by age group per country were computed using Kaplan-Meier estimates. Crude Kaplan Meier curves were plotted to estimate survival functions followed by log-rank test for equality of survivor functions across strata.

3.8.3 Cox Proportional Hazards Regression Analysis

Cox proportional hazards (PH) regression was used for the identification of factors associated with a 5-year survival differential between younger (<40) and older (>40) women, while accounting for excess mortality in women >65years.

Univariate Cox Modelling was carried out with a baseline adjustment for country for each variable. This was followed by Multivariate Cox Modelling with a sequential approach, and adjusted relative hazards presented to account for confounding. Hazards ratio estimates and their corresponding 95% Confidence Intervals were presented. Prior to carrying out Cox Modelling, STATA's *"stsplit"* command was used to generate data for follow-up to 5 years, so as to capture all the at-risk time of women in this timespan.

A test of the proportional hazards' assumption was carried out by means of Schoenfeld residuals to check final model's goodness of fit.

3.9 Ethical Considerations

Written permission for the utilization of ABCDO data was gotten from co-Principal Investigators of the study (Appendix III). Prior to receiving this dataset, a 6-digit unique ID was used to code each study participant, and all personal details were taken out of the dataset to maintain anonymity of participants. Ethical clearance was received from the Human Research Ethics Committee (Medical), University of the Witwatersrand (Clearance Certificate Number: M2111130; Appendix IV), after approval of the title of this research report (Appendix V).

CHAPTER FOUR: RESULTS

4.1 Introduction

In Chapter Four, a detailed summary of results is presented. Baseline attributes of study participants by age at diagnosis are reported. Breast cancer survival time is estimated using Kaplan Meier curves, and risk factors associated with a 5-year survival differential between younger and older women are summarized via Cox Regression Analysis.

4.2 Study Participants' Baseline Characteristics

This study comprised of 2158 participants, 462 (21.41%) were <40 years at diagnosis, 1314 were between 40-64years (60.89%) – constituting the highest number of study participants, while 382 patients were 65 years and above (17.70%).

Of the 2158 study participants, a total of 1211 deaths were recorded at 5 years, 438 women were administratively censored, while 509 women were still at risk after 5 years. The total time at risk and mortality incidence rate for the study population at 5 years was 6086.73 person years and 33 per 100 women respectively.

Only 57.32% of participants had subtyping for breast cancer done and most of these women were from South Africa and Namibia.

Tables 4.1 and 4.2 respectively show the participants baseline demographic and clinical characteristics; while in Figure 4.2, the age distribution by subtype is shown.

Table 4.1: Baseline Demographic Characteristics of Study Participants by Age at Diagnosis

Demographic Characteristics						P value
Year of Diagnosis (N=2158)						
Age at diagnosis	**2014** n (%)	**2015** n (%)	**2016** n (%)	**2017** n (%)		0.32
<40	27 (26.2)	170 (23.7)	171 (19.7)	94 (19.9%)		
40-64	58 (56.3)	434 (60.4)	532 (61.5)	290 (61.4%)		
65+	18 (17.5)	114 (15.9)	162 (18.8)	88 (18.7%)		
Total	103 (100)	718 (100)	865 (100)	472 (100)		
Country (N=2158)						
Age at diagnosis	**South Africa** n (%)	**Zambia** n (%)	**Namibia** n (%)	**Uganda** n (%)	**Nigeria** n (%)	**<0.001**
<40	102 (15.1)	55 (27.6)	88 (18.4)	115 (27.4)	102 (26.4)	
40-64	416 (61.6)	109 (54.8)	287(60.2)	257 (61.2)	245 (63.3)	
65+	157 (23.3)	35 (17.6)	102(21.4)	48 (11.4)	40 (10.3)	
Total	675 (100)	199 (100)	477 (100)	420 (100)	387 (100)	
Ethnicity (N=2158)						
Age at diagnosis		**Black n (%)**	**White** n (%)	**Mixed race (74)** n (%)		**<0.001**
<40		447 (22)	2 (3.3)	13 (17.6)		
40-64		1227 (60.7)	38 (63.4)	49 (66.2)		
65+		350 (17.3)	20 (33.3)	12 (16.2)		
Total		2024 (100)	60 (100)	74 (100)		
Educational Status (N=2158)						

Age at diagnosis	None	Primary	Secondary	Technical	University	Unknown	<0.001
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
<40	22 (7.1)	114(14.0)	173 (30.5)	70 (28.6)	56 (38.9%)	27 (34.2%)	
40-64	146(47.2)	524(64.5)	355 (62.5)	155 (63.3)	84 (58.3%)	50 (63.3%)	
65+	141(45.7)	175(21.5)	40 (7)	20 (8.1)	4 (2.8%)	2 (2.5%)	
Total	309(100)	813(100)	568 (100)	245 (100)	144 (100)	79 (100)	

Table 4.2: Baseline Clinical Characteristics of Study Participants, by Age at Breast Cancer Diagnosis (N=2158)

Characteristics	N (%)	<40 years N=462 n (%) (21.41)	40-64 years N=1314 n (%) (60.89)	65years+ N=382 n (%) (17.7)	P value
Stage at diagnosis					
I/II	843 (39.1)	151 (32.7)	521 (39.6)	171(44.8)	**0.006**
III	940 (43.5)	221 (47.8)	558 (42.5)	161(42.1)	
IV	295 (13.7)	65 (14.1)	191 (14.5)	39 (10.2)	
Missing	80 (3.7)	25 (5.4)	44 3.3)	11(2.9)	
TOTAL	2158(100)	462 (100)	1314 (100)	382 (100)	
Subtype					
LumA	686 (31.8)	122 (26.4)	406 (30.9)	158(41.4)	**0.023**
LumB	259 (12.0)	57 (12.3)	154 (11.7)	48 (12.6)	
HER2+	75 (3.4)	19 (4.1)	37 (2.8)	19 (5.0)	
TripNeg	217 (10.1)	25 (5.4)	144 (11.0)	48 (12.6)	
Unknown	921 (42.7)	239 (51.7)	573 (43.6)	109(28.5)	
TOTAL	2158(100)	462 (100)	1314 (100)	382 (100)	
Estrogen Receptor					
Positive	914(42.3)	172 (37.2)	546 (41.6)	196(51.3)	0.29
Negative	360(16.7)	55 (11.9)	220 (16.7)	85 (22.3)	
Missing	884(41.0)	235 (50.9)	548 (41.7)	101(26.4)	
TOTAL	2158(100)	462 (100)	1314 (100)	382 (100)	
Progesterone Receptor					
Positive	808(37.4)	153 (33.1)	479 (36.5)	176(46.1)	0.45
Negative	454(21.1)	73 (15.8)	279 (21.2)	102(26.7)	

Missing	896(41.5)	236 (51.1)	556 (42.3)	104(27.2)	
TOTAL	2158(100)	462(100)	1314(100)	382(100)	
HIV Status					
Positive	317(14.7)	78 (16.9)	226(17.2)	13 (3.4)	**<0.001**
Negative/Unknown	1841(85.3)	384(83.1)	1088(82.8)	369(96.6)	
TOTAL	2158(100)	462(100)	1314(100)	382(100)	

p-value gotten from Pearson chi-square for statistical difference within groups, significant at $p<0.05$. All significant values in bold face.

