BURDEN AND TRENDS IN CANCERS OF THE BREAST IN SUB-SAHARAN AFRICA

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DEDICATION

To the memory of my grandmothers,

Walburga Emily Zi Ukanwoke, whose life with breast cancer, taught me so much

and

“Dada” Mary Philomena Ejem Wango, who encouraged me always, but never lived on to see me finish.

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ABSTRACT

Despite breast cancer (BC) being the most common cancer in sub-Saharan Africa (SSA), there is insufficient evidence on its temporal trends across the continent, and on reasons for differences in the cancer burden observed. This thesis sets out to describe the BC burden and trends in SSA. Specifically, it aims at describing incidence trends and survival patterns across SSA using population-level cancer registry data from the African Cancer Registry Network and to summarise the aetiologic research from SSA.

The temporal trends in BC incidence rates in women from 10 SSA countries over the last 15 years are described. There are rising incidence rates in all registries; however, these temporal trends are of different magnitudes. Trends in registries with the longest temporal data show rising incidence rates across successive birth cohorts of women aged 45+.

Reasons for the differences observed in the incidence trends are explored. A systematic review was carried out summarising the evidence from SSA on reproductive, anthropometric, and lifestyle risk factors. The associations observed are similar to Western studies, however, quality aetiological research has been conducted in less than 75% of SSA countries. The population-level prevalence of these risk factors are described.

The short-term relative survival outcomes of women diagnosed with BC across 12 African countries are also estimated. There are large survival differences across the continent. Late-stage at diagnosis and limited access to quality care are drivers of survival differences. More than two-thirds of women present at stages III/IV, and approximately 50% of women with non-metastatic BC receive inadequate or no cancer-directed therapy. However, there are challenges of incomplete records and high rates of loss to follow-up.

In conclusion, the BC burden is rising in SSA. It is imperative to improve timeliness of diagnosis, access to care, aetiologic research, and the quality of cancer surveillance.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES:

TABLES

FIGURES

LIST OF ABBREVIATIONS

AA	African American
AAM	Age at menarche
AAPC	Average annual percentage change
ABC-DO	African Breast Cancer - Disparities in Outcomes
AFB	Age at first birth
AFCRN	African Cancer Registry Network
AFFP	Age at first full-term pregnancy
AJCC	American Joint Committee on Cancer
AMBER	African American Breast Cancer Epidemiology and Risk
ANM	Age at natural menopause
AOR	Adjusted odds ratio
ASIR	Age-standardised incidence rate
ASRS	Age-standardised relative survival
BBD	Benign breast disease
BC	Breast cancer
BMI	Body mass index
BRCA	Breast cancer gene
BWHS	Black Women's Health Study
CBE	Clinical breast examination
CC-BY	Creative Commons Attribution licence
CDT	Cancer-directed therapy
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CIV	Côte d'Ivoire
COC	Combined oral contraceptives
CONCORD	Global surveillance of cancer survival
COSMOS-E	Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology
CT	Computerised tomography
DALY	Disability-adjusted life-year
DCO	Death certificate only
DDT	Dichloro-diphenyl-trichloroethane
DHS	Demographic and Health Surveys
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECCR	Eastern Cape Cancer Registry
ECOG	Eastern Cooperative Oncology Group
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen-receptor
GBD	Global Burden of Disease
GICR	Global Initiative for Cancer Registry Development in Low- and Middle-Income countries
GLOBOCAN	Global Cancer Incidence, Mortality, and Prevalence
HBCR	Hospital-based cancer registry
HDI	Human Development Index
HER-2	Human epidermal growth factor receptor-2

HR	Hormone receptor
HRS	Hormone receptor status
IARC	International Agency for Research on Cancer
ICD-O	International Classification of Diseases for Oncology
ICSS	International Cancer Survival Standard
IGF	Insulin-like growth factor
IHC	Immunohistochemistry
KCR	Kampala Cancer Registry
LFU	Loss to follow-up
LMIC	Low- and middle-income countries
MAM	Mean age at menopause
MET	Metabolic equivalent
MHT	Menopausal hormone therapy (MHT)
MIR	Mortality-to-incidence ratio
NBCS	Nigerian Breast Cancer Study
NCCN	National Comprehensive Cancer Network
NCCP	National Cancer Control Plan
NCD	Non-communicable disease
NST	No special type
PBCR	Population-based cancer registry
PR	Progesterone receptor
PROSPERO	International Registry of Prospectively Registered Systematic Reviews in health and social care
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RS	Relative survival
SD	Standard Deviation
SDI	Socio-demographic index
SEER	Surveillance, Epidemiology, and End Results
SHBG	Sex hormone binding globulin
SSA	sub-Saharan Africa
STEPS	STEPwise Approach to NCD Risk Factor Surveillance
SURVCAN	Cancer survival in Countries in Transition
TNBC	Triple-negative breast cancer
TNM	Tumour-Node-Metastasis
UCI	Uganda Cancer Institute
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
USA	United States of America
VA	Verbal autopsy
WFS	World Fertility Surveys
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHS	World Health Surveys
WLHIV	Women living with HIV
YLD	Years lived with disability
YLL	Years of life lost

“Statistics are people with the tears washed off”

Dr. Ruth Sidel

Chapter 1. Introduction and Outline of Thesis

1.1 Introduction

Africa is undergoing a rapid demographic and epidemiological transition, with increasing life expectancies and changes in lifestyles and the environment. These changes influence the incidence and burden of cancers in this region.[1,2] Trends in cancers related to lifestyle factors such as cancers of the breast, colorectum,[3–5] and upper digestive tract[6] reveal rising rates, while the incidence of some infection-related cancers such as liver and stomach cancers are on the decline.[7]

Today, breast cancer is the most common cause of cancer and is the second leading cause of cancer deaths, after cervical cancer, in sub-Saharan Africa (SSA).[8] The young demographic distribution of the African population coupled with the relatively low survival rates from the most common female cancers, breast and cervical cancer, implies that early cancer deaths disproportionately affect women in SSA. This is most pronounced under age 50. According to GLOBOCAN 2020, there were an estimated 99,015 cancers deaths (with an age-standardised mortality rate of 46.0 per 100,000) among women under age 50, compared with 52,338 cancer deaths (with an age-standardised mortality rate of 24.0 per 100,000) among men under age 50 in SSA.[8] This corresponds to 47.2% more cancer deaths among women under age 50 compared with men. This high impact on younger women in Africa results in far-reaching economic and societal effects. Preliminary estimates from the African Breast Cancer Disparities and Outcome (ABC-DO) study revealed that, for every 100 breast cancer deaths occurring under age 50, there were 210 maternal orphans (children under age 18).[9] In terms of the economic impact of early deaths, there are high costs from productivity losses per cancer death, given the young population age structure. This was estimated at $101,000 per cancer death in South Africa.[10]

In these economies that battle with the coexistence of novel and old communicable diseases, as well as the rising trends of non-communicable diseases (NCDs), knowing on what interventions to focus prevention activities, is mandatory to achieve the highest gains for the communities served.[11] The complex interplay between lifestyle-related and infectious causes observed in SSA will lead to a rise in the burden of cancers in this region. Unfortunately, with limited and often over-stretched human and financial resources in SSA, cancers and other NCDs are not often considered major health priorities.[1] However, knowledge of the actual burden of breast cancer in SSA is needed to effectively understand this growing epidemic and help make effective cancer control plans.

The estimates made of the likely evolution of the cancer burden in SSA are only as good as the underlying measurements of the cancer incidence, and the estimates of the risk factor burden and distribution in these populations. For many countries in SSA, national estimates of the cancer incidence and mortality are made using modelled data,[12] due to the paucity of population-based cancer registry (PBCR) data. Furthermore, there is limited evidence on population-level survival outcomes in SSA. Women in SSA face challenges of access and availability of resources for cancer care, coupled with poor awareness and delayed presentation. More than two-thirds of women present with advanced stages at diagnosis (stages III/IV),[13] resulting in poor survival outcomes. However, there are disparities in survival outcomes observed across SSA, from evidence generated from mostly hospital-based cancer registries and the few population-based survival reports available.[14] The most recent "Global surveillance of cancer survival" study - CONCORD-3 included population-level breast cancer survival data from four sub-Saharan African countries, and these showed huge and sometimes questionable differences in the 5-year relative survival estimates ranging from 0.0% (no survivors) in Bamako (Mali) to 97.5% (95% CI: 95.8-100.00) at 5-years in Ibadan (Nigeria), in the period 2010-2014.[15] Until recent years, because of the limited availability of population-level data from SSA, there has been a paucity of research on reasons for the

differences observed in the breast cancer burden and survival outcomes at a population-level in SSA.

The establishment of the African Cancer Registry Network (AFCRN) in 2012,[16] led to a coordinated effort to improve the quality and comparability of PBCR data from SSA, making it now possible to study the burden and survival from breast cancer in more detail at population-level across more African countries than was possible before.

1.2 Objectives of thesis

The main aim of this thesis is to describe the breast cancer burden and incidence trends in SSA. The cancer burden would be described in terms of incidence and survival, using the available population-level data from the AFCRN. Specifically, I had the following objectives:

- To measure changes in the breast cancer incidence rates among women across different regions of SSA.
- To explore possible drivers of the changes in the breast cancer incidence rates observed across SSA.
- To estimate the population-level survival outcomes of women diagnosed with breast cancer across different regions of the sub-Saharan African continent at 1, 3, and 5 years after diagnosis and to determine reasons for these survival differences.

1.3 Thesis outline

This thesis is presented using the following outline:

Chapters 2 and 3 are background chapters, presenting an overview of the current evidence on this subject area. Chapter 2 describes the concept of cancer burden, the available sources of data for the study of the cancer burden in SSA, and the methodological considerations for estimating the population-level cancer burden. In Chapter 3, an overview of the breast cancer epidemiology in SSA is presented.

Chapters 4, 5, and 6, aim to answer the main thesis objectives. Chapter 4 describes the breast cancer incidence trends in 11 population-based cancer registries (PBCRs) and compares these population-level trends between pre- and post-menopausal women using age-50 as a proxy for the age at menopause. These trends are also described by birth-period and by birth-cohort, using data from the PBCR of Kampala, Uganda and Harare, Zimbabwe, which have over 20 years of cancer incidence data. In Chapter 5, I explore possible reasons for the differences observed in the cancer incidence burden across countries in SSA. The available evidence from case-control studies on reproductive, anthropometric, and lifestyle factors in SSA is synthesized. In the second part of this chapter, I summarise the available evidence on trends in the population-level prevalence of these studied breast cancer risk factors. In Chapter 6, the breast cancer survival outcomes in 14 PBCRs are estimated at 1,3, and 5-years after diagnosis. Reasons for the differences in survival observed across the continent are explored. In the second part of this chapter, the therapy routinely available to women in SSA is described, and I explore how the therapy received influences the observed survival outcomes. Comparisons are made between the therapy received and the therapy recommendations from the National Comprehensive Cancer Network (NCCN) Harmonized therapy guidelines for SSA.[17]

The final chapter, chapter 7, presents a summary of the main findings from this thesis, the implications of these findings, the study limitations, and suggestions for future work.

Chapter 2. Measuring the cancer burden in sub-Saharan Africa

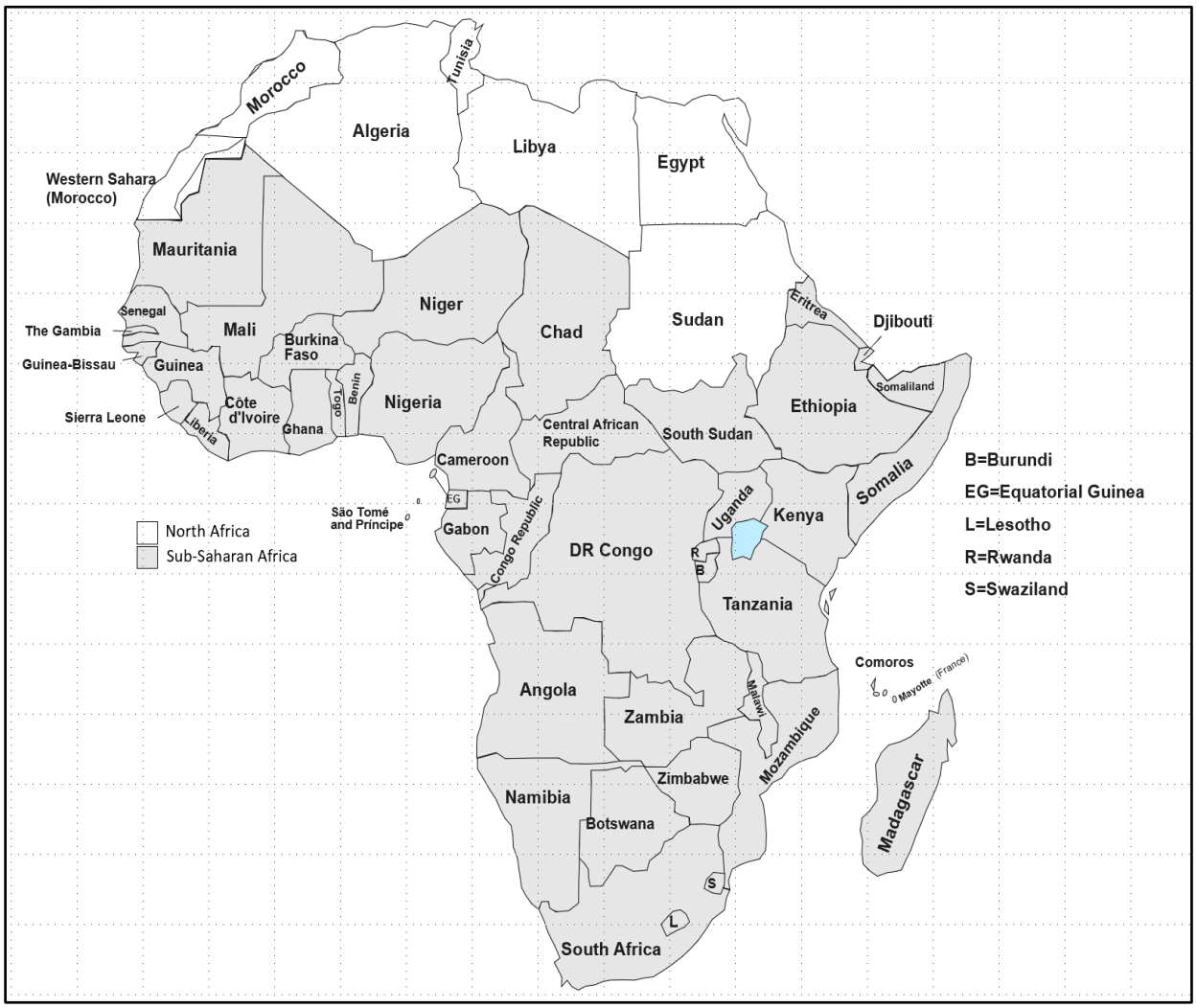
2.1 Introduction

The cancer burden refers to the occurrence and the outcome of cancers in a given region.[18] The cancer burden is often described in terms of incidence, mortality, prevalence, and survival. It also encompasses other measures of cancer outcome such as the years of life lost (YLL), the years lived with disability (YLD), the disability-adjusted life-years (DALYs), and the quality-adjusted life-years (QALYs).[18,19] Robust data on the cancer burden in a given community is essential for making and monitoring national cancer control plans.[20,21] Some of the data necessary for measuring the cancer burden in SSA are obtained from routine data sources, where they exist.

Routine sources of data are obtained from pre-established and ongoing data collection systems which are set up without the aim of answering a specific research question but are useful for monitoring the health and growth of populations, and for measuring the occurrence and outcome of multiple health states. These include data from birth and death records, census reports, population registers, medical records departments, health surveillance systems, and cancer registration systems. In this chapter, I present a descriptive literature review on the availability and quality of data sources used to quantify the cancer burden in the sub-Saharan African region – the region of focus in this thesis.

According to the United Nations Development Program, this region comprises 46 countries and these include: Angola, Benin, Botswana, Burkina Faso, Burundi, Cape Verde, Cameroon, Central African Republic, Chad, Comoros, Congo - Democratic Republic, Congo – Republic, Cote d'Ivoire, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles,

Sierra Leone, South Africa, South Sudan, Tanzania, Togo, Uganda, Zambia, and Zimbabwe.[22] The territories of Djibouti, Somalia, and Somaliland (internationally recognised as part of Somalia), are geographically part of SSA, although they are considered part of the Arab League. Geopolitically, Northern Africa is made up of seven nations: Algeria, Egypt, Libya, Morocco, Tunisia, Western Sahara, and Sudan (Figure 2.1).



Map source: Adapted from GeoCurrents customizable base maps.[23]

Figure 2.1: Map of Africa, showing the territoritories in Northern and sub-Saharan Africa (except for the Island Nations of Mauritius and Seychelles).

The overall goal of this thesis is to describe the burden and trends in cancers of the breast in SSA. In this first background chapter, I will define the different measures of cancer burden and discuss the sources and quality of the available information from SSA.

2.2 Cancer Incidence data: Counting cancers in sub-Saharan Africa

Cancer incidence refers to the number of new cancers occurring in a given population in a defined period.[18]

There are two main sources of cancer incidence data in SSA: hospital-based cancer registries (HBCRs) and PBCRs. HBCRs provide information on the occurrence and outcome of cancers in a hospital setting. Their main roles are for clinical research, patient care, and for administrative purposes. However, they cannot provide information on the incidence of cancers in the general population, given that the catchment area from which the cases arise cannot be readily defined, and they are prone to referral bias.[24,25] HBCRs serve as one of the sources of information for a population-based cancer registration system.

PBCRs aim to document all new cancers that occur in a defined population or catchment area. They are the gold standard for providing information on cancer incidence in a defined population. The registration of cancer cases to permit the calculation of population-level cancer incidence, is the most basic and core function of a PBCR.[20]

PBCRs require a coordinated health system to ensure complete case ascertainment and an unbiased picture of the cancer incidence in the population.[26] They include data from multiple sources within a population; hospitals, laboratories, private clinics, hospices, death certificates, and mortuaries. PBCRs are thus more resource intensive than HBCRs,[24] which is one of the barriers to their effective implementation in LMIC.

2.2.1 Population-based cancer registration in sub-Saharan Africa

Population-based cancer registration in sub-Saharan Africa dates to the 1950s. The International Agency for Research on Cancer (IARC) publication Cancer Incidence in Five continents (CI5) included PBCR data from the late 1950s from Lourenco Marques (present day Maputo) (Mozambique), Ibadan (Nigeria), Johannesburg (South Africa), Kampala (Uganda), and Bulawayo (Zimbabwe).[27] Between the late 1960s and 1980, the cancer

registration activities in SSA waned. This coincided with political and socio-economic changes occurring across the continent. From 1985 onwards there has been a slow increase in the number of population-based registries included in CI5 (Figure 2.2).

Population-based cancer registration is mainly active in almost all parts of SSA, and still makes use of paper records before data abstraction. Active data collection involves visiting sources of data, abstracting the data on specialised forms, and then entering the data in the registry database. In passive data collection, the data on new cancer cases from the various data sources are sent to the cancer registry. Some registries use a mixture of active and passive methods.[28]

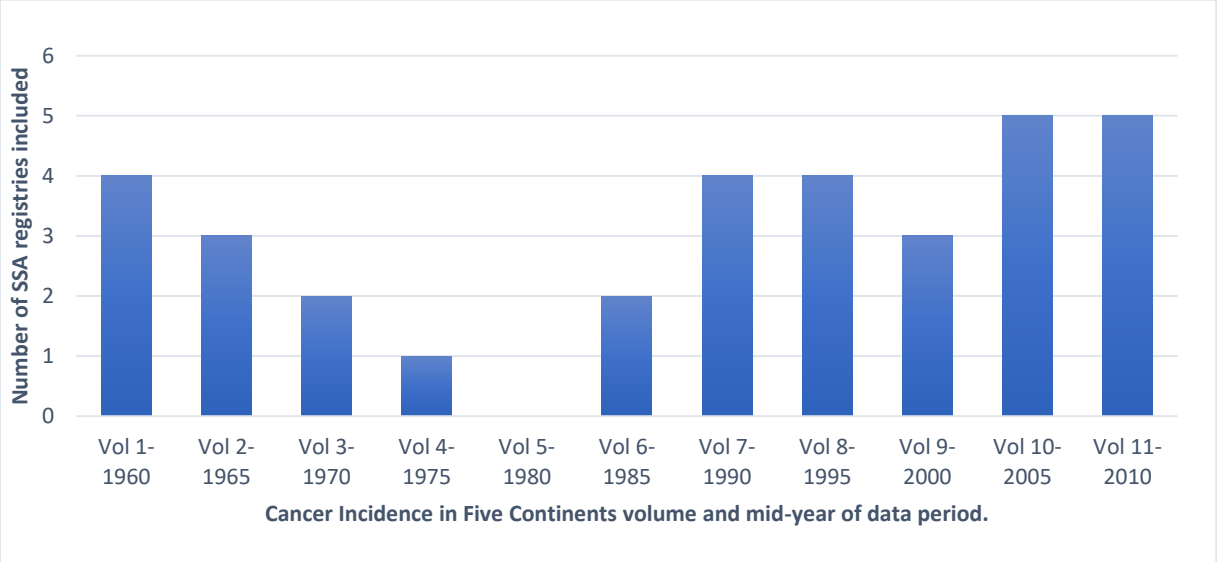


Figure 2.2: Number of population-based registries included in Cancer Incidence in Five Continents.

2.2.1.1 Challenges of cancer registration in sub-Saharan Africa

Cancer registration in SSA has faced several challenges over the years, some of which are:[29,30]

- The political and socio-economic instability in some nations influence the functioning of the registries in Africa. A recent example is the Zimbabwe National Cancer Registry which recorded a decline in the completeness of registration during the period 2007-

2009. This coincided with nationwide political and socio-economic challenges.[31] Similar challenges are observed across different parts of the continent.

- The paucity of quality health facilities and the challenge of ensuring complete case ascertainment, given that, for a cancer case to be recorded, the patient has to come in contact with the health system at some point. This would even be more of a challenge in rural settings where there are fewer health facilities, and where patients may resort to traditional healers. Most of the functional PBCRs in SSA are currently located in urban cities to facilitate case ascertainment.
- The challenge of ensuring the accurate documentation of "usual place of residence", given that, some patients visit urban centres to seek care or may return to their village homes if very sick, making the enumeration of all cases challenging.[30] In addition, some patients residing outside of urban areas will provide addresses of relatives who reside in these areas in order to receive care at urban facilities.
- The shortage of adequately trained personnel, and government support to ensure staff salaries, adequate work resources, and the continuity of cancer registration activities.
- The lack of unique identifiers for patients. In many SSA countries, the most commonly used personal identifier is the name. However, there are often variations in the name recorded, sometimes with name changes or omissions which may lead to errors in registration.
- Furthermore, many tumours are never biopsied and/or pathologically reviewed. When specimens are sent to laboratories, they often are of such poor quality that they render it very difficult to assign a pathologic diagnosis.
- The irregularity of population census reports and the challenge of obtaining accurate, and up-to-date estimates of populations at risk in many parts of SSA. These census data are necessary for the estimation of population-level incidence rates.

2.2.1.2 The African Cancer Registry Network

The AFCRN was established in 2012 to provide a unified framework for cancer registration and surveillance in SSA. It serves as IARC's regional hub for cancer registration in SSA, within the framework of the Global Initiative for Cancer Registry Development in Low- and Middle-Income countries (GICR). The AFCRN provides technical support to registries, through training and development of standard operating manuals for population-based cancer registration in SSA. It also plays a role in advocacy, to ensure adequate use of the data generated and supports local stakeholder engagement to ensure the sustainability of cancer registration activities.[16] The AFRCN is supported financially through the Challenge Fund, a UK based charity (charity number 1079181), which receives donations to support cancer registration in low- and middle-income countries. It also receives financial support from IARC's Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR), and via research grants and partnerships. Currently there are 35 PBCRs from 25 sub-Saharan African countries in the AFCRN (Figure 2.3).

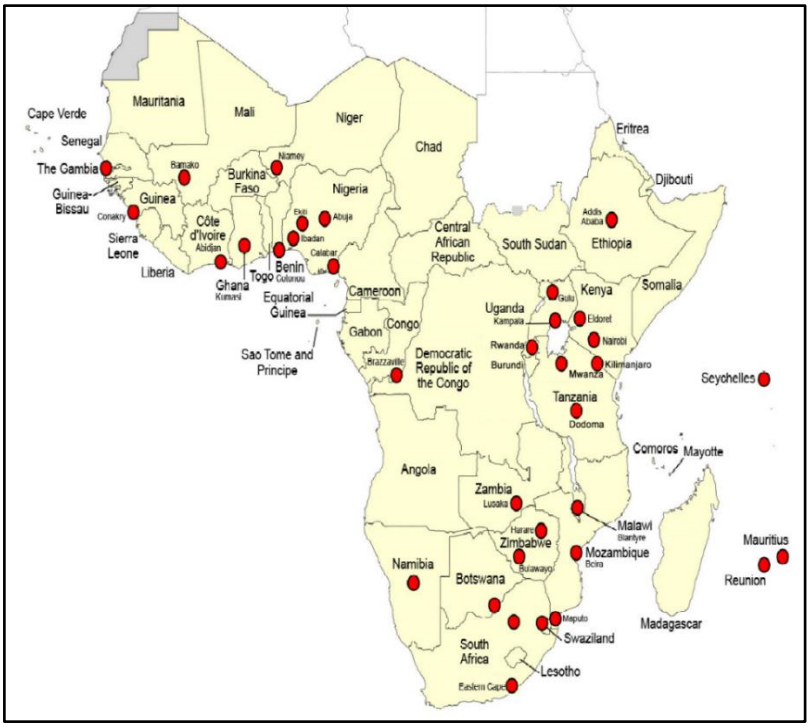


Figure 2.3: Member registries of the African Cancer Registry Network. Source: AFCRN 2021.

To qualify for membership in the AFCRN, the cancer registry must be in a sub-Saharan African country, be population-based and most have achieved at least 50% coverage of the target population. Membership will lapse if the registry fails to attain 70% of target population coverage within 3 years of joining the AFCRN.[32]

To help improve data quality, the CanReg software is used by all member registries of the AFCRN. It is an open-source software developed by IARC.[33] It is one of the tools that support the comparability and validity of the PBCR results. CanReg serves for data entry and management, with inbuilt morphology and topography coding systems for adult and paediatric cancers, it performs internal consistency checks and is used for basic data analysis and reporting.

2.2.1.3 Assessing the quality of cancer registration

To produce reliable estimates of population-level incidence, the registry data must be of good quality. The AFCRN's standard procedure manual provides a set of operating principles which are used as a guide by all member registries to enhance the quality of the data generated.[34] There are 4 dimensions for assessing the quality of cancer registration data: their comparability, completeness, validity, and timeliness.[35]

Comparability

This refers to how similar registration practices are across registries, permitting comparisons of results. Key elements taken into consideration when assessing the comparability of PBCR are:[35]

I. Similarities in the system of cancer coding and classification: The member registries of the AFCRN all use the International Classification of Diseases for Oncology (ICD-O), currently in its third revision. The ICD-O code is a dual-axes code: consisting of a topography and a morphology code.[36]

a. Topography: This refers to the site of origin of the tumour. It is standardised with section C (Chapter 2 – Neoplasms) of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[36]
b. Morphology (histologic or microscopic appearance): There are three parts of a complete morphology code.[36]
    - The first four digits of the morphology code refer to the histologic type.
    - The fifth digit, after the slash, refers to the behaviour of the tumour. It takes on the values; 0 – benign tumour, 1 – uncertain if benign or malignant, 2 - in situ, 3 – malignant; 6 – malignant of metastatic or secondary site; 9 – uncertain if primary or metastatic.
    - The sixth digit of the code is used to describe the grade or the degree of differentiation of the tumour cells. and it takes on the numbers: 1 – well differentiated cells, 2 – moderately differentiated tumour cells, 3 – poorly differentiated cells, 4 – anaplastic or undifferentiated cells, 9 – grade or differentiation not stated or not applicable.

II. Harmonisation of the definition of an incidence: this concerns definition of a new case and recording of the date of incidence. The AFCRN manual provides guidance on documenting incident cancer cases, and rules for abstracting date of incidence, to ensure comparability between all member registries.[34]

III. A unified system for dealing with multiple primaries: This is important for differentiating a new incident case, in contrast to a recurrence or metastases of an existing tumour. The AFCRN registries use rules in line with that of the IARC.[37] The guiding principles are:[34]
    - Recognition of the presence of two or more primary cancers is not time dependent.

- A primary cancer originates from a primary tissue, and it is not a metastasis, recurrence, or an extension of an existing tumour.
- There can only be one tumour arising from a primary organ or tissue.
- There are two exceptions to the third rule above:
  - Systemic tumours involving multiple organs are only counted once in a patient e.g., Kaposi Sarcoma and hematopoietic tumours.
  - Neoplasms of different morphologic types should be considered as distinct tumours, even if they occur in the same site.
- Tumours of completely different histologic classifications in paired organs (e.g., the breast) should be registered as separate tumours. Tumours of the same morphology, but of different laterality in paired organs should be registered separately as well, unless it is stated that they are of the same primary. These rules apply for paired tumours except for nephroblastoma, retinoblastoma, and ovarian tumours of the same morphology.[34]

Validity

This refers to the accuracy of the data recorded by the registries. What proportion of registered cases have been accurately registered as having the correct attributes (e.g. age, site, morphology). It depends on the accuracy and precision of the source information and the registrar's skill and accuracy in abstracting and coding. Methods to verify the accuracy of registry data include:[35]

I. Re-abstracting and recoding: Re-abstracting involves an external audit of recorded cases. A sample of cases are re-abstracted from the primary source, generally hospital records. These are then compared with what has been recorded in the PBCR. This process requires a detailed and documented method of dealing with discrepancies. Recoding, like re-abstracting, involves reassigning codes from primary

data sources and verifying how much discrepancy exists between the codes assigned by the external auditor and what is recorded in the PBCR.

II. Morphologic verification: The cancer diagnosis is more likely to be accurate if it has been confirmed by histology or cytology. The percentage of cases confirmed histologically or by cytology, referred to as morphologically verified cases (MV%) is used as an indicator of the diagnostic accuracy.

III. Internal consistency checks: This verifies the inter-record consistency and accuracy. It involves internal checks for the accuracy and logic between variables. For example, sex/site verifications and age/site/histology verifications. Inconsistencies are flagged for verification.

IV. Missing data: The proportion of cases with missing data for each variable is used to evaluate the quality of the registry data. Sometimes this depends on how complete the source information is at the time of data abstraction. It could be differential by age at diagnosis, with higher proportions of missing data recorded among the most elderly.

V. Death certificate only (DCO) cases: This represents the proportion of cases for which no other information is available apart from what was recorded from a death certificate. It is a measure of accuracy, given that the data from a death certificate would have less information on the cancer diagnosis than would have been obtained from a primary medical or diagnostic record. The proportion of DCO cases is compared against regional norms, given that the proportion of DCO cases would depend on the quality of death certificates, the ability to trace back cases from death certificates, and linkages with clinical records.

Completeness

This describes the extent to which all cases occurring in a given catchment area are recorded in the PBCR. The completeness of a PBCR can be evaluated through semi-quantitative and quantitative methods.[38]

A. Semi-quantitative Methods:

Semi-quantitative methods provide an indication of the level of completeness of the PBCR database but cannot exactly quantify the number of missing cases. The different semi-quantitative methods used include: [39]

I. Historic data methods

- Stability of incidence rates over time:

  This involves verification of the number of cases recorded over time for the presence of any sudden dips or peaks in the number of cases recorded. Comparisons are also made with the age-standardised rates in earlier years of the registry. Any significant changes which cannot be explained may indicate changes in the completeness of case ascertainment.

- Comparison of incidence in different populations:

Here, the incidence rates in a given registry are compared with incidence rates from similar regional registries. If there are consistently lower incidence rates for several cancer sites, this raises concerns of incomplete case finding.

- Age-specific incidence curves:

Age-specific curves are compared for the most common cancers among males and females. Any sudden dents in the age-specific curves may indicate incomplete case ascertainment among these age groups.

- Childhood cancer incidence rates:

There is generally less variability in the incidence of childhood cancers as compared with adult cancers. The age-specific incidence rates among children are compared with previous years, to study if there are any declines or sudden increases in the incidence rates; this could indicate either incomplete case finding or duplicate records.

II. Proportion of cases morphologically verified (MV%)

Although MV% is primarily used as an indicator of validity, very high values of morphologically verified cases may indicate over-reliance on pathology laboratories for case finding. These MV values are compared against national and regional norms, given that, very high percentages of MV for some tumour types, for example, liver cancer[40,41] or Kaposi Sarcoma[42] in some low-resource settings, may indicate an over-reliance on pathology records and incompleteness of case finding.

III. Mortality-to-incidence ratio (MIR)

This is not a very useful tool for monitoring registry completeness in most African registries, because of the absence of good quality mortality data.[34] In countries with good mortality records, the MIR could help ascertain the degree of completeness of registration activities. The MIR is usually compared against regional norms, and statistically higher or lower MIR than what is expected may flag issues of registry completeness.

IV. Number of notifications or sources per case

The average number of sources or notifications per case is used to monitor the completeness of case finding.

A. Quantitative Methods:

Of the three quantitative methods described by Parkin and Bray to quantitatively assess the completeness of a PBCR[38], one of these methods – the independent case-ascertainment method may be the most relevant for registries of the AFCRN. This method entails comparing the registry database to an independently selected group of cancer patients in the registry catchment area; for example, patients independently enrolled in a clinical trial or in a cohort study. It could also involve comparing the registry's database with that from an independent case finding audit, usually from hospital sources. The proportion of patients "missed" by the PBCR provides an objective estimate of the completeness of the registry for the given cancer under study or for the data source audited.[38]

The other two quantitative methods are the use of death certificate methods and the capture-recapture method. The use of the death certificate methods to determine registry completeness requires good mortality statistics and linkages to death records. Good mortality statistics are not available from most parts of SSA.[39]

The capture-recapture technique was initially developed for the study of animal populations. It involves tagging animals in different independent samples of the total population. The proportion of tagged animals common to different samples, is used to estimate of the total size of the population. This method has been applied to cancer registration to evaluate the completeness of registration activities. The capture-recapture technique assumes that record linkage is successfully carried out and that each of the sources of information are uniquely identified.[38] It assumes independence of sources, which would not be the case for cancer registration. To overcome this, methods have been proposed to evaluate the degree of dependence of the cancer notification sources.[38] One of the methods involves first evaluating the dependence of two or more sources, then grouping sources with greatest dependence (e.g. pathology and hospital-based), and then comparing this with a third source (with less dependence e.g. death certificates). However, if all sources show strong

interdependence, a log-linear modelling is used with interaction terms between the different sources of data.[38]

Timeliness

This refers to the speed with which registries can accurately collect and report reliable and complete data. It comprises the time for the case file to reach the cancer registry from the reporting facility; and the time for the registrars to abstract the data, code, and do any trace-back for death certificate notified cases. There are no set rules to govern timeliness for registries worldwide, with different PBCR systems using different guiding principles governed by the feasibility of obtaining complete case records.[35] The U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program recommends complete recording of incident cases within 22 months of the end of the year of diagnosis.[43] There is as yet no comparable data on the timeliness of cancer registration from sub-Saharan African registries.

2.2.1.4 Evaluating the quality of member registries of the AFCRN

Thus far, there have been four registry-specific published reports appraising the quality of the PBCRs which are members of the AFCRN. Parkin et al. evaluated the completeness of the Kampala Cancer Registry in Uganda in the period 1994-1996 using the independent case-ascertainment method.[44] The authors used a large case series of 674 patients who were independently recruited to study the influence of HIV infection on cancer risk. The overall level of completeness in this cohort was 89.6% (95% CI: 87.0-91.7). Completeness was higher for younger patients and was lowest for the most recent year (1996) of diagnosis. This is not surprising, as registries continue updating their records after the close of the reporting period, to ensure completeness, even though it may impede on timeliness.[44]

The quality of the Gambian cancer registry was evaluated for the period 1990-2009 by Shimakawa and colleagues.[45] The comparability of the registry's findings were in line with

international standards, as they used internationally recommended cancer coding systems. They found a relatively low proportion of morphologically verified cases compared with regional registries. There was also a high proportion of registered cases with unknown age. It also found incomplete case ascertainment among older persons and rural populations.[45]

Zullig et al. evaluated the validity or accuracy of the Kilimanjaro Cancer Registry in Tanzania, using data from 2014-2015.[46] They did an independent audit of 100 cases, and re-abstracted and recoded the data. Recording of the tumour morphology was accurate for 94% of cases and the recording of tumour site was accurate for 98% of cases. However, some discordance was observed in recording the date of diagnosis; for 32% of cases, the date of diagnosis was within 30 days of the recorded date.[46]

The Eastern Cape Cancer Registry is one of the few rural PBCRs in SSA. They recently evaluated the validity of their results, using an independent audit. There was 89% concordance in the tumour topography in 2014 and 90% in 2015, with a lower agreement in the morphology of 83% in 2014 and 76% in 2015. They highlighted the importance of active case finding in addition to passive case notification to improve the completeness of cancer registration in rural South Africa.[47]

Prior to the establishment of the AFCRN, Crocker-Buque and Pollock appraised the quality of registries included in GLOBOCAN 2008. Unfortunately, they used very limited publicly available data to evaluate the data quality of the 26 registries used in GLOBOCAN 2008. They reported that only the Gambian PBCR met more than 10 of their 15 quality criteria, with a score of 11, in comparison with the UK National Cancer Registry which had a score of 14 on 15,[48] a surprising finding given the very low completeness (~50%) estimated by Shimakawa and colleagues,[45] and the fact that the Gambian National Registry has not qualified for inclusion in Cancer Incidence in Five Continents since 1998.

2.2.1.5 Confidentiality

Cancer registration in most parts of Africa is voluntary (not mandated by law), [49] however, in recent years four sub-Saharan African countries have made notification of cancer cases mandatory by law. These are - South Africa since April 2011,[50] Kenya (Nairobi), Seychelles,[51] and Cameroon, as of October 2020.Safeguarding the anonymity of registered cases, the reporting physician, and the source is an important role of the PBCR. The AFCRN requires that all staff members sign confidentiality documents to protect the confidentiality of the cancer registry data, even after employment ends.[34] Some of the measures put in place by the AFCRN member registries to ensure data confidentiality include: keeping paper-based forms under lock and key in a filing cabinet, encrypting names, using password protected-files for transmission of data, separating name files from files with tumour information, changing log-in details to computers regularly, and limiting access to registry offices to authorised staff.[34,49]

2.2.2 Cancer Incidence in Five Continents (CI5)

The Cancer Incidence in Five Continents (CI5) series includes cancer incidence data from high-quality cancer registries worldwide and has been published since the 1960s. Its main objective is to make available comparable data on cancer incidence from PBCRs worldwide.[52] The first volume published data on 32 PBCRs in 29 countries, and the latest iteration, CI5 volume XI, includes data from 343 PBCRs from 65 countries.[51] 15% of the total world population is covered in CI5 volume XI, and with differential population coverage by continent. 1% of the African continent is covered in CI5 volume XI, 7% of Asia, 8% of Central and South America, 46% of Europe, and 98% of North America.[51] Of the 343 PBCRs included in CI5 volume XI, there were only six African PBCRs included; Batna (Algeria); Nairobi (Kenya), Seychelles, Eastern Cape (South Africa), Kyadondo County (Uganda), and Harare (Zimbabwe).

Despite the non-inclusion of these registries, there exist African PBCRs which have attained 70% registry catchment area coverage, required for membership in the AFCRN.[32] Although this is not of the high standard required for inclusion in CI5, it still provides invaluable information from health systems with a dearth of population-level data. There have been three comprehensive publications from IARC on cancer registration in Africa: Cancer in Africa - Epidemiology and Prevention (2003),[30] Cancer in sub-Saharan Africa (2018),[53] and Cancer in Africa Volume III (2019).[54] They serve to provide additional information on the quality and availability of data from SSA, the region with the lowest coverage in CI5.

2.2.3 National estimates of cancer incidence - GLOBOCAN

Whereas CI5 publishes high-quality incidence data directly derived from population-based registries, the IARC GLOBOCAN database makes national estimates of cancer incidence, mortality, and prevalence using all available sources of data. The latest iteration GLOBOCAN 2020, includes cancer statistics from 185 countries or territories.[55] It uses different methods for making national estimates of the cancer burden, and the methods used depend on the data availability (Figure 2.4). High-quality population-based cancer registration systems are the bedrock for these estimates of national cancer incidence.

2.2.3.1 Methods used in GLOBOCAN 2020 for estimation of cancer incidence in SSA

Ferlay et al. 2021 summarise the methods used for estimation of national incidence rates in GLOBOCAN 2021.[56] As concerns SSA, the methods used, in order of decreasing priority are presented in Table 2.1.[57] Figure 2.4 shows the countries in SSA with available population-level incidence data at either national or sub-national level which were used for making estimates of national incidence in GLOBOCAN 2020.

Table 2.1: Methods used in GLOBOCAN 2020 for estimation of national incidence rates in sub-Saharan Africa. [57]

Method	Description	SSA countries ǂ
1	For countries with national incidence data, the observed national incidence rates were projected to the year 2020.	Botswana and Mauritius (n=2)
2	For countries with no historic national incidence data or mortality data, the most recently observed incidence rates from a. one cancer registry b. multiple cancer registries within the country were applied to the 2020 population.	2a: Benin, Cameroon, Congo, Cote d'Ivoire, Gambia, Ghana, Guinea, Eswatini, Ethiopia, Gabon, Malawi, Mali, Namibia, Niger, Rwanda, and Zambia. (n=16) 2b: Kenya, Mozambique, Nigeria, Tanzania, Uganda, and Zimbabwe. (n=6)
3	For countries with sub-national incidence data and with national mortality data available, incidence rates were estimated from mortality data by modelling the mortality-to-incidence ratios. The MIR used were obtained from: a. Cancer registries in the country b. Cancer registries from neighbouring countries scaled according to the human-development index (HDI). NB: A single model was used for SSA.	3a. none (n=0) 3b: Cape Verde, Sao Tome and Principe, and South Africa. (n=3)
4	By averaging overall rates for all cancers combined from neighbouring countries and partitioning these rates using country-specific cancer frequency data.	Angola, Burkina Faso, Sierra Leone, and Togo. (n=4)
9	Estimated as an average of the rates from selected neighbouring countries.	Burundi, Central African Republic, Chad, Comoros, Congo- Democratic Republic, Eritrea, Equatorial Guinea, Guinea-Bissau, Lesotho, Liberia, Madagascar, Mauritania, Senegal, and South Sudan. (n=14)

ǂ All SSA countries were included in GLOBOCAN 2020 except Seychelles.