4.2.1 Baseline Characteristics of Study Participants by Age-Stage Distribution

Women below 40 years in this analysis had the least proportion of early-stage (Stages 1 &2) diagnosis (32.7%), when compared to the older age groups (39.6% for ages 40-64 years & 44.8% for 65years+), with early-stage diagnosis increasing progressively with age (Figure 4.1). Furthermore, most women in the <40 years group were diagnosed at Stage 3 (47.8%), and this accounted for the highest proportion of women across all groups diagnosed at this stage.

Across all age groups, the least number of participants were diagnosed at Stage 4.

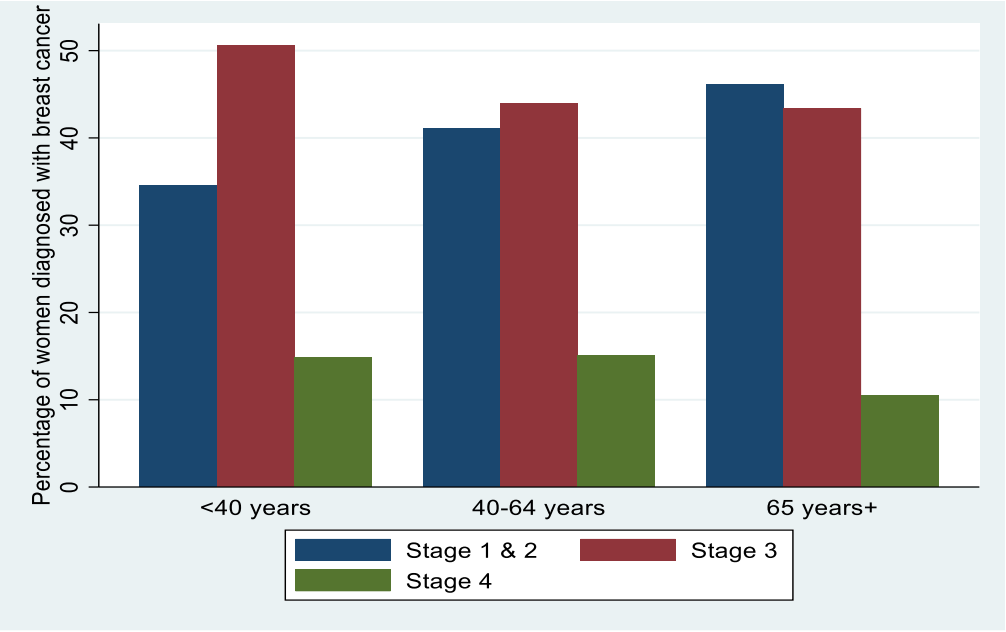


Figure 4.1: Bar Chart Depicting Stage Distribution of Breast Cancer among participants by age at diagnosis

4.2.2 Baseline Characteristics of Study Participants by Age-Subtype Distribution

Across all age groups, Luminal A subtype was most predominant (54.71%, 54.79% and 57.87% respectively in women <40 years, 40-64 years and 65years+ respectively), followed by Luminal B, Triple Negative and HER2+ subtypes respectively (Figure 4.2).

Women <40 years had the lowest proportion of triple negative tumors (11%), when compared to middle aged women between 40-64 years, for whom the number of triple negative tumors were close to 20%. Although the least represented subtype across all age groups, HER2+ subtype was commonest in participants <40 years.

The above findings were significant, with a p value < 0.05 (p=0.023)

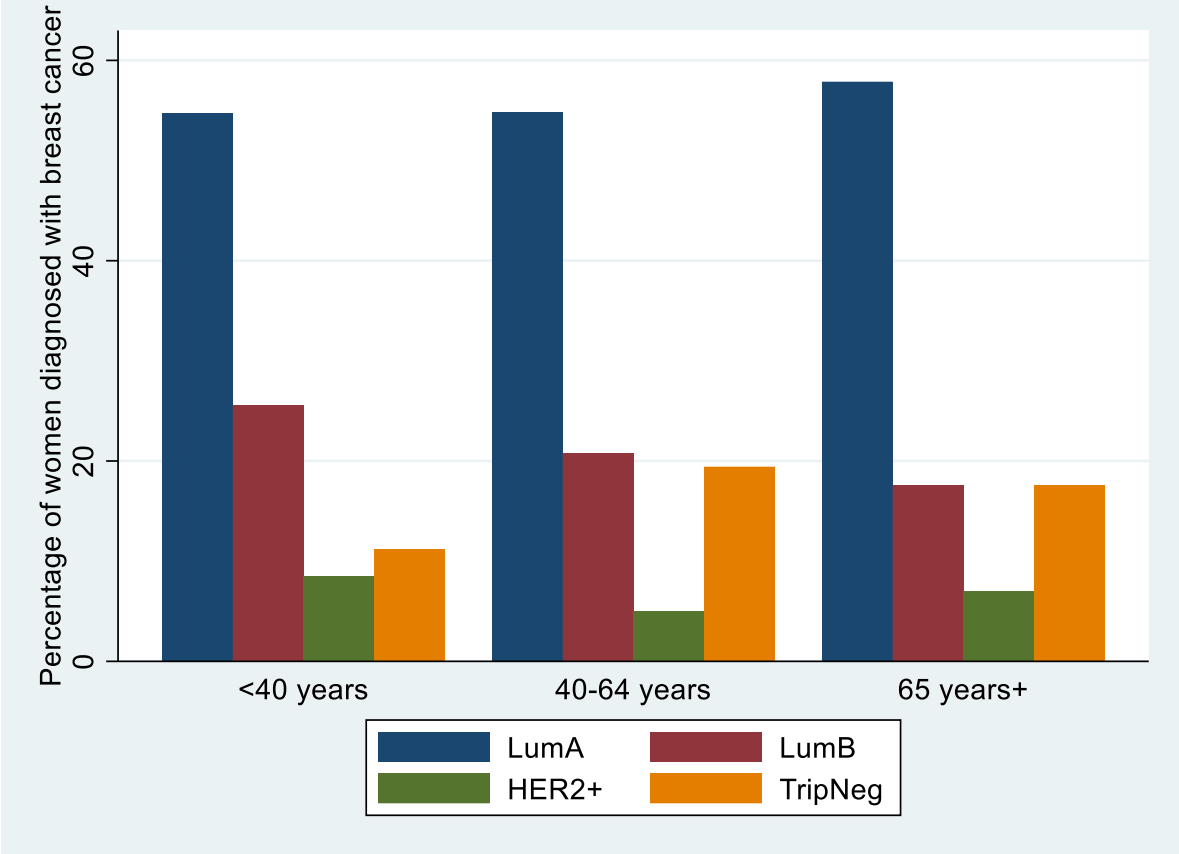


Figure 4.2: Bar Chart Depicting Subtype Distribution of Breast Cancer among participants by age at diagnosis

4.3 Overall Breast Cancer Survival (by Age Group) of Study Participants

Table 4.3 below shows the Kaplan Meier survivor functions by age group at 5 years.

After being followed up for 5 years, out of the 2158 total participants at the start of the study, 509 women were at risk of death (i.e., women with breast cancer still alive at this point), out of which 54 died and 455 were censored.

Lowest overall survival at 5 years was found among women <40 years (33%; CI of 0.28-0.38), followed by women aged 65 years+ (38%; CI of 0.32-0.42), and the highest overall survival was among women in the 40-64 years age group (42%; CI=0.39-0.45)

Table 4.3: Kaplan Meier 5-Year Survival by Age Group of Study Participants (N=2158)

Age group (years)	Total no. of women (N=2158)	No at risk till 5 years (N=1649)		No at risk after 5 years (N=509)	5-year survival	95% CI
		No of deaths at 5 years (N=1211)	No censored at 5 years (N=438)			
<40	462	286	81	95	0.33	(0.28-0.38)
40-64	1314	702	274	338	0.42	(0.39-0.45)
65 +	382	223	83	76	0.38	(0.32-0.42)

Further graphical representation of 5-year survival is depicted by the Kaplan Meier survival curves in Figure 4.3.

4.3.1 Kaplan Meier Survival Curves by Age Group At 5 Years

In keeping with findings reported in Table 4.3, the Kaplan Meier survival shown below (Figure 4.3) suggests that the probability of survival after being followed up for 5 years was lowest among study participants <40 years; followed by those aged 65+ years, while participants aged 40-64yrs had the highest survival probability.

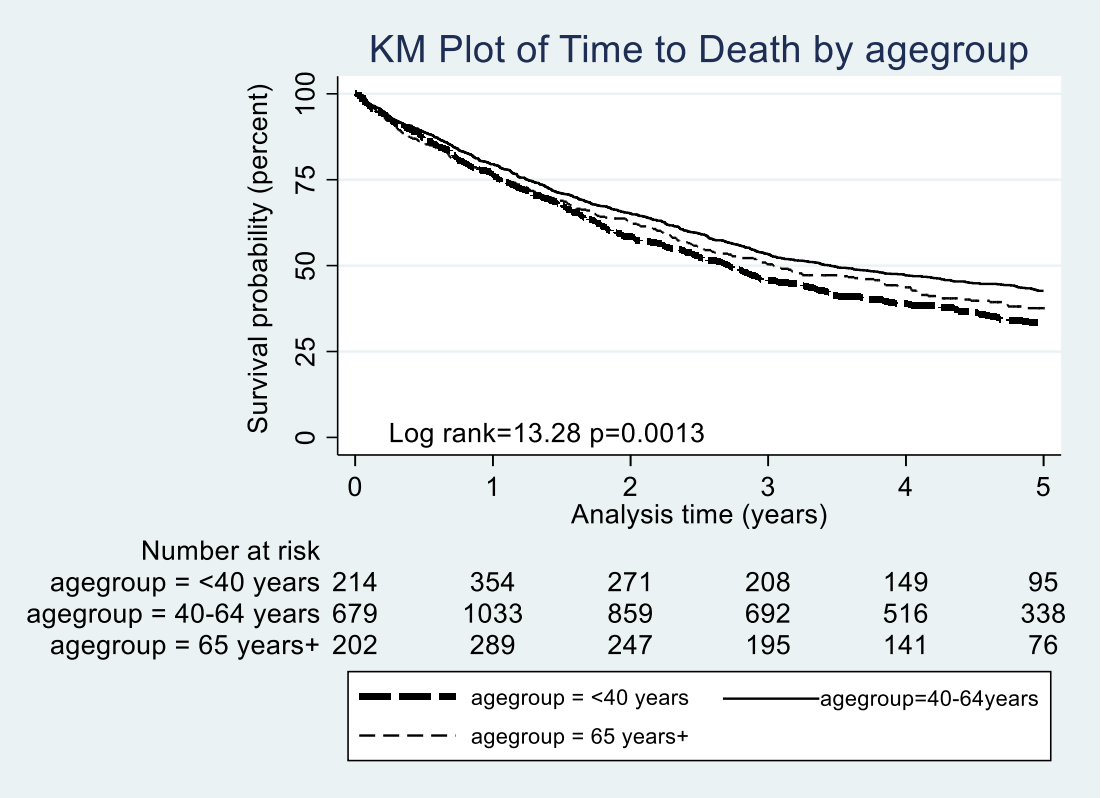


Figure 4.3: Kaplan-Meier Survival Curve Showing time-to-death by Age Group

Since the time-to-death findings above are inclusive of all countries where the study data emanated from, further investigation on survival was carried out for each country to identify any notable differences.

4.4 Breast Cancer Survival by Age Group of Study Participants Per Country

The Kaplan Meier survival function tables and curves shown below depict survival after 5-years for each age group by country.

4.4.1 Breast Cancer Survival by Age Group of Study Participants for South Africa

Table 4.4 below depicts the Kaplan Meier survivor functions by age group for South African participants at 5 years.

After being followed up for 5 years, out of the 675 participants at the start of the study, 330 women died, 281 were censored while 64 women remained at risk of death.

Lowest overall survival at 5 years was found among women 65+ years (40%; CI of 0.30-0.50), followed by women aged <40 years (45%; CI of 0.33-0.55), and the highest overall survival was among women in the 40-64 years age group (48%; CI=0.42-0.53).

Table 4.4: Kaplan Meier 5-Year Survival by Age Group of Study Participants for South Africa (N= 675)

Age group (years)	Total no. of women (N=675)	No at risk till 5 years (N=611)		No at risk after 5 years (N=64)	5-year Survival	95% CI
		No of deaths at 5 years (N=330)	No censored at 5 years (N=281)			
<40	102	52	38	12	0.45	(0.33-0.55)
40-64	416	176	196	44	0.48	(0.42-0.53)
65 +	157	82	67	8	0.40	(0.30-0.50)

Based on the Kaplan-Meier curve in Figure 4.4 below, the 5-year survival probability among South African women was highest in participants aged 40-64years, followed by those aged <40 years, while the lowest survival probability was among participants aged 65 years and above. The log rank test revealed no statistical difference in survival distributions for the three groups (log rank Chi square of 1.64 on two degrees of freedom at p=0.4395). However, incidence of death was higher than expected among participants <40 years (52 observed cases compared to 48.55 expected cases).