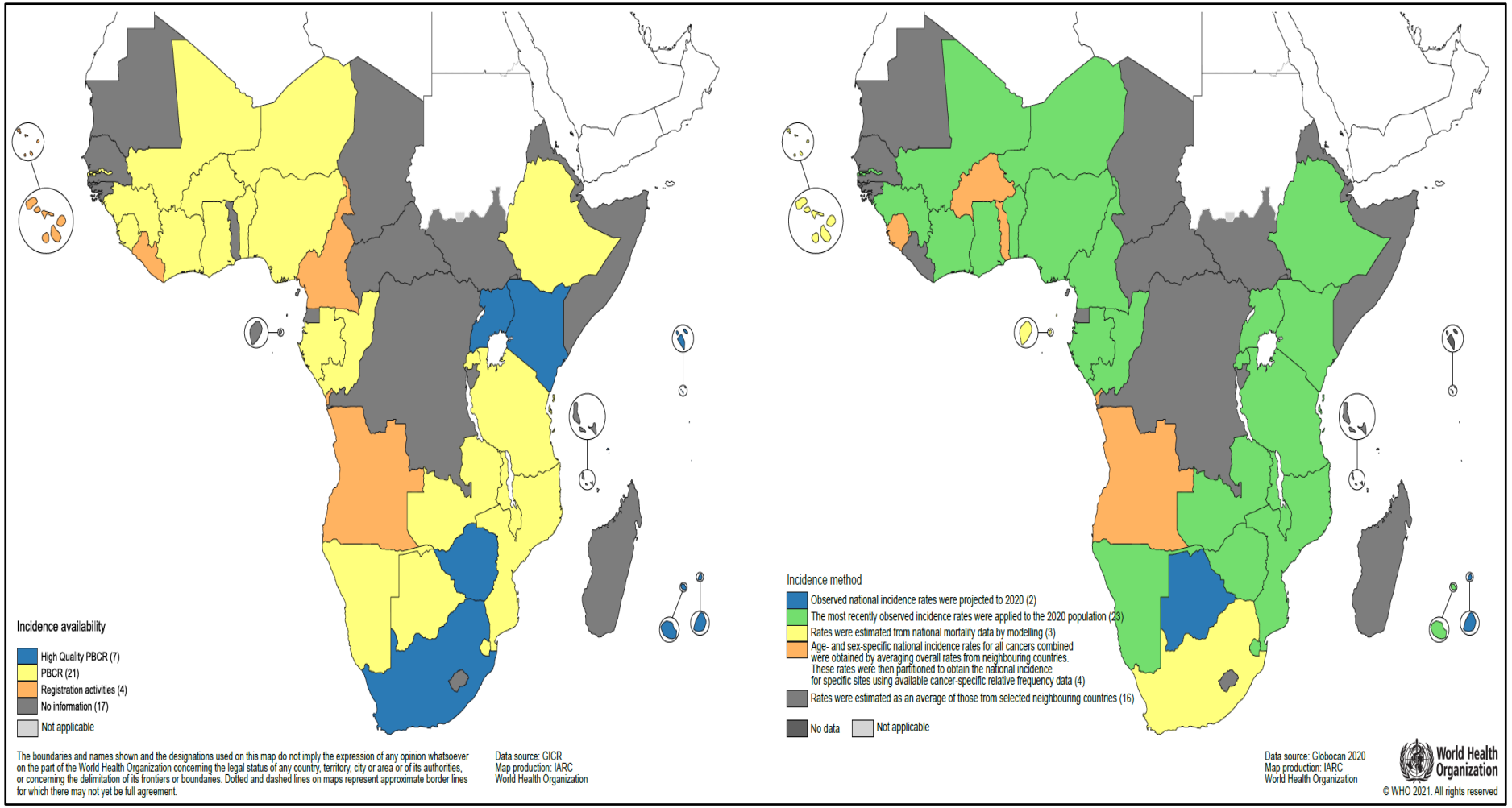


Figure 2.4: Availability of and methods used for estimation of national population-level cancer incidence rates in sub-Saharan Africa.

GLOBOCAN 2020 estimated that there were 129,415 new breast cancer cases in SSA in 2020, corresponding to an age-standardised incidence rate of 37.8 per 100,000 women.[8] Global disparities in the incidence rates are observed across regions, with higher incidence rates recorded in high income countries (Figure 2.5). In SSA, breast cancer was the leading cause of cancer in 2020.

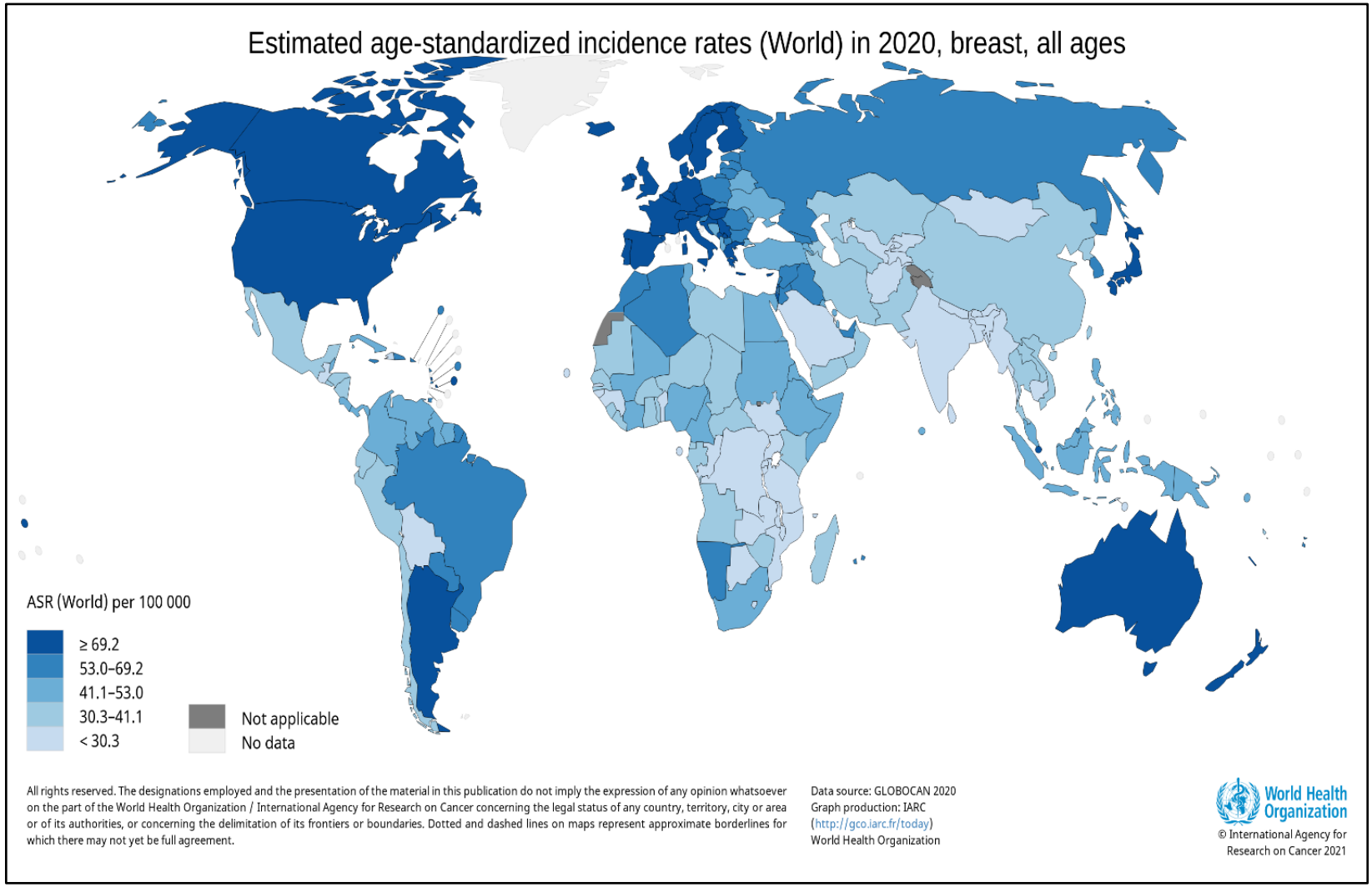


Figure 2.5: Breast cancer incidence rates worldwide, GLOBOCAN 2020.

2.3 Cancer Mortality data: counting deaths in sub-Saharan Africa

Cancer mortality refers to the number of deaths from cancer in a given population during a specific time period, usually a year. It can also be expressed as a rate, i.e. the number of cancer deaths per 100,000 persons per year.[58] It counts the number of deaths for which cancer is stated as the underlying cause of death. Cancer mortality is dependent on the cancer incidence and the case fatality of a given cancer – the probability of dying from one's cancer. It is an important measure of cancer outcome in a population.[58] Mortality statistics are obtained from vital registration systems, which rely on accurate certification of cause of death by a medical practitioner. The cause of death is coded using the International Classification of Diseases nomenclature.[58] The quality of mortality data will depend on the accuracy of coding and the degree of completeness of death registration.[59] Completeness refers to the proportion of all deaths in a given population that are registered in a vital registration system while the coverage refers to the proportion of the population that is effectively covered by the vital registration system.[60] Africa is one of the regions with the poorest coverage of death registration systems, where 90% of African countries had no vital registration systems, and no data on cause of death after 1990. Based on the 1996 data, the only vital registration systems in SSA with more than 50% completeness were found in South Africa (although judged to be of low quality with less than 70% coverage), and in the Island nations of Seychelles and Mauritius (of medium quality).[60] Improvements have been observed in the South African civil registration systems, with coverage among adults estimated at 89% in 2000.[61] Improvements are still being made to the quality of the cause-specific data. Data from South Africa are particularly important, as they are used by many research agencies as a basis for estimates in many SSA countries.[62]

In contrast to high-income countries, where the underlying cause of death is certified by a medical practitioner, in most low-income countries, many deaths occur away from health facilities, and the cause of death may not be accurately registered.[60] In the absence of robust

vital registration systems in many low- and middle-income countries (LMIC), some of these countries make use of sample registration, which is based on representative samples of subnational surveillance sites and this has been shown to be an effective method of obtaining cause of death information in resource-constrained settings.[60]

2.3.1 Sources of cancer mortality data

Data on mortality rates are generally obtained from country-specific statistics units by age, 5-year age group, sex, and year. When a death occurs, this is usually registered by the national civil registry and compiled annually. Some of the main sources of mortality data in SSA include:

2.3.1.1 The World Health Organization Mortality Database

The World Health Organization (WHO) mortality database is a compilation of mortality data collected from national vital registration systems and coded using the ICD system. It presents data by country, age, sex, year of death, and by cause of death, as reported by the member countries. It publishes data only on medically certified deaths. No adjustments are made for the under-reporting of cases in the WHO database, however, information on the level of coverage by country is reported. When coverage is too low, death rates are not presented to prevent misinformation.[63] From SSA, it includes mortality data from Cape Verde, Mauritius, Sao Tome and Principe, Seychelles, South Africa, and Zimbabwe. For Zimbabwe, it includes data only for a single year, 1990.[63] IARC's cancer mortality database contains selected cancer-specific mortality data, extracted from the parent WHO Mortality Database.[61]

2.3.1.2 Verbal autopsies in Africa

Verbal autopsies (VA) are an important means of obtaining information on cause of death for deaths which occurred out of a health facility, and which would have otherwise been unregistered or uncertified. This is particularly important in LMIC with poorly developed vital registration systems. In 2015, of 56 million deaths, only 27 million (48%) of these were

registered with the cause of death, and 21.4 million were reported to the WHO (38.2%).[64] VA involves doing a standardised interview with family members or caregivers with good knowledge of the signs and symptoms before the patient's death. The WHO sets international standards for the structure and format of VA questionnaires, and for categorisation of the cause of death data derived. The interview data are either reviewed by physicians to ascribe the most likely cause of death or processed by probabilistic models.[65] The InterVA-5 model is a probabilistic modelling tool that facilitates this process. It is harmonised to the WHO VA standards and generates cause-specific mortality data suited to different contexts.[66] Strong concordance has been observed between VA cause of death codes from the InterVA tool and the physician-derived cause of death codes.[67] Cause-of-death data from VA from population-level surveillance sites such as the International Network for the Demographic Evaluation of Populations and their Health (IN-DEPTH) network have been used to supplement and evaluate the passively collected medically-certified mortality data reported via health facilities, and together, they present a more complete and accurate picture of cause-of-death in these settings.[62]

2.3.1.3 The WHO Global Health Observatory database

This database contains data on the cause of death and disability globally. It makes mortality estimates using multiple data sources. These include: the national mortality statistics from vital registration systems, census data and surveys, estimates from WHO technical programmes and partners, the Global Burden of Disease estimates, and from scientific publications.[61] It uses this amalgamated data, and data from the United Nations Population Division to produce country-specific life tables by country, 5-year age group, sex, and year. A life table is a tabulation that summarises the mortality pattern in a given population by age, sex, and calendar year. For countries, with low coverage of death registration systems, it relies on modelling based on data from comparable populations, to obtain life table estimates.[68]

2.3.1.4 The Global Burden of Disease estimates of mortality

The first Global Burden of Disease (GBD) study was commissioned in the early 1990s.[69] Currently, the latest iteration of the GBD study uses data from 2019 and reports on mortality from 369 disease states and injuries from 204 countries and territories.[70] The GBD uses data from varied sources including civil registration systems, sample registration, censuses, sibling-history data, and surveys.[70] However, there has been some criticism over the lack of transparency of the data input files, the decisions made on data inclusion and exclusion, and the modelling strategies employed. Although improvements have been made to improve the transparency of the methodology used, many of the outputs are still not easily replicable.[71]

2.3.1.5 GLOBOCAN estimates of cancer mortality

Similar to its estimates of national cancer incidence, GLOBOCAN uses different methods to estimate national cancer mortality rates. This is dependent on the completeness, coverage, and granularity of the available mortality data. The standard errors of these estimates are corrected for uncertainties as a result of incomplete coverage, timeliness of reporting, and the quality of the reported data.[56]

2.3.1.5.1 Methods used by GLOBOCAN for estimation of national mortality

Four methods are used by GLOBOCAN for making estimates of national mortality rates.[56] As concerns SSA, these methods are summarised in Table 2.2.[57]

Table 2.2: Methods of estimating national mortality rates in sub-Saharan Africa in GLOBOCAN 2020.

Method	Description	SSA Countries[‡]
1	Where national mortality data were available, the observed mortality rates were projected to 2020 and applied to the 2018 national population.	Mauritius, South Africa (n = 2)
2	Where there were no historic mortality data, the most recently observed mortality rates from a. one source b. multiple sources within the country were applied to the 2020 population.	2a= Sao Tome and Principe (n = 1)
3	Where recent mortality data were not available, national mortality was estimated from incidence by modelling the incidence: mortality ratio derived from cancer registries scaled according to the country-level HDI. For breast and cervical cancers, the 5-year relative survival was used to obtain estimates of mortality. The 5-year relative survival has been used to approximate the complement of the mortality-to-incidence ratio: 5-year relative survival ~ 1 - (MIR).[72]	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Congo – Democratic Republic, Cote d'Ivoire, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Sudan, Tanzania, Togo, Uganda, Zambia, and Zimbabwe (n = 42)
4	In the absence of mortality data, and where incidence cannot be obtained for use with the incidence: mortality ratio, the country-specific cancer mortality rates reflect rates of neighbouring countries.	None (n = 0)

[‡] All SSA countries were included in GLOBOCAN 2020 except Seychelles, due to the small population size and risk of fluctuation of rates. HDI = Human Development Index. MIR=Mortality-to-incidence ratio. SSA=sub-Saharan Africa.

According to GLOBOCAN 2020, breast cancer was the second leading cause of cancer mortality, after cervical cancer in SSA, with an estimated 64,234 deaths in 2020, corresponding to an age-standardised mortality rate of 19.3 per 100,000 women.[8] Globally, although incidence rates are higher in high-income countries, mortality rates are higher in LMIC (Figure 2.6) reflecting poorer survival outcomes.

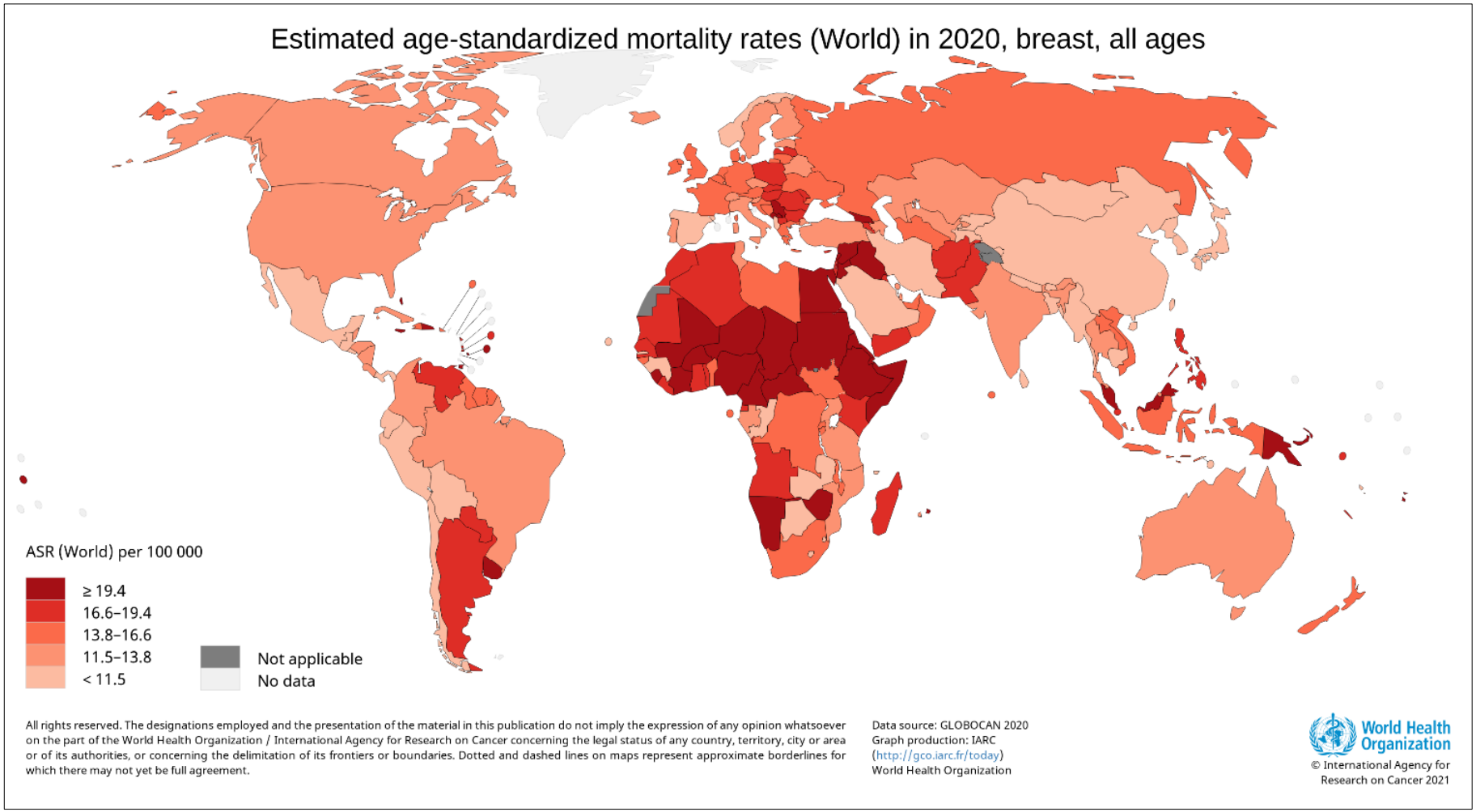


Figure 2.6: Breast cancer mortality rates worldwide, GLOBOCAN 2020.

2.4 Measuring cancer prevalence in SSA

Cancer prevalence refers to the number of people living with cancer in a population in a given period. It includes both newly diagnosed cases (incident cases) and pre-existing cases. The annual prevalence refers to the number of people living with cancer at any time in a given year, while the period prevalence refers to the number of people living with cancer diagnosed at any time during a pre-defined period e.g., in the last 5 years.[73]

In GLOBOCAN 2020, the estimates of national prevalence were made based on country incidence, the national prevalence from the Nordic registries and scaled by country-level Human Development Index (HDI) using the following formula:[57]

$$Prevalence\ \text{"country"} = Incidence\ \text{"country"} \times \left(\frac{Prevalence\ \text{"Nordic"}}{Incidence\ \text{"Nordic"}}\right) \times \left(\frac{HDI\ \text{"country"}}{HDI\ \text{"Nordic"}}\right)$$

For breast and prostate cancers, they used the national prevalence from the pre-screening era in the Nordic countries (1980-1989). GLOBOCAN estimates that breast cancer was the most prevalent cancer in sub-Saharan Africa in 2020, with an estimated 5-year prevalence of 272,255 cases. The annual prevalence was estimated at 70,652 cases.[8]

2.5 Cancer survival data from sub-Saharan Africa

Cancer survival refers to the time between cancer diagnosis and death.[18] Cancer survival data are usually presented as the proportion of people alive for a specified period e.g., 1 year, 5 years, 10 years, after a primary cancer diagnosis. There are two main sources of cancer survival data from SSA: hospital-based and population-based cancer survival estimates.