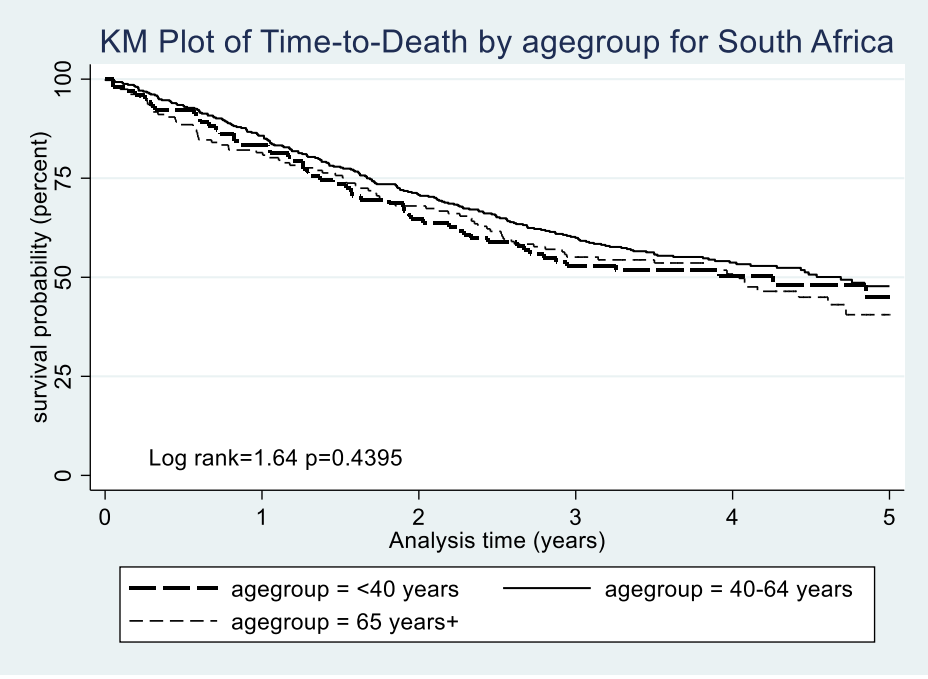


Figure 4.4: Kaplan-Meier Survival Curve Showing time-to-death by Age Group for South Africa

4.4.2 Breast Cancer Survival by Age Group of Study Participants for Zambia

In Table 4.5, the Kaplan Meier survivor functions by age group for Zambian participants at 5 years is shown.

After being followed up for 5 years, out of 199 women, 114 died, 50 were censored while 34 women remained at risk of death.

Highest overall survival was among women <40 years (42%; CI=0.28-0.55), followed by women aged 40-64 (37%; CI=0.27-0.46), with lowest overall survival recorded in women 65years+ (8%; CI=0.14-0.44).

Table 4.5: Kaplan Meier Survivor Functions at 5 years by Age group of study participants for Zambia (N= 199)

Age group (years)	Total no of women (N=199)	No at risk till 5 years (N=164)		No at risk after 5 years (N=35)	5-year Survival	95% CI
		No of deaths at 5 years (N=114)	No censored at 5 years (N=50)			
<40	55	29	16	10	0.42	(0.28-0.55)
40-64	109	61	30	18	0.37	(0.27-0.46)
65 +	35	24	4	7	0.08	(0.14-0.44)

The Kaplan Meier curve of time-to-death by age group for Zambia (Figure 4.5) shows the highest 5-year probability of survival among participants <40 years and lowest in the 65 years+ age group. The log rank test showed equality of survivor functions i.e., no statistical difference in survival distributions for the three groups (log rank Chi square of 2.35 on two degrees of freedom at p=0.3084).

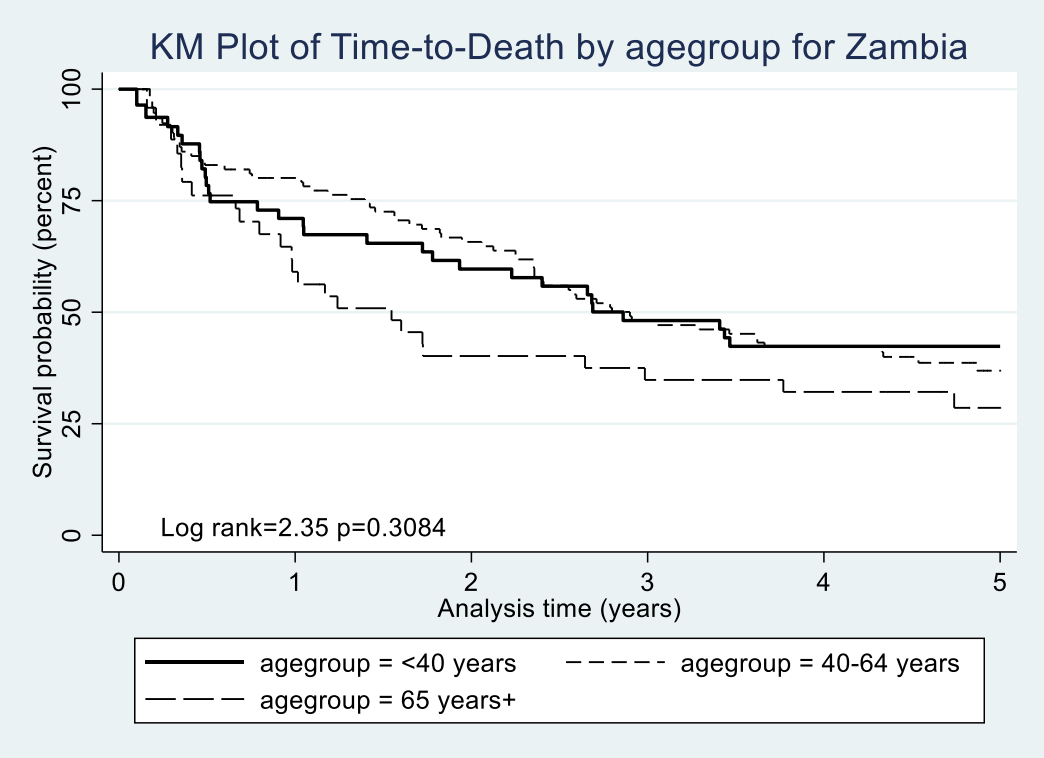


Figure 4.5: Kaplan-Meier Survival Curve Showing time-to-death by Age Group for Zambia

4.4.3 Breast Cancer Survival by Age Group of Study Participants for Namibia

Table 4.6 shows the Kaplan Meier survivor functions by age group for Namibian participants at 5 years.

After being followed up for 5 years, out of 477 women, 215 died, 18 were censored while 244 women remained at risk of death.

Highest overall survival was among women aged 40-64 (57%; CI=0.50-0.62), followed by women <40 years (46%; CI=0.35-0.56), with lowest overall survival recorded in women 65years+ (45%; CI=0.35-0.54).

Table 4.6: Kaplan Meier Survivor Functions at 5 years by Age group of study participants for Namibia (N= 477)

Age group (years)	Total no of women (N=477)	No at risk till 5 years (N=233)		No at risk after 5 years (N=244)	5-year Survival	95% CI
		No of deaths at 5 years (N=215)	No censored at 5 years (N=18)			
<40	88	45	5	38	0.46	(0.35-0.56)
40-64	287	117	9	161	0.57	(0.50-0.62)
65 +	102	53	4	45	0.45	(0.35-0.54)

Figure 4.6 shows the Kaplan Meier curve of time-to-death by age group for Namibia. The highest 5-year probability of survival among participants in the 40-64years age group, with an overlap in survival probability among those <40 years and 65years+. However, the log rank test revealed statistical difference in survival distributions among the three groups (log rank Chi square of 9.07 on two degrees of freedom at p=0.0107).

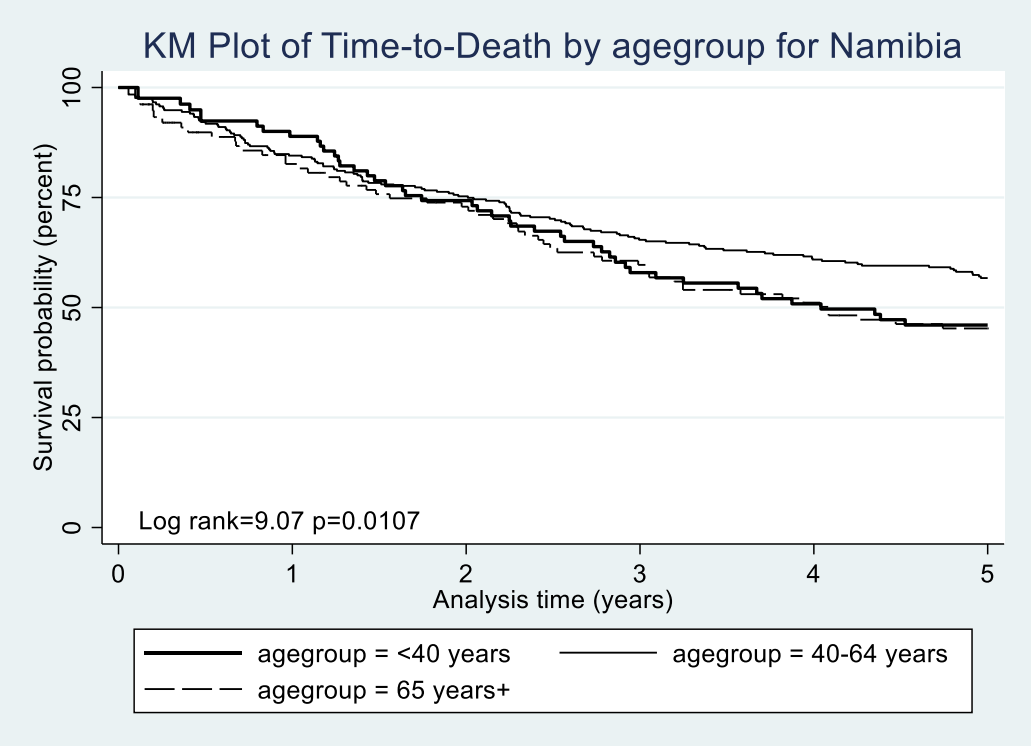


Figure 4.6: Kaplan-Meier survival curve showing time-to-death by Age Group for Namibia

4.4.4 Breast Cancer Survival by Age Group of Study Participants for Uganda

Table 4.7 shows the Kaplan Meier survivor functions by age group for Ugandan participants at 5 years.

After being followed up for 5 years, out of 420 women, 272 died, 37 were censored while 111 women remained at risk of death.

Highest overall survival was among women aged 40-64 (33%; CI=0.27-0.39), followed by women 65years+ (32%; CI=0.19-0.45), with lowest overall survival recorded in women <40 years (26%; CI=0.17-0.34).

Table 4.7: Kaplan Meier Survivor Functions at 5 years by Age group of study participants for Uganda (N= 420)

Age group (years)	Total No of women (N=420)	No at risk till 5 years (N=309)		No at risk after 5 years (N=111)	5-year Survival	95% CI
		No of deaths at 5 years (N=272)	No censored at 5 years (N=37)			
<40	115	80	11	24	0.26	(0.17-0.34)
40-64	257	161	21	75	0.33	(0.27-0.39)
65 +	48	31	5	12	0.32	(0.19-0.45)

For Uganda, the Kaplan Meier curve of time-to-death by age group (Figure 4.7) showed almost equal 5-year survival probability for participants in the 40-64years & 65years+ age groups, with a lower survival probability for those in the <40years age group. The log rank test, however, did not show any statistical difference in survival distributions among the three groups (log rank Chi square of 2.19 on two degrees of freedom at p=0.3341).

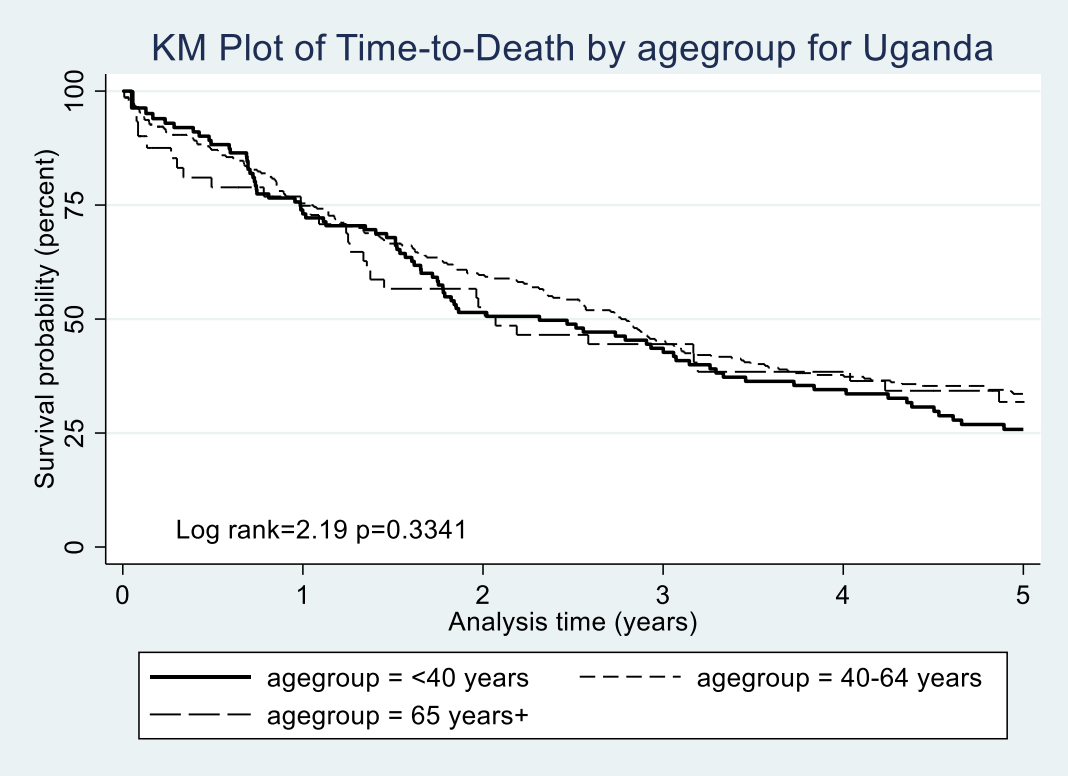


Figure 4.7: Kaplan-Meier Survival Curve showing time-to-death by Age Group for Uganda

4.4.5 Breast Cancer Survival by Age Group of Study Participants for Nigeria

In Table 4.8, the Kaplan Meier survivor functions by age group for Nigerian women is shown.