Hospital-based survival estimates describe the survival experience of patients referred to and treated in a particular hospital or clinic(s). Results from a hospital-based registry cannot be generalised to the population, given that they refer to the survival experience of only patients

treated at a given clinic or hospital. The hospital-based registry is useful for the administration, the hospital's cancer care team, and the individual patients.[74]

On the other hand, population-based survival describes the survival experience of all patients diagnosed with cancer in a given population, and not just limited to patients treated at hospitals. Population-based survival is of public-health interest, given that, it is a measure of the overall progress in cancer control in a community.[75] Data on population-level cancer survival are usually obtained from PBCRs.[75] PBCR collect data on all incident cases and also can collect follow-up data on these patients, permitting the estimation of population-level cancer survival. These findings are generalisable to the population, as they represent the different diagnostic journeys, therapeutic decisions, and survival outcomes in that population.

There are relatively few data on population-level survival from population-based African registries. IARC's Cancer Survival in Africa, Asia, the Caribbean, and Central America (SURVCAN-2) study published in 2011, included data from 3 SSA countries, the Gambia, Uganda, and Zimbabwe.[76] The CONCORD-3 study, published in 2018, included data from 4 sub-Saharan countries (Mali, Mauritius, Nigeria, and South Africa).[15] These studies showed large variability in cancer survival by tumour type and across different countries of the continent.

In the absence of population-level survival data, and in settings where the mortality data are good, and the incidence and survival rates are steady, the complement of the MIR has been used as a proxy for 5-year relative survival. However, these estimates are more accurate for some cancer sites compared with others.[72] Other authors argue that the MIR is not a valid proxy of population-level cancer survival, given that it accurately predicted net survival within 5% of the observed net survival values for less than a third of tumours.[77] Unfortunately, in SSA, in the absence of good mortality databases, population-level survival cannot readily be estimated by using the complement of the MIR. However, as explained in Table 2.2, for the

few cancers in SSA with available data on population-level incidence and survival, these were used to estimate cancer mortality based on this equation linking the 5-year cancer survival and the complement of the MIR.

2.5.1 Measuring cancer survival

Two main methods are used by cancer registrars to obtain follow-up data after a cancer diagnosis:[78]

- Passive follow-up: In passive follow-up, registries rely on receiving death notifications from vital statistics databases. If notification of death has not been received for a patient, the patient is considered to still be alive. Passive follow-up requires a robust mortality surveillance system and technical resources for data linkage.
- Active follow-up: In active follow-up, registrars find and update information on the patients' vital status at pre-determined time points. This information is obtained from clinical records, physicians, or by contacting patients or their next-of-kin directly.

Most registries in SSA use active follow-up in the absence of robust mortality databases. In instances where passive follow-up can be used, some registries complement passive follow-up with active follow-up such as in the Eastern Cape Cancer Registry, South Africa, to obtain more accurate data on patient survival outcomes.[47]

Patients who are lost to follow-up or who withdraw from the study before the closing date of the study are referred to as censored cases. If the reasons for loss to follow-up (LFU) are unrelated to the study outcome, this is referred to as random censoring. However, if the reason for LFU is related to the study outcome, this is referred to as non-random censoring.[78] The SURVCAN-2 study used a Cox-regression model to test for non-random censoring, with the outcome being LFU, and patients who had died or were known to be alive at study close were considered "censored" for this analysis. This helped determine if there were any study variables associated with being LFU.[78] Most methods used for survival analyses assume

random censoring. In the presence of non-random censoring, survival estimates should be interpreted with caution.[78]

2.5.1.1 Estimating cancer survival probabilities

Two related approaches are often used to estimate cancer survival: the Kaplan-Meier and the life table or actuarial methods.[79] The Kaplan-Meier method uses the exact information on the date of death or censoring to obtain survival estimates. In the life table approach, study participants who were alive at the beginning of the study period but became LFU before the end of the study period are considered to have been followed up for half of the period.[79] These two methods can be used to estimate the "all-cause" or "observed" survival among study participants.

However, a cancer patient is at risk of death from their cancer, and from other causes not related to the cancer under study. In order to compare survival outcomes between groups of patients with different risks of death from other causes, another measure of cancer survival is used – the "net survival". The net survival estimates the survival probability of cancer patients if the cancer was the only cause of death.[79] The net survival can be estimated by censoring deaths from other causes – this is often referred to as the corrected or the cause-specific survival.[79] Unfortunately, in most SSA countries, there are poor mortality record systems and inadequate information on cause-specific mortality rates. In the absence of cause-specific mortality data, the "relative survival" is used to estimate the net survival. The "relative survival" is the ratio of the observed survival among cancer patients to the expected survival of the general population with the same demographic profile as the cancer patient at the beginning of the study interval. It assumes independence between cancer-specific mortality and mortality from other causes.[80]

There are different methods for estimating the expected survival probability – the Ederer I, the Ederer II, the Hakulinen, the Pohar-Perme, and model-based estimates.[81] Of these methods, the Ederer II, the Pohar-Perme, and model-based methods are most often used.[82]

In the Ederer I method, the time of death of the cancer patient does not influence the expected survival, as the matched individual in the general population is considered to be at risk of death indefinitely, even after the study ends.[83] Although this method produces an unbiased estimate of the expected survival probability, it produces biased relative survival ratios because it does not adjust for differences in length of patient follow-up.[84]

In the Ederer II method, the matched individual in the general population is considered to be at risk of death till the matched patient dies or is censored. It could produce biased estimates if there are differences in the relative survival in different subgroups.[84] This is generally the default estimator in statistical packages.[81]

In the Hakulinen method, the matched individual in the general population is at risk for different lengths of time depending on the outcome of the matched cancer patient. If the cancer patient is censored, the matched individual will be censored, but if the matched cancer patient dies, the matched individual remains at risk until the end of the study.[84]

In the Pohar-Perme method, the net survival for a given population is obtained by weighting the inverse of the individual-level expected survival probabilities. Higher weights are given to older cancer patients, this is because older persons in the general population are more likely to have died from other causes.[85]

In practice, the Ederer II and Pohar-Perme methods give comparable results when estimating the 5-year survival outcome, with less than 0.5% difference in units.[86] However, for longer-term follow up (≥10 years), the Ederer II and model-based estimates produce more precise estimates of the age-standardised net survival.[82]

Relative survival estimates have to be age-standardised in order to make comparisons between populations of cancer patients of different age structures because the excess cancer mortality can be influenced by age.[78] The direct method of age-standardisation is used to obtain the summary age-standardised relative survival rates (ASRS). This can be achieved using an internal standard (usually the ratio of patients in each category at the start of the study period) or by using an external standard such as the International Cancer Survival Standards, derived from mostly European populations,[87] or the recently updated world cancer patient population.[88] The world cancer patient population was developed to better reflect the age distribution of cancer patients in LMIC, which could be markedly different from the age distribution of patients in HIC for some cancers. It was derived from the global distribution of cancer patients by age group from GLOBOCAN 2018, in contrast to the International Cancer Survival Standards which were derived from European populations.

2.6 Other measures of cancer burden: Years of Life Lost

2.6.1 Disability-adjusted life years in SSA

A DALY sums the years of life lost (YLL) due to premature death and the years of life lived with disability (YLD). One DALY represents one year lost of healthy life, either from premature mortality or from sequelae or disability from a disease or an injury. The concept of premature mortality used in the estimation of DALYs refers to the death before the age to which the person was expected to have lived using a standardised life expectancy table, where the life expectancy at birth is 80 years for men and 82.5 years for women.[89] Only two characteristics are considered in determining the life expectancy – the age and sex, and not socio-economic status, or country-level HDI. This measure was developed by the Global Burden of Disease study, with the aim of creating a single measure of disease burden based on egalitarian principles which captures both mortality and disability.[69] The YLL are obtained by multiplying the number of cancer deaths occurring at a given age by the standard life expectancy for that age.[89] The YLD are obtained by multiplying the number of new cases, the mean duration of

disability, and the standard weight assigned to that disability, which ranges from 0 (perfect health) to 1 (death).

Although DALYs have been widely used in measuring the burden of disease, there has been some criticism of its use and estimation. Some of this criticism involves how disability is measured and how the standard weights for different health states were assigned. Although these weights were determined by "experts", this may not adequately reflect the lived experiences of people in different contexts.[90]

The GBD Cancer Collaboration estimated DALYs for 29 cancer groups from 1990 to 2017 from 195 countries and territories.[19] They first obtained mortality estimates from vital registration systems, cancer registries, and verbal autopsies. Then they estimated the incidence for all sites based on mortality rates, using the MIR, derived separately. They correlated survival and the MIR to obtain an estimate of 10-year prevalence. The prevalence is divided into 4 sequelae phases: diagnosis and therapy, remission, metastasis, and end-of-life. The prevalence of each of these phases is multiplied by a standard disability weight for estimation of the YLD. Based on these calculations, they estimated that cancer caused 233.5 million DALYs in 2017, with 97% of these DALYs due to premature cancer mortality.[19] Breast cancer was the most common cause of mortality and DALYs among women in 2017. Although countries with a high socio-demographic index (SDI) accounted for 50% of incident cases, they accounted for 30% of cancer deaths and 25% of cancer DALYs, reflecting the disproportionately higher burden of cancer mortality and DALYs in countries of middle and lower SDI.[19] The SDI is a composite measure that aims to capture development parameters related to health outcomes. It comprises three key elements: educational attainment, total fertility rate before age 25, and per capita income.[91]

Similar disparities in the contribution of YLL to DALYs by country-level HDI were reported by Soerjomataram et al. 2012 using population-based data on incidence, mortality, and survival in 2008. The contribution of premature mortality to cancer DALYs was highest in SSA and

lowest in North America;[92] indeed, years of life with disability (YLD) was a very small component of DALYs in low-income countries.

2.6.2 Quality-Adjusted Life Years

The quality-adjusted life year (QALY) is a predecessor of the DALY. It was first introduced in the 1970s.[93] It is a measure of the state of health of a person, in which the length of life is adjusted for the quality of life lived. A QALY is a product of the utility value assigned to a particular health state and the duration of life lived in that state. A utility is a preference or a desirability weight.[94] One QALY represents one year of life in perfect health. The main use of the QALY is in cost-effectiveness analyses to assess the improvement in quality of life relative to a given health intervention. In contrast to DALYs, in which the disability weights are obtained from expert valuation, QALYs rely on preference-based choices obtained from the general population or groups of patients. Furthermore, earlier calculations of DALYs were age-weighted, assigning more weight to young adults, while the QALY is not.[93]

Although there have been studies on the quality of life of patients with cancers in SSA, there is a dearth of research on QALYs and the cost-effectiveness of cancer care in SSA. The majority of studies on cost-per-QALY have been carried out in high-income countries (Figure 2.7), with approximately a quarter of these funded by pharmaceutical companies.[95]

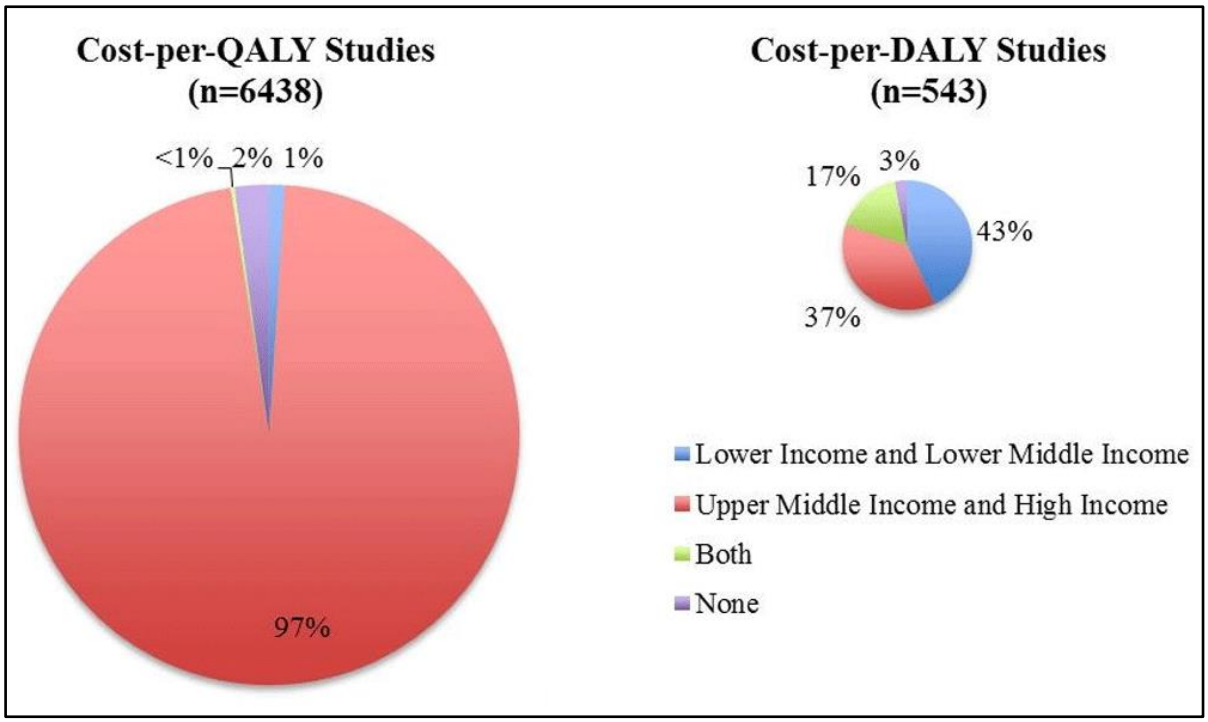


Figure 2.7: Cost-per-QALY vs. cost-per-DALY studies by world bank income level.

Source: Neumann PJ, Anderson JE, Panzer AD et al. Comparing the cost-per-QALYs gained and cost-per-DALYs averted literatures. Gates Open Research 2018, 2:5 (doi: 10.12688/gatesopenres.12786.1)

2.7 Uses of data on the burden of cancer in SSA

Data on the magnitude and trends in the cancer burden in a given community are essential for setting cancer control priorities and for monitoring the effects of interventions. At the national level, a National Cancer Control Plan (NCCP) is set up whose role is to monitor the cancer burden, set priorities for interventions, and monitor the outcome of these interventions. All countries are encouraged to have a NCCP, which produces a roadmap to guide the nation in setting up prevention and cancer management strategies, which are tailored to their unique country-level cancer profile.[20] According to the WHO, in 2017, 72.3% of countries in the WHO African region had an operational policy/strategy/action plan for cancer control.[96] However, many of these NCCPs are not underpinned by a functional PBCR. The NCCP's cancer surveillance system should ideally be based around a PBCR. Cancer surveillance is critical for developing and implementing the NCCP's cancer control policy.

Surveillance involves the systematic measurement, recording, transmission, analyses, and interpretation of data, in order to detect changes in the health status of the population. The cancer surveillance program provides information on the current cancer burden and trends, serves as a basis for research on cancer aetiology and primary prevention, monitors the effects of interventions to promote early detection/screening, and the outcome of cancer treatment and palliation at population-level.[20]

2.8 Summary

In this chapter, an overview of the different measures of cancer burden in SSA has been presented, as well as the challenges of measuring the cancer burden accurately in the absence of strong health information systems. In this thesis, I will mainly focus on two of these measures of cancer burden in SSA – the cancer incidence (chapter 4) and the cancer survival (chapter 6) using population-level data from the AFCRN. Obtaining good quality population-level data are necessary to permit accurate measurement of the actual cancer burden in SSA.

Chapter 3. Breast cancer epidemiology in sub-Saharan Africa

3.1 Introduction

The breast cancer burden is on the rise on the African continent, due to population ageing and westernization of lifestyles. Its incidence is increasing rapidly in some parts of this continent, with an annual percentage increase of 4.9% (95% CI: 2.9-6.9) in 1991-2010, in the black population of Harare[31] and 2.3% (95% CI: 1.3-3.4) in 1991-2015 in Kampala, Uganda.[7] In contrast, there are slower rates of change observed in Western countries, with annual percentage change estimates of 0.4% among Caucasians and 0.7% among black women in the United States (US) in the 2009-2018 period.[97] Although the incidence rates are lower in SSA than in Western countries, breast cancer has higher mortality rates in SSA, and thus, higher mortality-to-incidence ratios reflecting the poorer survival outcomes.[98]

This rising breast cancer burden in SSA necessitates a deeper understanding of its epidemiology on the continent. In this chapter, I present a review of the breast cancer epidemiology in SSA, which will serve as a contextual background for the subsequent results and discussion chapters.

3.2 Breast cancer incidence

Breast cancer is the most common cancer (Figure 3.1) and the second leading cause of cancer deaths after cervical cancer in SSA. Together with cervical cancer, they account for approximately 50% of incident cancer cases among women in SSA.[8] The burden of cancer among women in Africa continent shows geographical variation. Cervical cancer is the most common cancer in Eastern Africa and some parts of Western Africa, but in the rest of the continent, breast cancer is the leading cause of cancer among women (Figure 3.2).