After a follow-up period of 5 years, out of 387 women, 280 died, 52 were censored while 55 women remained at risk of death.

Highest overall survival was among women aged 40-64 (28%; CI=0.22-0.34), followed by women <40 years (18%; CI=0.22-0.34), with lowest overall survival recorded in women 65years+ (16%; CI=0.06-0.28).

Table 4.8: Kaplan Meier Survivor Functions at 5 years by Age group of study participants for Nigeria (N= 387)

Age group (years)	Total no of women (N=387)	No at risk till 5 years (N=332)		No at risk after 5 years (N=55)	5-Year Survival	95% CI
		No of deaths at 5 years (N=280)	No censored at 5 years (N=52)			
<40 years	102	80	11	11	0.18	(0.10-0.26)
40-64 years	245	167	38	40	0.28	(0.22-0.34)
65 years+	40	33	3	4	0.16	(0.06-0.28)

In Figure 4.8, the Kaplan Meier survival curve of time-to-death by age group in the Nigerian participants showed the highest 5-year survival probability in participants aged 40-64years, followed by those aged <40 years, and the lowest survival probability among participants aged 65 years and older. However, no statistical difference in survival distribution was noted among the three groups on the log rank test (log rank Chi square of 3.11 on two degrees of freedom at p=0.2111).

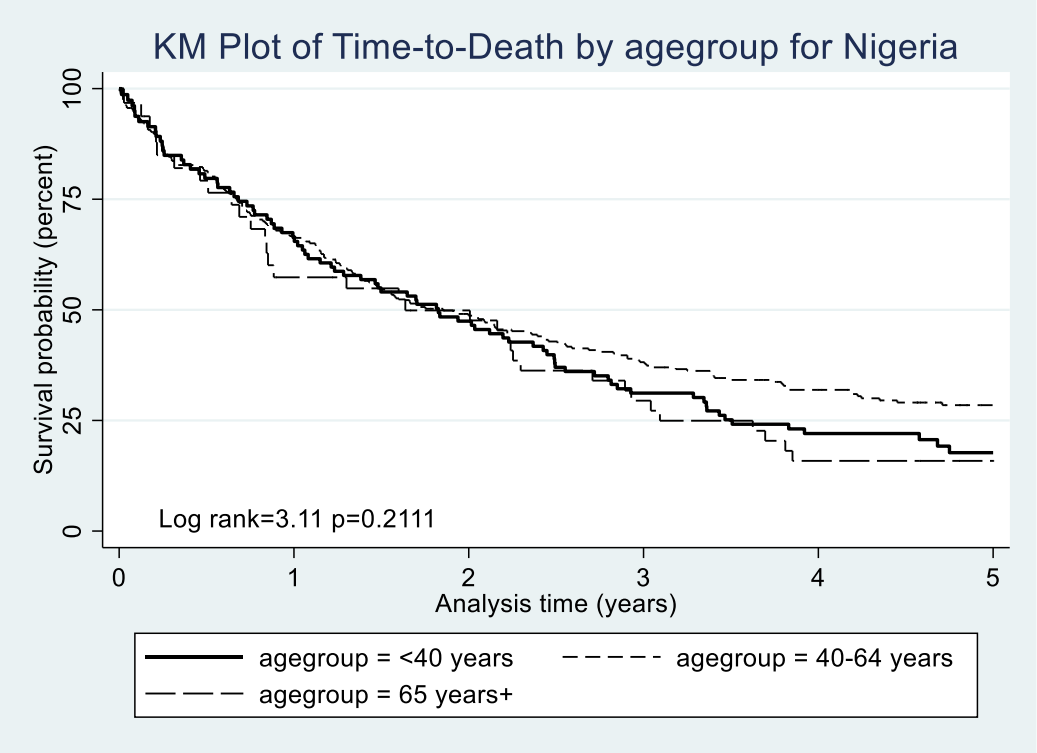


Figure 4.8: Kaplan-Meier Survival Curve showing Time-to-Death by Age Group for Nigeria

4.5 Cox Proportional Hazards Regression Analysis

To investigate which variables accounted for the lower survival in <40 compared to 40–64-year-old women, Cox Proportional Hazards Regression Analysis (Breslow method) was conducted. Unadjusted hazard ratios for univariate analysis, and adjusted hazard ratios for multivariate analysis (restricted to 5 years) were computed. Baseline adjustment for country was carried out on all variables in the univariate analysis to account for the multi-country nature of this study.

Table 4.9 presents the results of fitting the univariate model, with baseline adjustment for country carried out on all variables (since the study results were gotten from 5 different

countries). When compared to women between 40-64 years, women < 40 years with breast cancer had an 18% rise in mortality (HR 1.18; 95% CI= 1.03-1.36). On univariate analysis at $p<0.05$, variables significantly associated with 5-year survival differential between younger and older women were: HIV status, Educational status, Residence, Breast Cancer Subtype, and Stage at Diagnosis. Person years at risk (PYAR) and number of failures were reported for each of these variables.

Table 4.10 depicts the findings from fitting a multivariable Cox regression model with sequentially adjusted hazard ratios for age. A simple model with age alone as the exposure variable was used to estimate the HR for age, after which other factors; viz: country, HIV, ethnicity, residence, tumour stage and tumour subtype were sequentially added to the model whilst observing any change in HR as regards the effect of age on survival. The multivariable model showed significant differences in the adjusted HRs for age, with a 20% rise in mortality among women <40 years compared to those between 40-64 years in the final model (aHR of initial model: 1.18 (95% CI=1.03-1.36); aHR of final model: 1.20 (95% CI=0.97-1.49)). As such, there was some evidence that the factors adjusted for, as outlined above, slightly modified the survival differential by age in this study.

Table 4.9: Cox Proportional Hazards Model depicting Unadjusted Hazard Ratios for Factors associated with 5-Year Survival Differential (Univariate analysis)

Baseline adjustment for country was carried out on all variables

Characteristic	Number of women	Number of deaths	Person years at risk	Unadjusted HR (95% CI)	p-value
Agegroup	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.18 (1.03-1.36)	**0.016**
65yrs+				1.08 (0.93-1.26)	**0.004**
Educational status	2158	1211	6086.73		
No education				1.00	
Primary				0.70 (0.59-0.82)	**0.000**
Secondary				0.63 (0.53-0.76)	**0.000**
Technical				0.45 (0.36-0.57)	**0.000**
University				0.40 (0.30-0.53)	**0.000**
Missing				0.80 (0.57-1.14)	0.237
Residence	2158	1211	6086.73		
Urban				1.00	
Rural				1.26 (1.12-1.42)	**0.000**
Ethnicity	2158	1211	6086.73		
Black				1.00	
White				0.22 (0.11-0.43)	**0.000**
Mixed				0.66 (0.45-0.97)	**0.038**
Stage at diagnosis	2158	1211	6086.73		
Stage 1 & 2				1.00	
Stage 3				2.78 (2.41-3.22)	**0.000**
Stage 4				7.66 (6.44-9.11)	**0.000**
Missing				1.76 (1.28-2.42)	**0.000**
Subtype	1237*	598*	3856.65		
LumA				1.00	
LumB				1.23 (1.00-1.51)	0.405
HER2+				1.49 (1.07-2.08)	**0.017**
TripNeg				1.69 (1.38-2.08)	0.300
HIV Status	2158	1211	6086.73		
Negative				1.00	
Positive				1.34 (1.15-1.58)	**0.000**

significant at $p<0.05$. Significant values shown in bold face.

*Values drop to reflect the number of participants whose subtypes were unknown

Table 4.10: Cox Proportional Hazards Model depicting Sequentially Adjusted Hazard Ratios for Factors associated with 5-Year Survival Differential (Multivariate analysis)

Characteristic (Variables adjusted for in bracket)	**No of women**	**No of deaths**	**PYAR**	**Adjusted HR (95% CI)**	**P value**
Age group (country)	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.18 (1.03-1.36)	**0.016**
65yrs+				1.08 (1.07-1.45)	**0.004**
Age group (country + hiv)	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.18 (1.03-1.35)	**0.017**
65yrs+				1.32 (1.13-1.54)	**0.000**
Age group (country+ hiv + ethnicity)	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.16 (1.01-1.33)	**0.075**
65yrs+				1.34 (1.14-1.56)	**0.020**
Age group (country + hiv + ethnicity + residence)	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.18 (1.03-1.36)	**0.016**
65yrs+				1.30 (1.11-1.52)	**0.001**
Age group (country + hiv + ethnicity + residence + education)	2158	1211	6086.73		
40-64years				1.00	
<40 years				1.25 (1.09-1.45)	**0.053**
65yrs+				1.16 (0.98-1.36)	**0.071**

Age group (country + hiv + ethnicity + residence + education + stage)	2078*	1164*	5862.64		
40-64years				1.00	
<40 years				1.24 (1.08-1.44)	**0.003**
65yrs+				1.22 (1.03-1.44)	**0.017**

significant at p<0.05. Significant values shown in bold face.

*Values drop to reflect the number of participants whose stages were unknown

4.5.1 Testing Cox Proportional Hazard Assumption

Using the proportional hazards assumption test based on Schoenfeld residuals, the proportionality assumption was tested on the full sequentially adjusted multivariate model (Table 4.10), with results shown in Appendix VII. With a global p value >0.05, the proportionality assumption was not violated.

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

Breast cancer remains a serious health challenge, both globally and in SSA. Very few studies have estimated breast cancer survival rates in SSA. This chapter comprises a discussion and conclusion on main outcomes from this study in light of existing literature on breast cancer survival time estimation. This chapter also discusses factors associated with a 5-year survival differential for young women (<40 years) in the ABC-DO Cohort Study in SSA and describes the study's strengths and limitations.

5.2 Summary of Main Findings

This study reports a 33.46% overall breast cancer survival rate at 5 years for women <40 years. When broken down by country, Namibia had the highest overall survival (46.02%), followed by South Africa, Zambia, Uganda, and Nigeria respectively. Factors significantly associated with 5-year survival differential between women under 40 years and older women were: area of residence, stage of diagnosis and HIV status; while ethnicity, level of education, hormone receptor (ER, PR) status and breast cancer subtype were not significantly associated with 5-year overall survival.

One out of five women in this study was less than 40 years, resulting in a 21.41% incidence rate for breast cancer. Compared to the 6.4% incidence rate for women <40 years reported from the United States SEER study of over 200,000 women (Gnerlich *et al.*, 2009), the incidence rate reported in this study is much higher. Factors that may be responsible include the multi-country nature and the relatively lower number of participants in this study.

This study also reports comparatively lower overall survival among women <40 years compared to older women, which correlates with prior research results (Hartley *et al.*, 2006; Anders *et al.*, 2008). In SSA, projected 5-year survival estimates for women with breast cancer are near or lower than 50% (Joko-Fru *et al.*, 2020; McCormack *et al.*, 2020), while more developed countries show 5-year survival estimates of 85-90% (Brenner *et al.*, 2016; Allemani *et al.*, 2018). This trend is further corroborated by findings from this SSA study, where overall 5-year survival and all country-specific estimates are below 50%. With such low survival rates,

there is a serious need for solutions that target increased breast cancer survival among young women in SSA.

Three factors were associated with the 5-year survival differential between women <40 years and older women in this study; namely: area of residence, stage at diagnosis and HIV status. However, there was very little change in the Hazard Ratios for age on sequential adjustment. These results are somewhat in keeping with prior studies where women with concomitant breast cancer and HIV were diagnosed at younger ages (McCormack *et al.*, 2018; Chasimpha *et al.*, 2022) and stage at diagnosis (Gakwaya *et al.*, 2008) was a potent determinant of survival from breast cancer among young women in SSA.

Seeing as advanced disease stage at diagnosis has a negative impact on survival in sub-Saharan African women under 40 years, the need for downstaging cannot be overemphasized. This can be accomplished through targeted education of young women, and communities in SSA countries on early signs of breast cancer, as well as the urgent need to present at health facilities for prompt diagnosis and management (McCormack *et al.*, 2020). As the number of breast cancer patients who are HIV-positive continue to rise (McCormack *et al.*, 2018), further research is required, especially on HIV's impact among young breast cancer patients and specific management strategies aimed at improving survival among this population. In addition, residing in an urban area might positively influence presentation of patients with breast cancer to treatment centres.

5.3 Study Limitations

This study has some noteworthy limitations, which are discussed in this section.

Since this study involved secondary data analysis, the data collection and screening process of the primary researchers was completely depended on, thereby streamlining the research objectives of this study.

Again, since survival estimates were only recorded from women who present at treatment centres, it is hard to extrapolate this study's findings to all countries from which data was sourced, as well as the entire sub-Saharan African populace. Unfortunately, survival estimates might be a lot worse among breast cancer patients that fail to present at the hospital. Lastly, censoring is a challenge experienced on survival analysis, and this study was not exempted from it.

5.4 Strengths of the Study

Despite this study's limitations, it provides insight into the impact of age-at-diagnosis on breast cancer survival in 5 countries in sub-Saharan Africa, with a sufficient sample size to power the analysis and suitable adjustment for confounders. With these factors in mind, a reasonable conclusion that survival of breast cancer patients <40 years is consistently less than survival among women aged 40-65 years is reached. The multi-country nature of this study also gives it good generalizability.

5.6 Conclusion

The key conclusion from this report is that breast cancer survival in SSA is age-specific, with lower 5-year overall survival among women < 40 years in comparison to older women. Breast cancer survival was also lower in all understudied countries (South Africa, Zambia, Namibia, Uganda, Nigeria) for women <40 years when compared to older women. Factors independently associated with lower survival on univariate analysis include stage at diagnosis, HIV status, area of residence and educational status. Breast cancer in young African women, therefore, remains a cause concern and as such, community-driven policy efforts that target education, screening, and early treatment should be put in place to reduce the survival disparities between younger and older women with breast cancer.