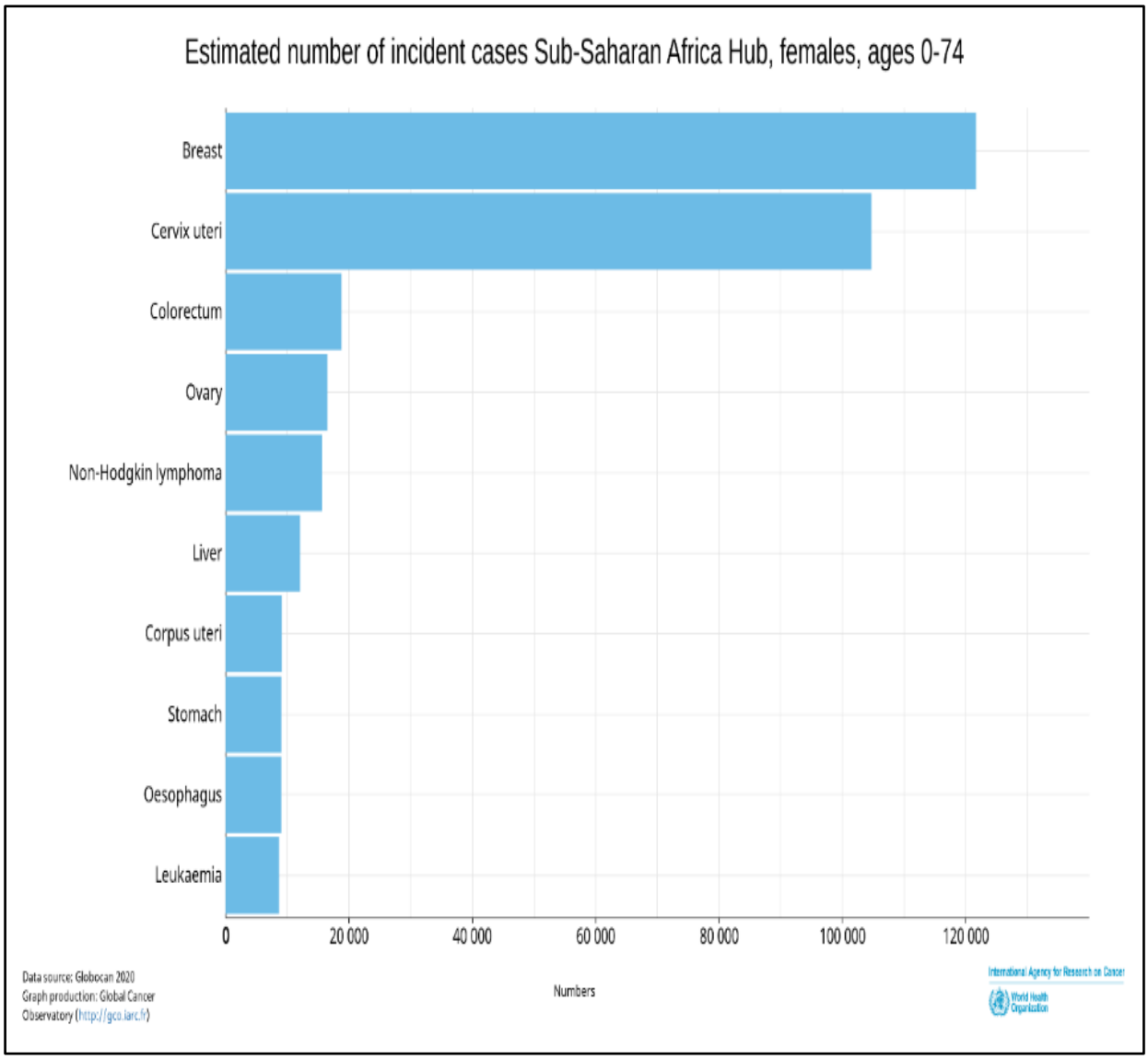
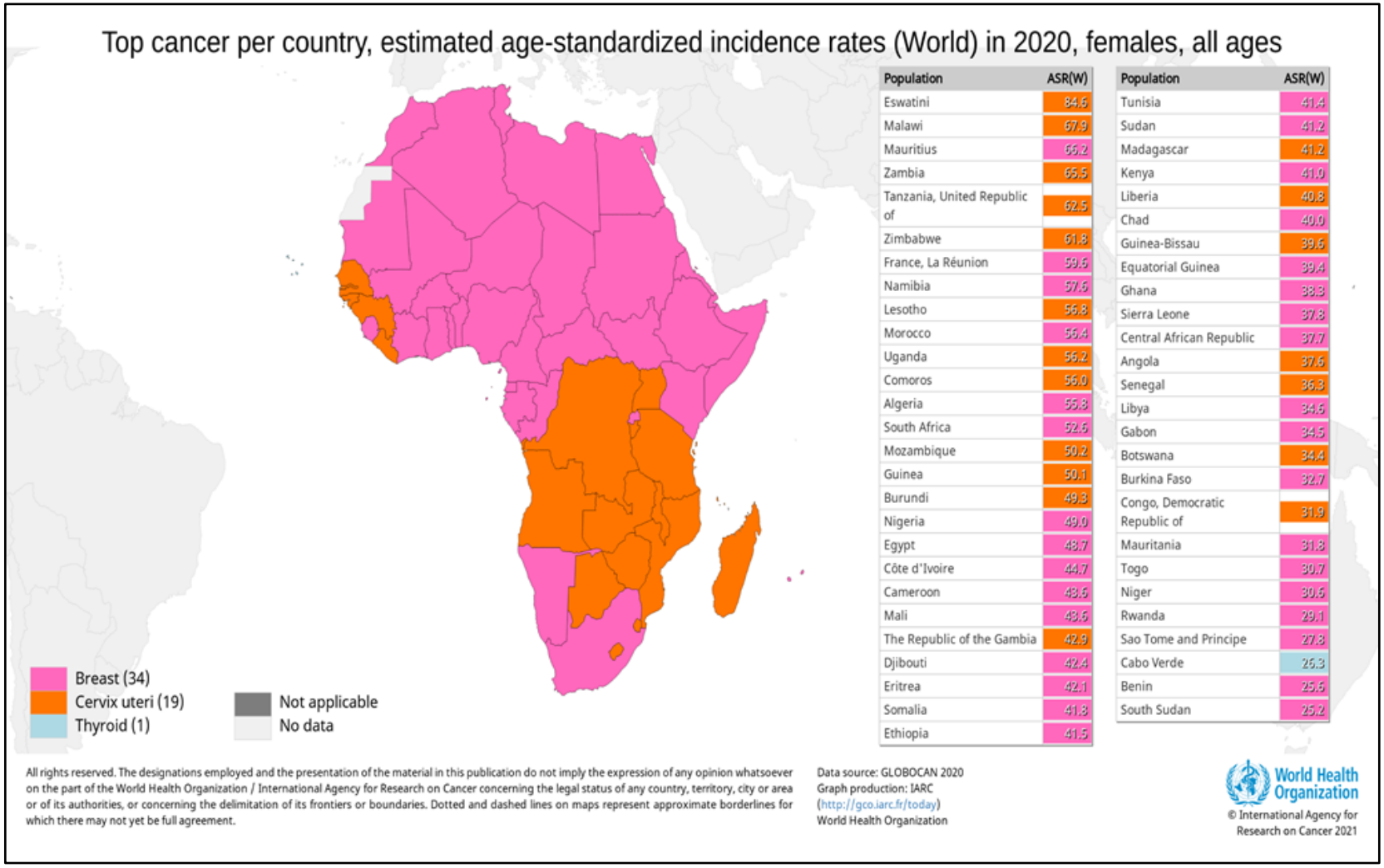


Figure 3.1: Most common cancers among women in sub-Saharan Africa, GLOBOCAN 2020.



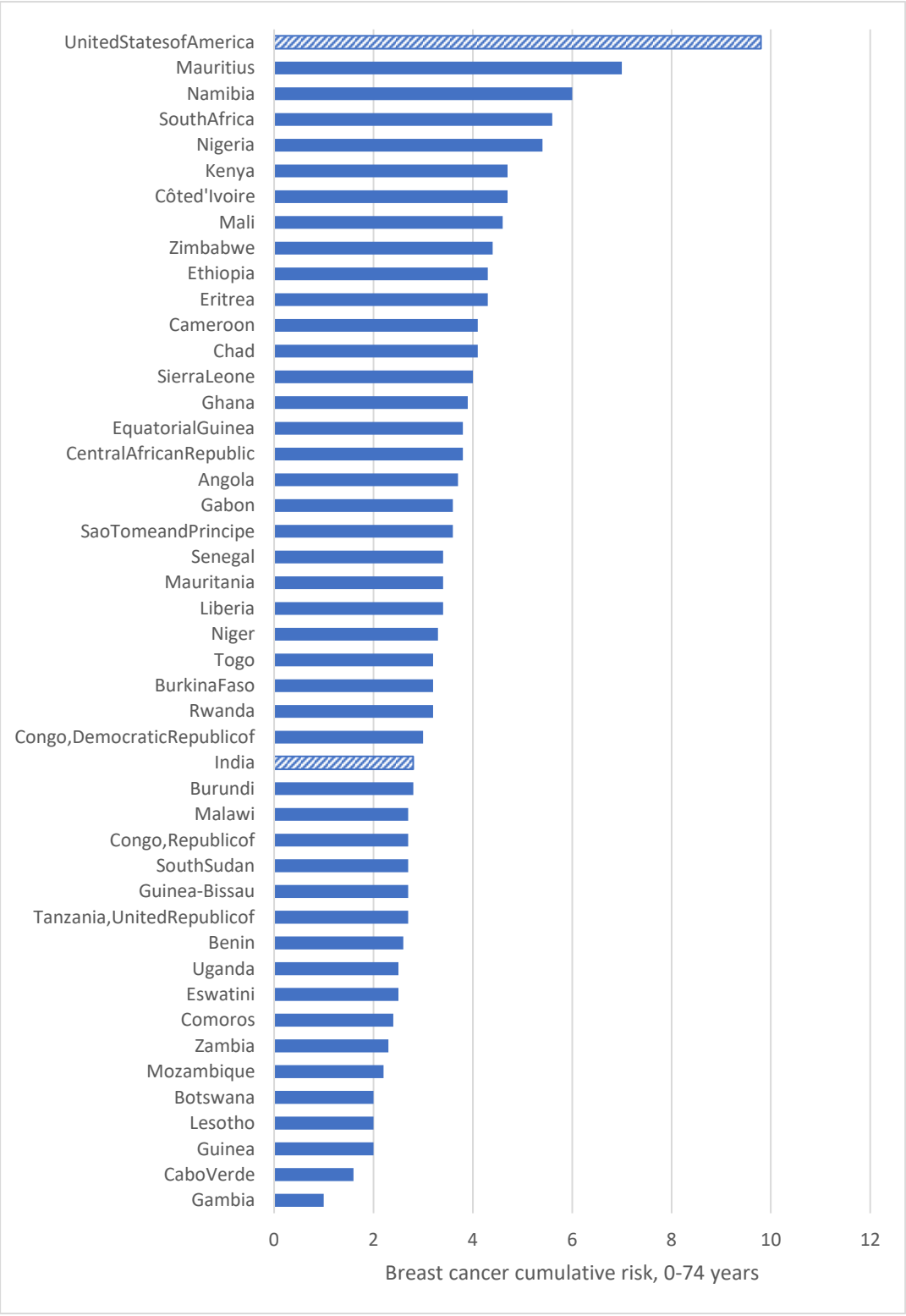
Population	ASR(W)
Eswatini	84.6
Malawi	67.9
Mauritius	66.2
Zambia	65.5
Tanzania, United Republic of	62.5
Zimbabwe	61.8
France, La Réunion	59.6
Namibia	57.6
Lesotho	56.8
Morocco	56.4
Uganda	56.2
Comoros	56.0
Algeria	55.8
South Africa	52.6
Mozambique	50.2
Guinea	50.1
Burundi	49.3
Nigeria	49.0
Egypt	48.7
Côte d'Ivoire	44.7
Cameroon	43.6
Mali	43.6
The Republic of the Gambia	42.9
Djibouti	42.4
Eritrea	42.1
Somalia	41.8
Ethiopia	41.5

Population	ASR(W)
Tunisia	41.4
Sudan	41.2
Madagascar	41.2
Kenya	41.0
Liberia	40.8
Chad	40.0
Guinea-Bissau	39.6
Equatorial Guinea	39.4
Ghana	38.3
Sierra Leone	37.8
Central African Republic	37.7
Angola	37.6
Senegal	36.3
Libya	34.6
Gabon	34.5
Botswana	34.4
Burkina Faso	32.7
Congo, Democratic Republic of	31.9
Mauritania	31.8
Togo	30.7
Niger	30.6
Rwanda	29.1
Sao Tome and Principe	27.8
Cabo Verde	26.3
Benin	25.6
South Sudan	25.2

Figure 3.2: Most common cancer by country among women in Africa, GLOBOCAN 2020.

As shown in Figure 3.2, breast cancer incidence rates are not uniform across the continent. According to GLOBOCAN 2020, the age-standardised incidence rates (ASIR) were estimated at 33.0 per 100,000 women in Eastern Africa, 32.7 per 100,000 in Middle Africa, 41.5 per 100,000 women in Western Africa, 50.4 per 100,000 women in Southern Africa, and 49.6 per 100,000 women in Northern Africa.[8] Although the rates observed in SSA are a third to a quarter lower than the rates observed among blacks in the United States, these rates are rising rapidly in some parts of Africa.[7,31] According to the SEER Program, among blacks in the United States, the 5-year ASIR in the 2014-2018 period was estimated at 124.7 (123.7–125.8) per 100,000 women. Slightly higher incidence rates of 131.8 (131.3-132.2) per 100,000 women were observed among whites in the same period.[99] Reasons for differences in the magnitude of rates include; the absence of systematic population-level screening in SSA as compared with Western populations, the relatively younger age structure of African populations, the differences in the risk factor distributions in these populations, and to an extent under-reporting in many sub-Saharan African countries. According to the first volume of Cancer Incidence in Five Continents, in the pre-screening era in the United States (1960-1963), a breast cancer ASIR of 58.0 per 100,000 women was observed among Caucasians in Hawaii, with lower rates observed among the Hawaiian (37.2 per 100,000) and Japanese (20.1 per 100,000) residents of Hawaii. In Finland, an ASIR of 26.1 per 100,000 was observed in 1959-1961. In the South Thames region of the UK, an ASIR of 46.1 per 100,000 was observed in 1960-1963. Among Chinese residents in Singapore, a much lower ASIR of 7.4 per 100,000 were observed in 1950-1961.[100] However, it is known that incidence rates for breast cancer among migrants from countries with lower incidence rates, are initially low among first-generation migrants, but these rates increase over time in subsequent generations to reflect more closely the rates in the host country.[101–104] Thus some of these reported incidence rates are influenced by the duration of stay of the migrant communities in the host nations.

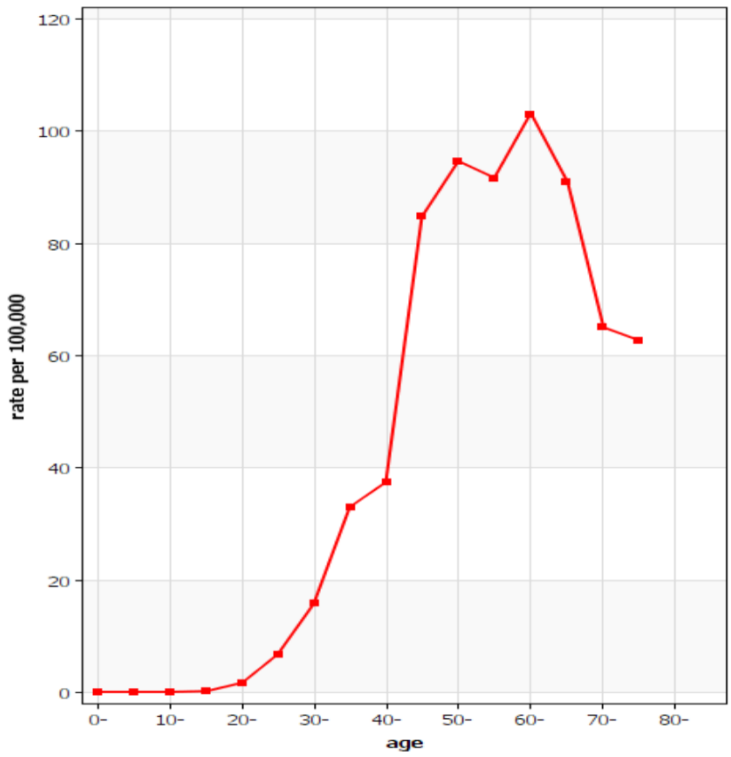
The cumulative risk refers to the probability of developing cancer in the absence of competing causes of death over the lifespan, usually considered 0-74 years.[105] In SSA we see great variability in the cumulative risk, with higher cumulative risks observed in Mauritius, Namibia, and South Africa and very low risks observed in Gambia, Cape Verde, and Guinea (Figure 3.3). In Figure 3.3 we compare these cumulative risks with the USA, and with India, in order to put the rates observed in SSA in 2020 in context with other nations. These estimates of the national cumulative risk presented, are obtained from GLOBOCAN 2020, which estimate the national cancer incidence from available PBCRs estimates. In many of these countries in SSA, and in India, there would be differences in the cancer burden in rural and urban areas, correlated with the risk factor distribution and the level of development in different regions of these countries. Among blacks in the 2016-2018 period in the USA, the cumulative risk of developing breast cancer before age 75 was 8.3% (95% CI: 8.2-8.4).[99]



Data source: GLOBOCAN, 2020.

Figure 3.3: Breast cancer cumulative risk (0-74 years) in sub-Saharan Africa, India, and the USA in 2020.

The age-specific incidence curves in SSA show rising rates till about the age of menopause (50), followed by a decline in rates (Figure 3.4). This reflects a sharp decrease in levels of circulating oestrogens after menopause as well as a cohort effect with higher rates observed among younger women born in more recent cohorts, and lower rates observed in older women born in earlier periods.[106] Africa has the youngest population distribution. In 2019, 3% of the sub-Saharan African population was above the age of 65, compared with 16.4% of the North American population and 20.4% of the population of the European Union.[107] This young age distribution of the African population is reflected in the median age at diagnosis in Africa. On average, women with breast cancer in SSA are diagnosed a decade earlier than women in Northern America and Europe.[108] This younger age distribution reflects the younger ages structure of these populations, and also, differences in genetics and tumour biology which may also be partly responsible for some of these age differences observed.[109] In the USA, higher incidence rates at younger ages (<45) are also observed among black women compared with Caucasians.[110] And the median age at diagnosis is younger (58 years) for black women as compared with white women (62 years) in the United States.[111] In 2006, The National Cancer Registration and Analysis Service, reported a median age at diagnosis of 50 years among black women, in contrast with 62 years among white women in the England.[112] More recent evidence on age differences by ethnicity for women diagnosed between 2012 and 2017 in England show a similar age differential, with a mean age at diagnosis among black African women of 50.5 years in comparison with 59.3 years among white women.[113]



Source: Cancer Incidence in Five Continents, IARC

Figure 3.4: Breast cancer age-specific incidence rates in 2008-2012, Uganda - Kampala.

Although the incidence rates among whites have been slightly higher than among black women in the USA; in recent years, there has been a convergence of the incidence rates observed in black and white women. Similarly, in SSA there have been rapid increases in incidence rates observed, especially in its urban cities.[7]

There are urban-rural differences in the breast cancer burden in SSA. Higher incidence rates are observed in urban cities compared with rural populations of the same country. In the predominantly rural registry of Gulu – Uganda, the breast cancer ASIR was estimated at 12.7 per 100,00 women in the 2013-2016 period,[114] while in the urban registry of Kampala-Uganda, the breast cancer ASIR was 30.7 per 100,000 women in the 2011-2015 period.[7] Some of this reflects differences in the risk factor distribution in these areas, as well as, to some extent, differences in diagnostics and detection facilities.

3.3 Breast cancer stage at diagnosis

3.3.1 Breast cancer staging

3.3.1.1 The TNM Classification

The TNM nomenclature is an anatomically based system of describing the extent of cancer.[115] The TNM characters refer to:

T – This stands for “Tumour”. The T category is used to describe the size of the primary tumour.

N – This stands for “Nodes”. This describes whether there is any regional lymph node involvement and the extent of the regional lymph node involvement.

M – This stands for “Metastasis”. This describes whether there is any distant spread of the tumour cells.

The prefix “c” is used when the stage is determined clinically following physical examination and imagery but before surgery or neoadjuvant therapy. The prefix “p” is used when the stage is determined following surgery and pathological examination.

For breast cancer, the following TNM classification system is used (Table 3.1).

Table 3.1: Breast cancer TNM categories.

Category	Sub-category	Description
T	Tx	The primary tumour site could not be evaluated.
	T0	No evidence of primary tumour.
	Tis	In situ tumour.
	T1	≤ 2cm
	T2	>2cm to ≤5cm
	T3	>5cm
	T4	Tumour of any size with extension to the chest wall and/or with skin nodules, inflammation, or ulcerations.
N*	Nx	The presence of regional nodes was not evaluated.
	cN0	No evidence of regional lymph nodes after physical examination and imagery.
	cN1	Presence of ipsilateral movable axillary lymph nodes
	cN2a	Presence of ipsilateral matted (fixed) axillary lymph nodes
	cN2b	Presence of ipsilateral clinically detectable internal mammary lymph nodes, and absence of axillary lymph nodes
	cN3a	Presence of ipsilateral sub-clavicular lymph nodes
	cN3b	Presence of ipsilateral clinically detectable axillary and internal mammary lymph nodes
	cN3c	Presence of ipsilateral supraclavicular lymph nodes
M	M0	Absence of distant metastases
	M1	Presence of distant metastases

Source: Adapted from the Union for International Cancer Control (UICC) TNM classification system.[116,117]
**The pathological nodal (pN) classification system, also takes into account the number and size of the regional lymph nodes.*

These different TNM categories are grouped to form the anatomical stage classification system (Table 3.2).

Table 3.2 Breast cancer anatomical stage grouping.

Category	Stage	T	N	N
Stage 0	0	Tis	N0	M0
Stage I	IA	T1	N0	M0
	IB	T0 or T1	N1(micrometastasis >0.2mm but ≤ 2mm)	M0
Stage II	IIA	T0 or T1	N1	M0
	IIA	T2	N0	M0
	IIB	T2	N1	M0
	IIB	T3	N0	M0
Stage III	IIIA	T0, T1, T2	N2	M0
	IIIA	T3	N1, N2	M0
	IIIB	T4	N0, N1, N2	M0
	IIIC	Any T	N3	M0
Stage IV	IV	Any T	Any N	M1

Source: Adapted from the Union for International Cancer Control (UICC) TNM classification system.[18]

Stages I and II will be referred to as “early stages” and stages III and IV will be referred to as “advanced stages” in this thesis.

The eighth edition of the American Joint Committee on Cancer (AJCC) classification system incorporates prognostic or predictive biomarkers such as - tumour grade, oestrogen and progesterone receptor expression, human epidermal growth factor receptor-2 (HER-2) overexpression or amplification, and genomic profiling - to the anatomical stage. This is to increase the clinical, therapeutic, and predictive value of the breast cancer staging system.[117]

3.3.1.2 The Essential TNM

Anatomic staging remains the cornerstone of cancer management for clinicians in LMIC in the absence of routinely available prognostic and predictive markers.[117] In many population-based registries from LMIC, there is inadequate information on the cancer stage from the patient records. A simplified version of the anatomical TNM staging referred to as the

essential TNM was developed to help registrars in LMIC abstract stage information from clinical records in the absence of pre-recorded stage. This is in order to help improve the completeness of stage reporting from PBCRs.[118] Table 3.3 describes the guiding principles of the essential TNM classification system.[34,118]

Table 3.3: The Essential TNM classification guidelines.

TNM nomenclature	Essential TNM nomenclature	Description of tumour extent.
M	M+	Presence of metastasis recorded in the clinical file.
	M-	No mention of metastasis in the clinical records.
N	R+	Presence of regional lymph nodes described in the clinical records.
	R-	No mention of regional lymph nodes in the clinical records.
T	A	Locally advanced tumours (for breast cancer - with chest wall extension or skin ulceration or inflammation)
	L	Localised tumours.
	X	Primary not described.

The different symbols used ("+", "-", "A", and "L") differentiate the essential TNM as abstracted from the clinical records by the cancer registrar and the regular TNM as described by the clinician (Table 3.3). The essential TNM can then be grouped as stages I-IV.[118]

3.3.2 Breast cancer stage in sub-Saharan Africa

A systematic review of hospital-based studies including approximately 24,000 sub-Saharan African women found that 77% of breast cancer patients in SSA were diagnosed at stages III and IV.[13] Similar results were reported from the population-based registries of Abidjan - Côte d'Ivoire and Brazzaville – Congo, with 74% and 81% of patients diagnosed at stages III and IV

respectively.[119] This is in sharp contrast to results from the SEER, in which 33% of all women in the period 2012-2016 were diagnosed with regional or distant breast cancer. However, differences existed by race, with 31% of white women diagnosed with regional or distant breast cancer in contrast with 41% of black US women.[120]

Early breast cancer diagnosis aims at diagnosing symptomatic patients as early as possible, while breast cancer screening involves checking for the presence of unrecognized disease in an asymptomatic target population. Cancer screening is a more resource-intensive activity that requires a coordinated health care system.[121] In SSA, there are as yet no population-level screening programmes for detecting asymptomatic patients. The median time from first symptom recognition to diagnosis in SSA ranges from about 7 months to 15 months, with a resultant adverse effect on the stage distribution.[122–124] This delayed diagnosis is a result of both patient and system-related factors.[124] Patient-related reasons for delayed presentation and diagnosis include fear of diagnosis and treatment, fear of death (cancer fatalism), fear of abandonment by spouses or others, stigmatisation, poor awareness, preference for traditional medicine, denial, cultural norms concerning health-seeking behaviours, low cancer literacy rates (having the knowledge and skill to find, understand and act upon health information on how to access cancer screening, diagnosis, and treatment) and financial constraints. System-related factors include difficulties in access to health facilities, lack of diagnostics, inadequately trained staff, delayed referrals, absence of cancer navigation pathways, and costs of diagnostics and treatment.[124–129] This delayed presentation and diagnosis is associated with a higher risk of tumour growth in the primary care setting before therapy start,[130] with the inherent adverse survival outcome.

Results from the African Breast Cancer-Disparities in Outcomes cohort (ABC-DO), a large hospital-based multinational study that included women with breast cancer from Namibia, Nigeria, Uganda, South Africa, and Zambia showed differences in the length of the diagnostic journeys across these different countries and by socioeconomic status and race.[131] The

shortest diagnostic delays were observed among non-black Namibian women (2.4 months (95% CI: 0.6 – 5.5), while the longest diagnostic journeys were observed in Kampala, Uganda (11.3 months (95% CI: 5.7 – 21.2)). The time from first contact with a health care provider to diagnosis accounted for more than 60% of the delay in diagnosis. The diagnostic journey was 3.6 months shorter for more educated women. The length of the diagnostic journey was halved if the woman suspected a cancer on symptom presentation.[131] In the ABC-DO cohort, 61% of women were diagnosed at stages III/IV. A more advanced stage at diagnosis was observed among younger women, women with a recent pregnancy, and women with higher grade, or triple-negative tumours. The lowest proportion of advanced-stage disease was observed among non-black Namibian and South African women.[132]

3.4 Breast cancer tumour biology

3.4.1 Breast cancer tumour classification

Cancers of the breast are heterogeneous at the histopathological and the molecular level.[133] There are approximately 21 distinct histological types of breast cancer.[134] The most common histologic type are adenocarcinomas. Adenocarcinomas represent 95% of cancers in the USA. Almost 80% of these adenocarcinomas are “invasive carcinoma of no special type”, which were previously called “ductal carcinoma, not otherwise specified”. This is to differentiate them from more distinct histological types. Lobular cancers are the next largest histological group of cancers.

These histological types can be further classified by molecular characteristics. This is especially relevant for the invasive carcinomas of no special type (NST), which is the largest and most heterogeneous group of tumours. Based on immunohistochemistry (IHC), breast tumours are classified based on their expression of oestrogen receptors (ER), progesterone receptors (PR), and HER-2. They are classified as:[134]

- hormone-receptor positive (HR+) if they express ER (ER-positive) or PR (PR+). These respond to endocrine therapy and are often of good prognosis.
- hormone-receptor negative (HR-) if they do not express ER or PR.
- HER-2 positive if they overexpress the *HER2 (ERBB2)* oncogene. These respond to anti-*ERBB2* agents such as trastuzumab.
- triple-negative if they do not express either ER, PR, or HER-2. Triple-negative breast cancer (TNBC) are not susceptible to targeted therapy nor endocrine therapy. They usually have a genetic predisposition, occur in younger women, and are of poor prognosis.[135]

The tumour grade, which is also determined by histological examination is an important determinant of breast cancer clinical outcomes. The tumour grade refers to the degree of cellular differentiation of the tumour. Higher grades are associated with higher rates of cellular proliferation. In breast cancer, the tumour grade is related to the Ki67 index. Ki67 is a marker of cell proliferation identified by the immunohistochemistry (IHC) technique. Cells are considered highly proliferative if >20% of nuclear cells are Ki-67 labelled. Ki-67 positivity is associated with early breast cancer recurrence.[136] In SSA, only the histological tumour grade is most often reported, given the cost and plateau-technique required for Ki67 assays. There are different methods used for IHC, with different scoring systems. The accuracy of the results obtained would depend on the tissue preparation and techniques used. Challenges in adequately preparing tissue samples for histology and IHC, decreases the accuracy of histological reports in many parts of SSA.

Using gene expression techniques, breast cancer tumours can further be classified into four intrinsic sub-types:[133,134]

- Luminal A: These are usually low-grade tumours, which express ER and PR and do not overexpress HER-2. They show a low expression of proliferative genes. By IHC classification, these tumours are ER-positive and/or PR+ and HER-2 negative. These are the most common tumours among women in the USA and are generally considered to be of good prognosis.

- Luminal B: These tumours show a higher rate of proliferation than luminal A tumours, have higher grades at diagnosis and over-express HER-2. They also express ER and PR at lower levels than luminal A tumours. By IHC classification, these tumours are generally ER-positive/PR+ and Ki67 high.

- Basal-like: These tumours do not express ER, PR, or HER-2 (triple-negative). These tumours are usually of high grade and aneuploid with complex genetic aberrations. They are usually of poorer prognosis.

- HER-2 enriched: These tumours do not express ER or PR but overexpress HER-2. They are usually high-grade tumours at diagnosis.

These molecular types of tumours are of increasing relevance in the clinical and research communities, first as a guide for therapy options and prognosis,[117] and secondly because these different molecular sub-types are associated with different aetiologic pathways.

3.4.2 Breast cancer tumour biology in sub-Saharan Africa

Breast cancers in women of African descent in comparison with breast cancer in Caucasian women have been reported to be of more aggressive disease phenotypes.[120] Black women in the United States have the lowest proportion of luminal A and the highest proportion of TNBC as compared with women of other ethnicities.[111] Results from the Carolina breast cancer study in the United States showed that 16% of women had TNBC, however among black pre-menopausal women, 39% of them presented with TNBC. Lower proportions of TNBC were observed among post-menopausal African American women.[137] However, these findings

may not be generalisable to the entire US population. Among black women in England, a similar picture emerges, with a higher proportion of high grade and ER-negative tumours.[138]

In SSA, a more heterogeneous picture is observed. Some studies from Western Africa show a higher proportion of triple-negative tumours,[139–142] while studies among women from Eastern Africa show a higher proportion of better prognosis ER-positive tumours.[143–145] The prevalence of ER-negativity was 34.7% in the East African Ethiopian cohort, and this prevalence decreased with increasing age at diagnosis.[145] However some Eastern African studies do report higher proportions of TNBC and ER-negative disease.[146–149] A challenge of comparing the prevalence of these different tumour sub-types in SSA is the heterogeneity in the quality of tissue preparation in different parts of the continent as well as the available plateau technique for assays. A study using data from the SEER database comparing the prevalence of ER-negative breast cancers among US-born, Western-African-born, Eastern-African-born, and Jamaican-born black women with US-born white women living in the United States show similar higher proportions of ER-negative tumours among US-born, Western-African-born, and Jamaican-born black women in the United States, while Eastern-African-born women had lower rates of ER-negative breast cancer which were similar to rates observed among US-born white women.[150] Sung et al. 2019 also report higher proportions of TNBC among US-born and Western-African born black US women in comparison with Eastern-African-born black women after controlling for the effect of the stage at diagnosis, the tumour grade, and the histology.[151] Similar results were reported by Newman and collaborators, who found higher proportions of TNBC among Ghanaian (49%) and African-American women (44%) in comparison with Ethiopian (17%) and white American women (24%). In this study, there was a higher frequency of the Duffy-null variant (rs2814778) - which conferred increased resistance to malaria - among women of Western African ancestry. This allele was associated with an increased risk of TNBC (p <0.0001).[152] It is understood that during the trans-Atlantic slave trade, slaves were captured mainly from Western Africa, which

may explain the higher proportion of ER-negative and TNBC observed in Western African and African-American women.[135] Eng and collaborators in 2014 carried out a systematic review and meta-analysis of studies on receptor-defined breast cancer subtypes in African populations.[153] They included 26 studies from SSA and 46 from North Africa. For all studies combined, irrespective of study design, the pooled proportion of ER-positive breast cancer was 0.59 (95% CI: 0.56-0.62) in North Africa, 0.60 (95% CI: 0.56–0.64) in Southern Africa, 0.41 (95% CI: 0.33–0.50) in Eastern Africa, and 0.35 (95% CI: 0.23–0.46) in Western Africa. There were lower proportions of ER-positive breast cancer among South African blacks in comparison with South African whites. When limited to prospectively collected samples, the pooled proportion of ER-positive breast cancer was similar in Northern and sub-Saharan African studies at 59.0%. The pooled proportion for TNBC among prospectively collected samples was 0.21 (95% CI: 0.17–0.25), while this was 0.34 (95% CI: 0.26-0.41) among retrospectively collected samples. For luminal A tumours, the pooled proportion among prospectively collected samples was 0.52 (95% CI: 0.43-0.62), while this was 0.38 (95% CI: 0.30-0.46) among retrospectively collected samples. They highlighted the paucity of quality data on HR and HER-2 status in SSA and the lack of standardized methods for determining receptor status. Prospectively collected samples reported a higher proportion of ER-positive disease as compared with studies on stored samples.

The possibility of differences in the receptor-status distribution by ethnicity or geography in SSA may have implications for treatment recommendations in SSA, particularly in the absence of routine testing for hormone-receptor status. The later presentation and diagnosis in SSA, coupled with the more aggressive disease phenotypes in younger women, and inadequate resources for treatment contribute to the poorer survival rates observed in sub-Saharan Africa.

3.5 Breast cancer survival in sub-Saharan Africa

Data on breast cancer survival from SSA originates from both hospital-based and population-based studies. There are relatively few population-level survival estimates from the sub-Saharan African continent. Ssentongo et al. 2018 presented a systematic review and meta-analysis on breast cancer survival rates in Africa.[14] They included primarily hospital-based reports; the only population-based study included was that by Sankaranarayanan et al. 2010 from SURVCAN-2. Twenty-two study populations were included from 10 of the 46 SSA countries – there were seven studies from Nigeria, four from Ethiopia, three from South Africa, three from Uganda, and one from Burkina Faso, Gambia, Ghana, Guinea, and Tanzania. They included studies from 1977 to 2017. The 5-year survival probability was poorest in Western (35.2, 95% CI: 21.4-49.0) and Eastern Africa (37.7, 95% CI: 26.0–49.3) and higher in Northern (63.3, 95% CI: 57.6-68.9) and Southern Africa (48.1, 95% CI: 17.7-78.5). These regional survival differences observed may be partly attributed to better access to diagnostics and cancer care in the Northern and Southern African region (represented by South Africa in this study) as compared with Western and Eastern Africa. Whites in SSA had better survival outcomes than the black population. Survival was not influenced by age at diagnosis in this meta-analysis of African studies. As expected from the literature, they reported poorer survival outcomes from TNBC in SSA as compared with patients with ER-positive breast cancer.[14]

Prior to the work presented in chapter 6 of this thesis, there had been only two multinational population-based survival studies including sub-Saharan African countries – the SURVCAN-2 study (Cancer Survival in Africa, Asia, the Caribbean, and Central America)[154] and the CONCORD studies.[15,155] Together these two international studies have reported population-level survival estimates from seven of the 46 SSA countries. From SSA, the SURVCAN-2 study presented survival estimates from Gambia, Uganda, and Zimbabwe for cancers diagnosed in the period 1993-1997.[154] From SURVCAN-2 the breast cancer 5-year age-standardised

relative survival for all ages was estimated at 9.5% in the Gambia, 36.1% in Uganda (Kampala), and 54.8% in Zimbabwe (Harare).[76] From SSA, the CONCORD studies presented population-level survival estimates from the Gambia, Mali (Bamako), Mauritius, Nigeria (Ibadan), and South Africa (Eastern Cape). The most recent CONCORD study (CONCORD-3) includes patients diagnosed in the period 2000-2014.[15] In the CONCORD-3 study, the 5-year breast cancer net survival was estimated at 83.8% (95% CI: 75.9-91.3) in the period 2005-2009 in Mauritius, 00.0% (no 5-year survivors) in 2010-2014 in Mali (Bamako), 97.5% (95% CI: 89.9-100.0) in 2010-2014 Nigeria (Ibadan), and 40.1% (95% CI: 30.7-49.6) in 2010-2014 in South Africa (Eastern Cape). The credibility of the findings from Nigeria and Mali have been debated and were flagged by the study authors as being of less reliability.[15]

The largest prospectively collected hospital-based cohort study of breast cancer survival in SSA is the ABC-DO study, which included follow-up data from 2,156 women recruited from Soweto, South Africa, the Imo and Abia states of Nigeria, and from the capital cities of Namibia, Uganda, and Zambia.[156] The 3-year overall survival in this cohort was 50% (95% CI: 48-53) but with large variations observed between and within countries. The 3-year survival was highest among Namibian whites (90%, 95% CI: 78-95) in contrast with 56% (95% CI: 51-62) among Namibian blacks. In South Africa, differences by race were also observed with a 3-year observed survival among mixed-race South Africans estimated at 76% (95% CI: 56-87), while this was 59% (95% CI: 53-64) among black South African women. In Uganda and Zambia, the 3-year observed survival was 44-47%. Survival was lowest among Nigerian women from the Imo and Abia states who were diagnosed and followed-up in the private sector (represented by a private facility in Aba), with a 3-year overall survival estimated at 18% (95% CI:9-29); while women diagnosed in the public sector had a 3-year overall survival estimated at 36% (95% CI:30-42)". The cost of breast cancer therapy was minimal or free for women in South Africa and Namibia, but women from Nigeria, Uganda, and Zambia paid out-of-pocket for cancer care. Women with ER-negative tumours had 69% increased hazards of

death (HR=1.69, 95 CI: 1.38-2.06) in comparison with women with ER-positive tumours, and women with TNBC had 70% increased hazards of death (HR=1.70, 95% CI: 1.32-2.18) in comparison with women with luminal A tumours. Similar higher odds of death with TNBC were described in earlier studies in Kampala, Uganda and Soweto, South Africa.[157,158] The main factors associated with a poorer survival outcome in the ABC-DO study were advanced stage and inadequate therapy. Other factors included very young age at diagnosis (<30 years), higher tumour grade, being HIV positive, being of low socioeconomic status, and rural residence.[156] The rural-urban difference in breast cancer survival has also been described in Ethiopia, where poorer survival outcomes were observed among women residing in rural areas as compared with women in Addis Ababa, with an observed 2-year survival estimated at 53% in rural Ethiopia and 74% in Addis Ababa.[159,160]

The lower breast cancer survival odds for women living with HIV (WLHIV) observed in this prospective study has also been described in a recent cohort from Johannesburg, South Africa (women diagnosed in 2015-2017).[161] These results are in contrast with an earlier study in Johannesburg which did not find increased hazards among WLHIV after adjusting for age, stage, grade, and receptor status.[158] Given the relatively higher HIV prevalence in SSA, researchers have explored if comorbidity with HIV influences breast cancer survival outcomes in these settings. A meta-analysis on survival outcomes of WLHIV in SSA reported 90% more adverse survival outcomes as compared with HIV-negative women (HR=1.90, 95% CI: 1.21-2.99).[162]

3.6 Breast cancer treatment in sub-Saharan Africa

Breast cancer treatment is multidisciplinary or multimodal. This includes local (surgery and radiation therapy) and systemic therapies (chemotherapy, biologic or targeted therapy, and endocrine therapy).[163] Access to comprehensive breast cancer therapy is challenging in many parts of Africa. Breast cancer treatment requires a coordinated surgical, pathological, oncological, nursing, and palliative care team. Unfortunately, there are challenges of limited

health infrastructure and few trained personnel in SSA.[164] Vanderpuye and colleagues reviewed the treatment options available for breast cancer in SSA.[165] They highlighted that surgery is often the main therapeutic option available and used in many parts of SSA. The other forms of therapy are less used due to limited availability.[165] Several studies have described the limited oncology workforce, the shortage of chemotherapy and palliative care medication, and the absence of radiotherapy facilities in many parts of SSA.[166–172]

To take into consideration the limited therapeutic arsenal available in LMIC, the Breast Health Global Initiative in collaboration with the National Comprehensive Cancer Network developed resource-stratified guidelines for cancer care.[17,173] The NCCN Harmonized Guidelines for sub-Saharan Africa provide therapy recommendations for cancer care in SSA adapted to the resource availability of its health care facilities.[174] It presents texts in different colours to serve as a guidepost to the minimum standard of care, to more advanced or optimal care that should be considered where available, as well as options that may not be feasible or available in these settings. These guidelines do not offer options for scenarios where the hormone-receptor status of the tumour is unknown. Unfortunately, in SSA, there is a paucity of pathology services and especially services for IHC. In a recent survey of 20 pathology services serving PBCRs from 17 SSA countries, IHC was available in 10 centres (50%), 8 of these centres also tested for *HER2* over-expression. Half of these pathology centres sent specimens for IHC testing abroad.[175] Adequate pathological assessment of tumours is necessary for optimal therapy planning. In addition to adequate pathological assessment of tumours, there is also a need for timely results. Many patients in SSA do not receive pathologic results for many months following their presentation, which makes it impossible to develop a coordinated care plan.

These system challenges in accessing quality diagnostics and care are coupled with problems of financing health care in LMIC.[176] Earlier detection of breast cancer is associated with better survival outcomes and lower costs of treatment. However, approximately 3 in 4

women with breast cancer in SSA present with advanced-stage disease.[13] The cost of treating patients with advanced breast cancer is a hundred-fold more expensive than treating patients with early-stage breast cancer.[177] In many SSA countries, patients still have to pay out-of-pocket for cancer care, which further impedes their ability to access quality care.[176] One of the major means of improving equitable access to cancer care and cancer outcomes in SSA will be by effectively implementing the Universal Health Coverage (UHC) model which aims at increasing the number of people with access to effective cancer care services, and ensuring financial protection through increasing the amount of government prepaid funds for cancer care and decreasing the proportion of out-of-pocket expenses.[178] UHC is a major policy objective in many countries in SSA, and its attainment will be pivotal for reaching the third Sustainable Development Goal – ensuring healthy lives and promoting well-being for all ages.

3.7 Breast cancer risk factors in sub-Saharan Africa

Breast cancer is a heterogeneous disease, and its aetiology is multi-factorial. Its aetiologic pathways vary with its intrinsic molecular subtypes.[179] Much of what is known of the pathogenesis of breast cancer has been studied in mainly Western and Asian populations. Although its risk factors would most likely be similar across ethnicities,[180] the distribution and relative risks of these risk factors may differ across populations. Breast cancer risk is related to menstrual and reproductive factors (including duration of breastfeeding),[181–186] anthropometric factors such as height and being overweight or obese,[187–189] alcohol consumption,[190–193] inadequate physical activity,[194,195] exposure to exogenous hormones,[196–198] mammographic breast density,[199–201] ionising radiation,[202,203] and the influence of familial history[204] and genetics,[205–208] amongst others. Breast cancer risk factors are categorised into modifiable and non-modifiable risk factors. Modifiable risk factors are those which we can influence by our lifestyle choices, while on the other hand, we have less influence on the non-modifiable risk factors.

In the UK in 2015, 23.1% of breast cancer cases were attributable to known modifiable risk factors - 8.4% were attributable to being overweight or obese, 8.1% to alcohol consumption, 1.5% to ionising radiation, 4.7% to not breastfeeding, 2.1% to post-menopausal hormones and 0.8% to oral contraceptives.[209]

Brinton et al. 2014 presented a literature review of the known and putative risk factors for breast cancer in SSA.[109] There were relatively few high-quality epidemiological studies from the continent. Most of these studies focused on reproductive risk factors such as age at first birth, parity, breastfeeding, age at menarche, and contraceptive use. Other studies also investigated anthropometric factors and breast cancer risk. The largest of the included studies was from the Nigerian Breast Cancer Study cohort.[210] In chapter 5 of this thesis, I present an updated systematic review of the case-control studies done in SSA that investigate reproductive, anthropometric, and lifestyle risk factors (alcohol and physical activity) for breast cancer in SSA. Brinton et al. also highlight the potential role of microbiomes, environmental oestrogens, exposure to pesticides, and the use of hair relaxers and skin lighteners which is more common among African women.[109]

Dichloro-diphenyl-trichloroethane (DDT) is a pesticide commonly used in many parts of SSA for malaria control. Cohort studies carried out in the USA, have shown an association between in-utero and pre-pubertal exposure to DDT and a 3-fold increased breast cancer risk.[211] DDT is classed as probably carcinogenic to humans by IARC.[212] The long-term effects of DDT in SSA and other LMIC require continuous monitoring and further research.