5.7 Recommendations

Considering the above findings, improved breast cancer screening of women <40 years in SSA to identify and manage earlier stages of the disease, and better HIV screening and management among young women with breast cancer in SSA are recommended, to target lower survival indices among this sub-populace.

Further recommendations include well-funded research on young women with breast cancer in African nations, aimed at providing more robust database on their survival and factors influencing it, and specific policies put in place to promote awareness and availability of breast cancer screening and treatment facilities for young women.

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APPENDICES

APPENDIX I: PLAGIARISM DECLARATION FORM



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Oyepeju Folashade Abioye (Student number: 2465583) am a student registered for the degree of MSc EPIDEMIOLOGY (Epidemiology & Biostatistics) in the academic year 2021/2022.

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: 20th October, 2022

1

APPENDIX II: ABCDO DATA DICTIONARY

Variable	Variable Label	Variable Value
PID	Patient ID Number	
date_bl	Date of Interview	08/09/2014– 29/12/2017
date_exit_t0	Date of Exit from Study	13/12/2014– 23/12/2021
agegroup	Age group of participants	1= "<40"
		2= "40-64"
		3= "65+"
education	Highest level of education	1 = "None"
		2 = "Primary"
		3 = "Secondary"
		4 = "Technical"
		5 = "University"
sitename	Country of study	1 = "South Africa"
		2 = "Zambia"
		3 = "Namibia"
		4 = "Uganda"
		5 = "Nigeria"
Relationship	Relationship status (current)	1 = "Married"
		2 = "Divorced"
		3 = "Widowed"
		4 = "Single"
		5 = "Other cohabitation"
		6 = "Other"
urban	Area of residence	1 = "Urban"
		2 = "Rural"
erstatus	Estrogen receptor status	1 = "Negative"
		2 = "Positive"
prstatus	Progesterone receptor status	1 = "Negative"
		2 = "Positive"
Her2status	What is the HER2 status?	1 = "Negative"
		2 = "Positive"
HIV	Have you ever been diagnosed with HIV?	1 = "Negative/Unknown"
		2 = "Positive"
Stage	What is the stage at diagnosis?	1 = "Stage 1 & 2"
		2 = "Stage 3"
		3 = "Stage 4"
Ethnicity	What is the participant's ethnicity?	1 = "Black"
		2 = "White"

		3 = “Mixed”
fhx	Has anyone in the family ever had breast cancer?	0 = “No” 1 = “Yes” 2 = “Don’t know”
subtype	Breast cancer subtype	1 = “LumA” 2 = “LumB” 3 = “HER2+” 4 = “TripNeg”

APPENDIX III: PERMISSION TO USE THE ABC-DO DATASET

International Agency for Research on Cancer
World Health Organization

150 cours Albert Thomas
69372 Lyon CEDEX 08, France
Environment and Lifestyle Epidemiology Branch
Tel: +33 4 72 73 85 66
Fax: +33 4 72 73 83 94
E-mail: mccormackv@iarc.fr
Web: www.iarc.fr

Dr Oyepeju Abioye
MSc Epidemiology & Biostatistics student
Witwatersrand University
Gauteng
South Africa

07 November 2021

Dear Oyepeju,

Re: Permission for data access to the African Breast Cancer Disparities in Outcomes study data for MSc Thesis

As co-PIs of the African Breast Cancer Disparities in Outcome study (ABC-DO https://abc-do.iarc.who.int/), we herein grant you permission to access anonymised data from ABC-DO for the purpose of a comparison of breast cancer survival in young (<40 years) women and older women in sub-Saharan Africa. Data will be shared with you via a safe password protected file transfer protocol site provided by IARC.

The dataset to be shared will contain individual-level data on women, but all personal details such as names, address and free-text fields which might contain personal information will not be shared. A 6-digit study participant ID will be included to identify unique women in the study. The data will be transferred to you, Oyepeju, and should not be shared with any other individual or party other than your university MSc thesis supervisor if necessary, who cannot share the data with other individuals. The data we transfer to you is to be destroyed once the publications are in press.

We will soon send you a data transfer agreement to sign prior to any data transfers.

Valerie McCormack is the data keeper at IARC (and co-PI), where data are stored on IARC secure servers. No biological specimen will be shared. The data to be shared will include sociodemographic data, clinical characteristics, survival data and basic treatment data.

We very much look forward to working with you on this analysis and the resulting publication.

Yours sincerely,

ABC-DO co-Principal Investigators

Valerie McCormack, PhD
IARC Environment and Lifestyle Epidemiology

Prof Isabel dos Santos Silva
London School of Hygiene &Tropical Medicine

APPENDIX IV: WITS HUMAN RESEARCH ETHICS COMMITTEE CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr O Abioye

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2111130

NAME: (Principal Investigator)	Dr O Abioye
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Breast cancer survival to 5 years amongst young (<40 years) women in the Sub-Saharan African Breast Cancer Disparities in Outcome (ABC-DO) cohort study*
DATE CONSIDERED:	2021/11/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/03/02

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 04/03/2022

Date: 05/03/2022

APPENDIX V: APPROVAL OF RESEARCH TITLE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

19 November 2021
Person No: 2465583
PAG

Dr OF Abioye
9 Princess Place
Parktown
Parktown North
2193
South Africa

Dear Dr Oyepeju Abioye

Master of Science in Epidemiology: Approval of Title

We have pleasure in advising that your proposal entitled *Breast cancer survival to 5 years among young (<40 years) women in the sub-Saharan African Breast Cancer ¿ Disparities in Outcome (ABC-DO) cohort study* 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 VI: TEST OF PROPORTIONAL HAZARDS ASSUMPTION

Characteristic	rho2	chi2	df	Prob>chi2
Agegroup (2)	0.03904	1.79	1	0.1807
Agegroup (3)	0.00143	0.00	1	0.9612
Country (2)	-0.08160	7.85	1	0.0051
Country (3)	-0.02604	0.79	1	0.3741
Country (4)	-0.01518	0.27	1	0.6052
Country (5)	-0.07139	5.82	1	0.0158
HIV (1)	-0.04458	2.27	1	0.1319
Race (2)	0.01951	0.45	1	0.5045
Race (3)	-0.02254	0.59	1	0.4419
Education (2)	0.01488	0.25	1	0.6177
Education (3)	-0.01489	0.26	1	0.6113
Education (4)	0.05399	3.27	1	0.0708
Education (5)	-0.03263	1.20	1	0.2732
Education (6)	0.00299	0.01	1	0.9191
Stage (2)	-0.05531	3.56	1	0.0590
Stage (3)	-0.13238	19.46	1	0.0000
Global Test		**47.84**	**16**	**0.2672**

APPENDIX VII: TURNITIN REPORT

Signed J Kagura

2465583 RESEARCH REPORT OCTOBER 2022.pdf

ORIGINALITY REPORT

12%	9%	10%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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