There have been relatively few case-control studies investigating the association between diet and breast cancer risk in SSA.[213–216] Jacobs et al. the largest of these studies, used food frequency questionnaires to study the association between diet and breast cancer in a population-based case-control study in Gauteng, South Africa. They reported a decreased risk

with consumption of fresh fruits and nuts, and an increased risk among postmenopausal women with consumption of savoury snacks.[216] Aglago et al. presented an ecological study on the association between food group availability and cancer incidence in Africa. They reported a positive correlation between the incidence of breast cancer and the consumption of animal products.[217]

Researchers continue to investigate the association between HIV and breast cancer.[218] Although there are similar breast cancer rates among WLHIV and HIV-negative women, breast cancer tends to occur at younger ages among WLHIV.[219] Currently, there is insufficient evidence for a direct association between HIV infection and breast cancer, however, there is a need for additional research on the potential altered breast cancer risk factor distribution among WLHIV. [220] In comparison with the general potential, there might be differences in - the duration of breastfeeding among WLHIV,[220] and an increased risk of central obesity and insulin resistance associated with some anti-retroviral medication.[221]

Of the non-modifiable risk factors, a family history of breast cancer is associated with increased breast cancer risk in SSA.[215,222–224] This familial risk is partially mediated through the action of high-penetrance genes such as the breast cancer genes *BRCA1* and *BRCA2*. There is a twofold increased breast cancer risk with a family history of breast cancer and the risk is even higher if there is a history of premenopausal breast cancer in a first-degree relative.[204] In a small cohort of 94 patients with a family history of breast cancer in Ghana, 60.6% of these patients presented with TNBC and 61.7% of them had mutations in the breast cancer gene (*BRCA)*.[225] In a cohort of 1,136 Nigerian women with breast cancer, unselected for family history or age at diagnosis, Zheng and collaborators found that 14.7% of these women carried a mutation in a breast cancer gene – 7.0% had *BRCA1* mutations, 4.1% had *BRCA2* mutations, 1.0% had *PALB2 (partner and localizer of BRCA2)* mutations, and 2.6% had other genetic mutations.[226] Although Africa has the greatest genetic diversity in comparison

with East Asian, European, or South Asian populations,[227] there have been relatively very few genetically characterised populations in SSA in relation to cancer risk. Abbad et al. reviewed case-control studies investigating the genetics of breast cancer in African populations.[228] This review included studies from only nine of the 54 African countries, the majority of these were from North Africa, Nigeria, and South Africa. Most of these studies focused on mainly *BRCA1* and *BRCA2* mutations. From this review, they found that 27 independent genes had been identified in Africa, however, the majority of these were identified in North Africa, with fewer genetic studies from the majority of SSA.

3.8 Breast cancer control

Although mammography is associated with a 12-30% reduction in breast cancer mortality in Western countries, it is not a cost-effective option for breast cancer screening in SSA and many low-resource settings.[229]This is because the sub-Saharan African population is predominantly young, with higher breast density and less mammographic sensitivity at these younger ages. Furthermore, effective mammographic screening requires a coordinated health delivery system, with adequate infrastructure, personnel, and linkage to care facilities. In the absence of adequate uptake of screening and linkage to care, systematic screening via mammography would have a higher harm-to-benefit ratio. It is estimated that among women aged 40-49 in LMIC, approximately 3,800 women would have to be invited for screening to prevent one death from breast cancer.[229] In the UK, with higher incidence rates, 1000 women aged 40-49 would have to be screened to prevent 1 death.[230]

Other methods have been proposed in LMIC for the early detection of breast tumours. Clinical breast examination (CBE) is a physical breast examination performed by a trained doctor or health care professional to detect breast tumours. The evidence for whether CBE reduces cancer mortality is still unclear but recent studies have suggested possible, albeit non-

significant, benefit in low resource settings. Although CBE is less sensitive than mammography, it may be associated with a reduction in breast cancer mortality in low-resource settings. Duffy et al. estimated that CBE has the potential to prevent 72 out of 1000 breast cancer deaths in settings where more than 70% of women present with advanced tumours.[231] A large prospective cluster-randomised clinical trial carried out in India, showed that CBE carried out every 2 years by trained personnel significantly reduced the proportion of women presenting with advanced-stage breast cancer. This trial showed a non-significant 15% reduction in breast cancer mortality in the screened arm compared with the control arm. Post-hoc sensitivity analysis showed an approximately 30% reduction in breast cancer mortality among women aged 50 and above, however, there was no significant reduction in breast cancer mortality among women <50 years.[232] Breast self-examination has not been shown to reduce breast cancer mortality.[233] An analysis of the Demographic and Health Surveys (DHS) data for the period 2010-2014 on breast cancer screening uptake (CBE, mammography, ultrasound) among women aged 15-49 in Burkina Faso, Ivory Coast, Kenya, and Namibia by Ba et al. (2020) reported that 12.9% of women had ever been screened for breast cancer in these SSA countries.[234] From these surveys of the general population of women aged 15-49, this data most likely captured the prevalence of opportunistic screening. Screening uptake was higher among urban women of higher socioeconomic status, with some form of health insurance, and aged 25 and above. By country, screening uptake was highest in Namibia, where 23.1% of women aged 15-49 had ever been screened for breast cancer.[234]

Earlier detection of symptomatic breast cancer (downstaging) and improving access to care, are pivotal for improving cancer survival outcomes in low resource settings..[229,235,236] Downstaging involves education and increasing awareness of staff and the general population, improvement of cancer referral pathways, clinical breast examination, and surveillance of cancer stage and mortality rates.[229] For clinical downstaging to positively

improve survival outcomes, it must be combined with early treatment and improved diagnostics and therapeutic facilities.[229,236]

3.9 Conclusions

Breast cancer disproportionately affects younger women on the African continent, and more than 70% of them present at advanced stages, as a result of which, survival is poor. Continuous efforts need to be made to improve awareness, downstage breast cancer, and improve access to cancer care in SSA. Further research is needed in SSA to fully understand its burden and aetiology. In the subsequent three chapters, I will explore population-level trends in breast cancer incidence in SSA (Chapter 4), present a systematic review on anthropometric, reproductive and lifestyle risk factors for breast cancer in SSA (Chapter 5), and finally, estimate population-level breast cancer survival from 14 population-based African registries as well as describe the therapy routinely available to women with breast cancer at a population-level in SSA (Chapter 6).

Chapter 4. Breast cancer incidence trends in sub-Saharan Africa

4.1 Foreword

The work presented in this chapter is adapted from a publication accepted by the International Journal of Cancer on April 1st, 2020, and published as:

Joko-Fru, W. Y.; Jedy-Agba, E.; Korir, A.; et al. The Evolving Epidemic of Breast Cancer in sub-Saharan Africa: Results from the African Cancer Registry Network. Int. J. Cancer, 2020, 147 (8), 2131–2141. https://doi.org/10.1002/ijc.33014, published CC-BY 4.0.

For the results presented in this paper and chapter, I did the data cleaning and the statistical analyses and produced all the tables and figures that are included. I wrote the paper drafts and made revisions based on co-authors' and reviewers' comments. Permission was obtained from my supervisors and co-authors to reuse this paper as a thesis chapter. This work was done using data from the AFCRN, and the co-authors from the African registries contributed primary data for the analyses (Appendix 2). I have made updates to some of the literature cited and included additional information in the methods, results, discussion, and appendix sections. Following the analyses presented in this chapter, I visited the Kampala Cancer Registry in January 2020 to help improve the completeness of the cancer cases recorded in 2014 and 2015. A brief report of this visit is presented in Appendix 3.

4.2 Introduction

Breast cancer incidence rates in Africa are increasing. The average annual percentage change (AAPC) in the breast cancer incidence rate was estimated at 4.5% between 1991 and 2006 in Kampala, Uganda, and at 4.9% between 1991 and 2010 in Harare, Zimbabwe.[31,237] In a recent study describing cancer trends in people aged 60 and above in SSA, breast cancer

incidence was estimated to be increasing at an annual rate of 5% in Harare and Kampala, while slower rates of increase were observed in women under the age of 60.[238] Conversely, an earlier study in Western Africa (Bamako (Mali) and The Gambia) had described a more rapid breast cancer incidence rate among women aged 55 and below.[239] In contrast, the U.S. SEER Program in the period 1992-2011 observed stabilising rates among White non-Hispanic women with an estimated AAPC at -0.4%, while incidence rates among black and Asian/Pacific women were still moderately increasing, at 0.2% and 0.6% respectively.[240]

The rapid rate of increase in breast cancer incidence in SSA in recent years has been attributed to a "westernisation" of lifestyles, that encompasses the effects of changing reproductive patterns – delayed age at first birth, fewer children and reduced breastfeeding duration – as well as changes in diet, alcohol intake, and body weight, among other factors.[241] Other determinants unique to women of African origin have been suggested, such as the use of skin lighteners and increased exposures to hormone modulators in skincare and hair products, as often used by women of African descent.[109,242,243]

Although this changing risk is common across populations, the incidence of breast cancer in SSA varies across countries and regions as shown in Chapter 3. The IARC publications "Cancer Incidence in Five Continents" (CI5) volumes I to XI have reported on the incidence of cancer at a population level worldwide since the 1960s. 11 out of the 46 SSA countries have appeared in any of these publications, although only 2 (Kampala-Uganda and Harare-Zimbabwe) have appeared in four successive volumes.[6] Thus, little is published on long-term cancer trends from other SSA countries. Clearly, more studies are needed to understand the breast cancer incidence trends in SSA; separating out the contributing effects of ageing of the population, the aetiological effects on successive generations, and changes that simultaneously affect all studied age groups in a particular period, which may represent changes in diagnostic capacity or completeness of cancer registration.

In this chapter, the temporal trends observed in the breast cancer incidence rates are described, using data generated by member registries of the AFCRN. Incidence changes among women <50 years and ≥ 50 years are described using PBCR data from 10 countries representing each of the four sub-Saharan African regions. Incidence trends in successive birth cohort effects are also explored.

4.3 Methods

4.3.1 Data sources

Completely anonymised data were obtained on incident cases of breast cancer (International Classification of Diseases, ICD-10 C50) from the database of the AFCRN (http://afcrn.org). Data were included on invasive primary tumours of the breast occurring in African females aged 15 and above. The AFCRN is a network of sub-Saharan African PBCRs that facilitates homogenization of registration activities, collaboration, advocacy, and research. For a PBCR to obtain membership into the AFCRN, it must have attained at least 50% coverage of its target population on admission and at least 70% coverage by its third year.[32] There are currently 35 population-based member registries within the network. For this trend analyses, only those registries with at least 10 years of continuous data on breast cancer incidence were included The registries were grouped according to the United Nations geoscheme for Africa.[244]

From the Eastern African region, data were included from; Blantyre – Malawi (1994-2011), Bulawayo – Zimbabwe (1963-1972 and 2011-2015), Harare – Zimbabwe (1990 – 2014), Kampala (Kyadondo County) – Uganda (1990 – 2014), Mauritius (2001-2014), Nairobi – Kenya (2003-2014) and Seychelles (2004-2015). From the Middle African region; Brazzaville – Congo (1996-2017). From the Southern African region; Eastern Cape – South Africa (1998-2014). Finally, from the Western African region, data were included from The Gambia (1986 – 2012) and Ibadan – Nigeria (1991 – 2010). The population-based registries of The Gambia,

Mauritius, and Seychelles cover the national territory, while all the others cover urban areas, except for the Eastern Cape registry of South Africa, which covers a rural population.

These registries use mainly active methods for case detection, and the data are entered electronically into the CanReg5 software, developed by IARC. This software helps identify duplicate cases and applies internal quality checks. The International Classification of Diseases for Oncology (ICD-O) topography and morphology coding[245] are used by all the registries.

4.3.2 Obtaining population estimates

Country-specific population censuses were obtained from their respective National Statistics Office reports. To obtain the population-at-risk for each year between census reports, intercensal interpolations by sex, and within 5-year age groups were made assuming a constant logarithmic increase. These estimates are made based on methods first described by Das Gupta for India in 1971.[246] It assumes a relatively stable population, which is not significantly affected by migration. The rate of change (r) in the population size in the intercensal period (assuming a constant logarithmic increase) is obtained by the formula:

$$r = Log_e \left({}^{CHANGE}/_{t} \right)$$

Where the "CHANGE" is the ratio of the population size in the most recent census, to the population size in the earlier census, within each age group and by sex, and "t" is the time difference between the two censuses.

Once the rate of change has been calculated, estimates of the intercensal population size for each inter-censal year, by age-group, and by sex were obtained based on the formula:

$$Population\ estimate = n \times e^{(r \times t)}$$

Where "n" = population size for that age group and sex from the last census, "r" = rate of change in population size and "t" = time difference in years since the last census.

Post-censal projections were made assuming a linear rate of increase at the rates observed following the preceding census.[247] This is because we cannot assume an indefinite exponential increase in population size post-census. In making linear projections, the difference in the population estimates between the last two censuses is obtained (instead of the proportional change as was the case for the logarithmic change) and this is divided by the length of time between the censuses. This gives us the value of the linear change in the population size by year. We then add this same amount each subsequent year to obtain post-censal population estimates. This is described by the equation:

$$Population_y = Population_{y-1} + \left(Population_{most\ recent\ census} - Population_{previous\ census} \middle| t\right)$$

Where "y" is the post-censal year for which you want to estimate the population size and "t" is the time in years between the last two censuses.

4.3.3 Data preparation

For the incidence trend analyses, registries with a minimum of 10 years of continuous data, with no major fluctuations by month and year were included. The longest periods of available data which met these conditions were used. For each registry, I then cleaned and re-categorised the data for subsequent statistical analyses.

4.3.4 Data analyses

For each registry, the proportion of cases registered based only on a death certificate – Death Certificate Only (DCO) cases – and of morphologically verified (MV) cases were calculated. These proportions are used as indicators of the data quality for each registry.[35]

Age-specific (5-year age groups) and crude incidence rates per 100,000 women were estimated by registry for the entire period and by 5-year calendar periods. Age standardisation was done by the direct method, using the World Standard population described by Segi and modified by Doll.[248] Direct age standardisation can be used when the age-specific incidence rates are known. It involves applying the registry's age-specific

incidence rates to a hypothetical standard population.[248] Age standardisation controls for differences in population structures by registry and across calendar periods. The age-standardised incidence rates were calculated by year and by 5-year calendar periods.

The cumulative risk for each 5-year period were also calculated. The first step in the estimation of the cumulative risk is the calculation of the cumulative rates by registry. The cumulative rate is the sum of age-specific rates for each year from birth till age 74 (for 0-74), or otherwise specified age. The cumulative rate is another form of direct age standardisation, which has the advantage of being independent of an arbitrary standard population.[105] The cumulative risk can be obtained from the cumulative rate by the formula:[249]

$$Cumulative\ risk = 100 \times \left(1 - e^{\frac{-cumulative\ rate}{100}}\right)$$

The cumulative risk (from 0-74) expresses the overall risk of developing breast cancer before age 75 in the absence of competing risks of death.[250] The cumulative risk were calculated by registry and for each 5-year calendar period.

Temporal trends in the age-standardised incidence rate were examined using joinpoint regression,[38] with a maximum of three joinpoints and with the changes in the trend expressed as an annual percent change. Joinpoint regression involves fitting a straight line to the log-transformed age-standardized incidence rates. It fits the simplest model first with the smallest number of joinpoints, and tests for the necessity of adding more joinpoints to the model using a Monte Carlo Permutation Method,[251] with a significance level set at 0.05. From this, the AAPC was obtained, which is a weighted average of the changing trends in each segment of the model. This weighting is based on the number of years represented by each segment. The AAPC was estimated for all women by registry, and among older (50-74) and younger women (15-49).

For two of the registries, Kampala - Uganda, and Harare - Zimbabwe, which have contributed to four successive volumes of CI5, an exploratory analysis of the age-specific breast cancer incidence rates by birth cohort for the age range 25-74 was done. For 5-year calendar periods between 1990 and 2014, the central age for each 5-year age group was subtracted from the mid-year of the period of diagnosis to obtain 10-year overlapping and synthetic birth cohorts. For Kampala, incidence rates for 1990 and 2014 were incomplete, as were those for Harare in 2007-2009 (due to problems with the medical services during the economic crisis in those years).[31] A modification of the method proposed by Schifflers et al. was used;[252] this involved fitting a fourth-degree polynomial rather than cubic splines to interpolate values for the missing years, based on the observations in adjacent periods. This graphical analysis is critical to understanding and interpreting what is observed in the summary age-standardized rates, as sometimes summary rates cannot adequately represent time trends in the presence of influential cohort effects.[253]

4.3.5 Ethical considerations

Approval for this study was obtained from the AFCRN Research Committee and from participating registries. The study made use of routinely collected population-level anonymized data. The study was performed in accordance with the Declaration of Helsinki.

4.4 Results

4.4.1 Registry characteristics

Table 4.1 presents an overview of the 11 PBCRs included, from 10 SSA countries, grouped by geographical region. Registry coverage ranged from 1.8% of the national population in Ibadan, Nigeria to 100% (national coverage) in Seychelles, Mauritius, and The Gambia. The Eastern Cape registry was the only sub-national PBCR covering a rural population, the rest covered urban areas. The percentage of morphologically verified cases ranged from 58.2% in Kampala, Uganda to 98.1% in Mauritius. The percentage of cases diagnosed based on a death certificate only was less than 10% for all registries. The included period differed by

registry. The earliest period included was the 1963-1972 data from Bulawayo, Zimbabwe. This was followed by a halt in cancer registration activities in this registry. Cancer registration resumed in Bulawayo in 2010, and data are included from 2011 to 2015. The other registries had continuous cancer registration activities; and dependent on the data availability by registry, data were included from the 1990s till 2017 (Table 4.1).

Table 4.1: Description of included registries for time trend analyses.

Region	Country	National population,* 2010	Registry Catchment Area	Catchment population,** 2010	Percentage of country covered,2010	Calendar period	Basis of diagnosis		
							MV %	Clinical %	DCO %
Eastern Africa	Kenya	42,030,676	Nairobi	3,237,000	7.7	2003 - 2014	82.9	14.1	3.0
	Malawi	14,539,612	Blantyre	701,000	4.8	1994 - 2011	60.7	38.8	0.5
	Mauritius	1,250,400	Mauritius	1,250,400	100	2001 - 2015	98.1	1.7	0.2
	Seychelles	89,770	Seychelles	89,770	100	2004 - 2015	97.3	2.3	0.4
	Uganda	32,428,167	Kampala	1,594,000	4.9	1990 - 2014	58.2	39.9	1.9
	Zimbabwe	12,697,723	Bulawayo	658,000	5.2	1963 - 1972	90.3	9.7	0.0
			Bulawayo			2011 - 2015	79.0	21.1	0.0
			Harare	1,475,000	11.6	1990 - 2014	80.1	11.6	8.3
Middle Africa	Republic of Congo	4,273,731	Brazzaville	1,574,000	36.8	1996 - 2017	69.7	33.8	0.0
Western Africa	Gambia	1,793,196	The Gambia	1,793,196	100	1986 - 2012	61.4	38.4	0.0
	Nigeria	158,503,197	Ibadan	2,814,000	1.8	1991 – 2010	75.0	21.2	0.4
Southern Africa	South African Republic	51,216,964	Eastern Cape	6,743,800	13.5	1998 - 2016	86.8	13.2	0.0

**World Bank Population Database*[254] ***UN World Urbanisation Prospects*[255] *MV%= Proportion of morphologically verified cases, DCO%= Proportion of death certificate only cases*

4.4.2 Age distribution of breast cancer cases

The modal age group at diagnosis for most of the registries was the 45-49 age group in the period 2005-2009 (Figure 4.1). Exceptions to this trend were observed in the PBCR of Mauritius and South Africa, with the modal age at diagnosis occurring after age 50. The modal age group was age 55-59 in Mauritius, and age 60-64 in Eastern Cape, South Africa. An even younger age distribution of patients with breast cancer is observed in Gambia (modal age 40-44), and in Blantyre, Malawi (Figure 4.1).

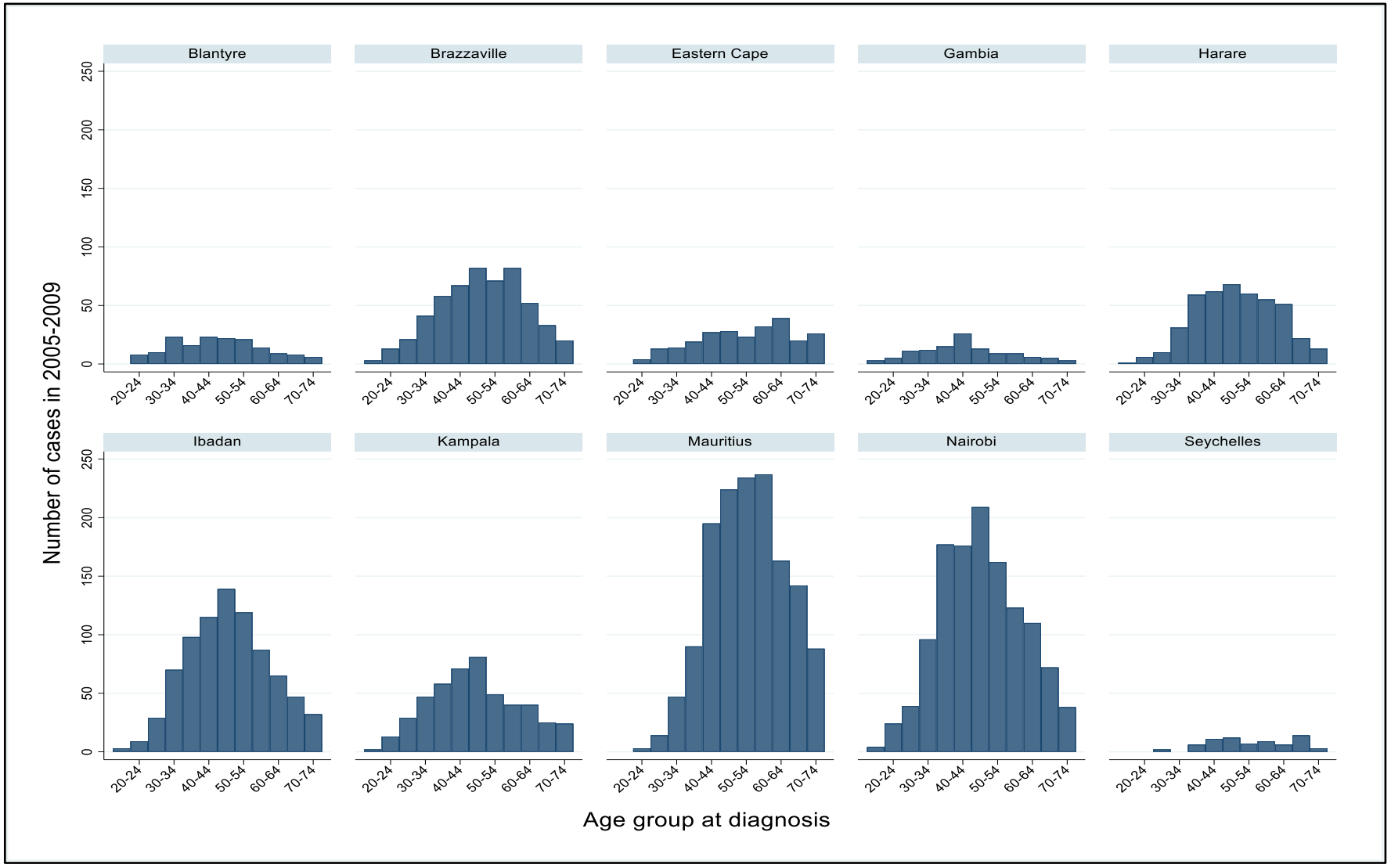


Figure 4.1: Age distribution of women with breast cancer in 10 sub-Saharan African registries in the period 2005-2009.

4.4.3 Crude, age-standardised, and cumulative incidence rates by period

Table 4.2 shows the numbers of cases and the incidence rates (crude, age-standardised, and cumulative risk) by five-year calendar periods. During the 2005-2009 calendar period (for which data are available for all registries except Bulawayo), the age-standardised incidence rate (ASIR) ranged between 7.9 per 100,000 women in The Gambia to 54.3 per 100,000 women in Nairobi-Kenya. (Table 4.2). Like the ASIR, the breast cancer cumulative risk varied between and within regions, with the highest values in the most recent calendar period observed in Nairobi-Kenya at 7.3% (approximately 1 in 14 women will develop breast cancer by age 74 with no other competing causes of death), followed by Mauritius and Seychelles at 5.7%. Lower cumulative risks were observed in Middle, and Western Africa. Data from South Africa was from the rural Eastern Cape cancer registry, where there are relatively lower breast cancer rates observed as compared with urban cities, however, there are gradual increases in the age-standardised incidence rates over time in this rural registry. The lowest cumulative risk was observed in The Gambia, which did not exceed 1% in any calendar period. A decline was observed in the incidence rates in Brazzaville from 2010 onwards. For Bulawayo – Zimbabwe, historical data was included from the 1963-1972 period as well as the most recently available data from 2011-2015. There was a more than 3-fold increase in the age-standardised incidence rates over this period, from 12.6 to 39.4 per 100,000 women, with a corresponding tripling in the cumulative risk (Table 4.2).

Table 4.2: Breast cancer crude incidence rates, age-standardised rates, and cumulative risk by registry area and calendar period.

Registry Catchment Area	Calendar period	Number of cases	Crude incidence rate (per 100000)	ASIR (per 100000)	Cumulative risk (0-74) %
EASTERN AFRICA					
Kenya, Nairobi	2003 – 2004*	339	14.2	44.0	5.1
	2005 - 2009	1277	18.2	54.3	6.3
	2010 - 2014	2007	22.7	63.2	7.3
Malawi, Blantyre	1995 - 1999	78	4.1	9.3	1.0
	2000 - 2004	132	6.1	13.2	1.4
	2005 - 2009	186	7.5	15.3	1.5
	2010 – 2011*	140	13.0	28.9	3.3
Mauritius	2001 – 2004*	1069	44.0	40.2	4.3
	2005 - 2009	1606	51.6	43.5	4.7
	2010 - 2014	1069	69.8	53.0	5.7
Seychelles	2005 - 2009	89	37.2	33.6	3.5
	2010 -2014	128	56.4	48.5	5.7
Uganda, Kampala	1990 – 1994ǂ	198	6.9	18.3	2.1
	1995 - 1999	301	8.7	23.9	2.5
	2000 - 2004	384	8.8	27.2	3.0
	2005 - 2009	521	9.9	29.3	3.2
	2010 – 2014ǂ	739	11.5	30.7	3.4
Zimbabwe, Bulawayo	1963-1972	31	4.2	12.6	1.4
	2011-2015	399	23.2	39.4	4.5
Zimbabwe, Harare	1990 - 1994	215	8.0	20.9	2.1
	1995 - 1999	274	9.0	25.9	2.8
	2000 - 2004	354	10.3	27.2	3.0
	2005 - 2009 ǂ	561	15.5	36.9	4.0
	2010 - 2014	781	20.8	44.6	5.1
MIDDLE AFRICA					
Congo, Brazzaville	1996 – 1999*	223	10.3	12.8	1.1
	2000 - 2004	313	10.4	15.0	1.6
	2005 - 2009	556	16.0	28.1	3.1
	2010 - 2014	515	12.7	22.6	2.4
	2015 - 2017*	343	12.5	23.9	2.6
WESTERN AFRICA					
The Gambia	1986 – 1989*	28	1.4	3.0	0.3
	1990 - 1994	66	2.7	6.0	0.5
	1995 - 1999	100	3.5	7.3	0.5
	2000 - 2004	112	3.4	6.4	0.5

Table 4.2 continued

Registry Catchment Area	Calendar period	Number of cases	Crude incidence rate (per 100000)	ASIR (per 100000)	Cumulative risk (0-74) %
	2005 - 2009	157	4.0	7.9	0.5
	2010 – 2012*	127	4.8	7.9	0.7
Nigeria, Ibadan	1991 – 1994*	188	4.9	7.7	0.8
	1995 – 1999	321	6.1	9.9	1.1
	2000 - 2004	675	11.5	17.5	1.9
	2005 - 2009	847	12.9	19.7	2.1
SOUTHERN AFRICA					
South Africa, Eastern Cape	1998 – 1999*	77	6.7	9.2	1.0
	2000 - 2004	165	5.7	7.5	0.8
	2005 - 2009	274	9.5	11.5	1.2
	2010 - 2014	296	10.1	11.8	1.3
	2015 – 2016*	147	12.3	13.8	1.4

*ASIR = Age-standardise incidence rate *This period had less than 5 years of data ǂ Includes interpolated data*

4.4.4 Temporal trends in age-specific rates

Figure 4.2 shows the age-specific rates by registry in successive calendar periods. We observe rapid increases in incidence rates in pre-menopausal women till about age 45, followed by a decline in the gradient of the curves after age 45 in most registries. In Brazzaville and Seychelles, this decline in the gradient of the curves is seen after age 55 for some calendar periods. There are fluctuations in the age-specific rates in The Gambia and in the 2005-2009 period in Seychelles due to the smaller number of diagnosed cases in these registries. Overall, these trends point towards a gradual increase in age-specific incidence rates in successive calendar periods for most registry areas, with the relative difference in age-specific rates over time being greater for women aged 45 and above. In Bulawayo (Zimbabwe), with historical and more recent data on breast cancer temporal trends, we observe more clearly a greater divergence in the curves at older ages, pointing at more rapid increases in incidence rates among older women.

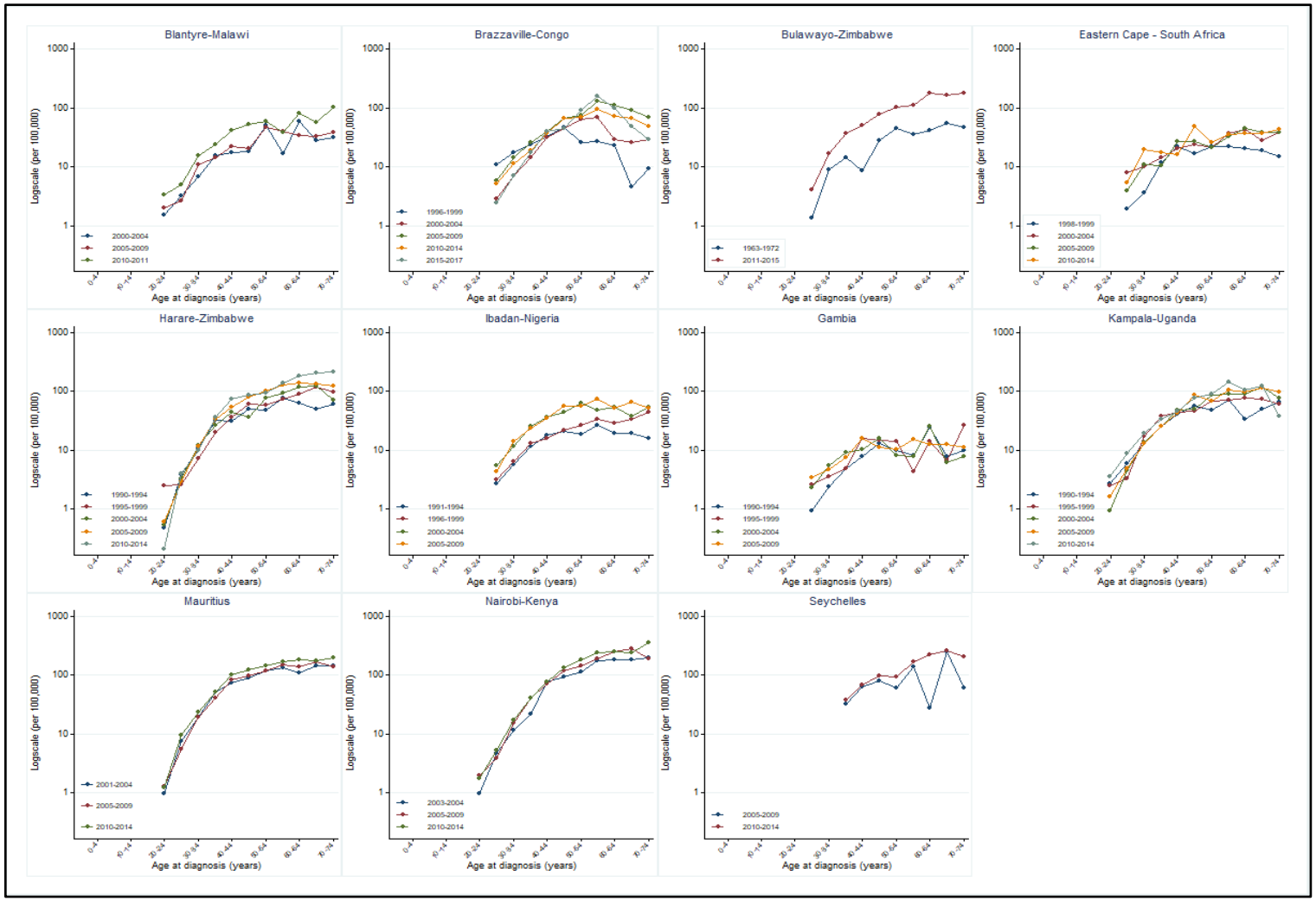


Figure 4.2: Breast cancer age-specific incidence rates by calendar period, and registry area.

4.4.5 Temporal trends in age-standardised rates

The breast cancer ASIR are of different magnitudes across the SSA continent. Figure 4.3 shows the age-standardised incidence trends for all registries by year, presented as 3-year moving averages, as well as the AAPC for all years of available data. Temporal trends in incidence rates continued to increase during the study period in all registries, except in Nairobi where rates stabilized during 2010-2014 after rapidly increasing from 2003-2010 (AAPC=8.5, 95% CI: 3.0-14.2), and in The Gambia where the rates are relatively stable (AAPC = 1.3, 95% CI: 0.0 – 2.6). In registries like the Blantyre cancer registry, which had historically very low rates, a higher burden of breast cancer is recorded in recent years, which is reflected in the high AAPC observed (AAPC = 7.6, 95% CI: 4.0 – 11.3). Although the majority of these registries cover urban cities, increasing breast cancer incidence rates are also observed in the rural Eastern Cape cancer registry (AAPC = 3.0, 95%: 1.2-4.6) (Figure 4.3).

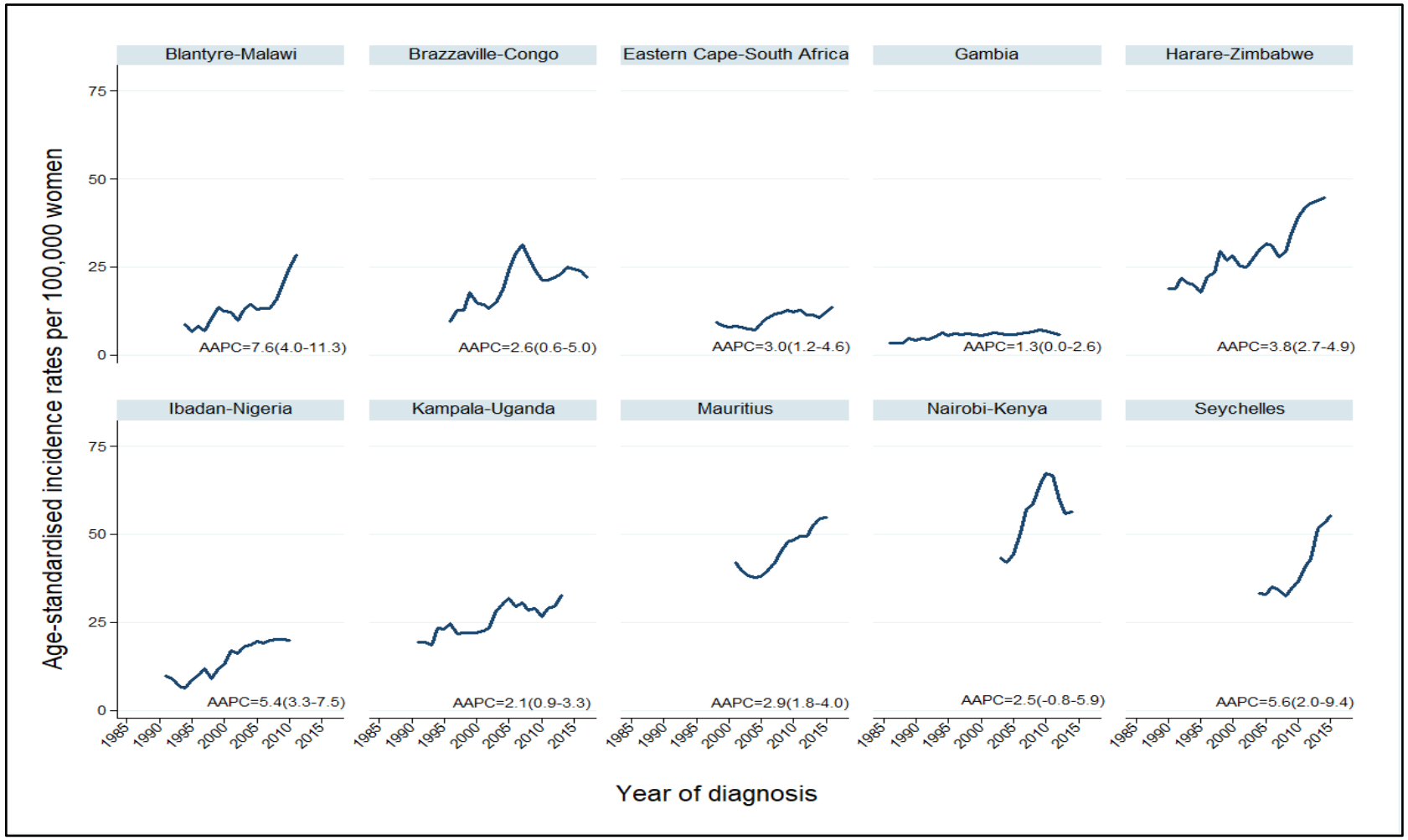


Figure 4.3: Breast cancer age-standardised incidence rates plotted as three-year moving averages and the average annual percentage change by registry area.

4.4.6 Incidence trends in women by age at diagnosiss

Figure 4.4 shows temporal trends in the ASIR for women aged <50 and ≥50 years, presented as 3-year moving averages. Incidence rates are higher in women aged ≥50 for all registries compared with younger women. In The Gambia, there is a progressive convergence of rates observed among women <50 and 50+, pointing at faster incidence rates observed in later years among younger women. Table 4.3 presents the Joinpoint regression analyses for all the years of available data for women <50 and ≥50 years. In The Gambia, the AAPC showed a significant increase in incidence rates among women <50 compared with women aged 50+. In Blantyre (Malawi), and Eastern Cape (South Africa), the AAPC is higher for women less than 50 compared with women aged 50 and above, although with overlapping confidence intervals. A faster rate of change in the breast cancer ASIR was also observed among women aged <50 years in Nairobi (Kenya) in the 2003-2010 period (AAPC = 5.8, 95% CI:1.5 -10.3). In Mauritius, the AAPC shows similar rates of increase, at approximately 2.9% per year, among older and younger women. For the other registries, the AAPC indicates a more rapid rate of increase in breast cancer incidence rates among women diagnosed aged 50 and above.

Figure 4.4: Breast cancer age-standardised incidence rates plotted as three-year moving averages, in women <50 and women 50+ by year of diagnosis and by registry area.

Table 4.3: Annual percentage change by registry among women of all ages, aged <50 and aged 50+

Region	Registry	Period of diagnosis	AAPC in women <50 (95% CI)	AAPC in women 50+ (95% CI)
Eastern Africa	Kenya-Nairobi	2003 - 2010	5.8* (1.5 - 10.3)	-
		2011 - 2014	-10.0 (-22.5- 4.6)	-
		2003 - 2014	1.7 (-1.5 – 5.0)	2.5 (-1.1-6.3)‡
	Malawi-Blantyre	1994 - 2011	8.6* (5.7 – 11.6)	6.0* (1.6 – 10.6)
	Mauritius	2001 - 2015	2.9* (1.7 – 4.1)	2.9* (1.6 – 4.2)
	Seychelles	2004 - 2015	4.0 (-2.5 - 10.9)	6.7* (1.5 – 12.0)
	Uganda-Kampala	1990 - 2014	1.0 (-0.3-2.4)	2.9* (1.0 – 4.9)
	Zimbabwe-Harare	1990 - 2014	2.7* (1.3 – 4.0)	4.3* (2.8 – 5.7)
Middle Africa	Congo-Brazzaville	1996 - 2017	-0.2 (-2.2 – 1.9)	4.8* (1.6 – 8.2)
Western Africa	Gambia	1986 - 2012	2.1* (0.7 – 3.5)	0.4 (-1.3 – 2.2)
	Nigeria-Ibadan	1991 – 2010	4.5* (2.0 – 7.1)	6.0* (3.9 – 8.1)
Southern Africa	South Africa- Eastern Cape	1998 - 2016	3.0* (0.5 – 5.5)	2.7* (0.9 – 4.5)

**Indicates the Average Annual Percentage Change (AAPC) is significant at the alpha = 0.05 level; CI= Confidence Interval*

‡ *A single trend line could best describe the data in women 50+ in Nairobi for the entire period 2003-2014*

4.4.7 Birth cohort effects

Age-specific incidence rates by year of birth are shown in Harare- Zimbabwe (Figure 4.5) and Kampala-Uganda (Figure 4.6). There is an increase in the breast cancer age-specific incidence rates in successive generations (by year of birth), for women aged 40-44 and older at time of diagnosis in Harare. In Kampala, this progressive increase in incidence rates is observed for successive generations of women aged 45-49 to ages 50-59. Among older women (60+) in Kampala, there is an attenuation of this increasing incidence rates in recent generations. Fluctuations in incidence rates are observed among younger women in both countries, with less steep increases in incidence rates observed among younger women across birth cohorts. (Figure 4.5 and Figure 4.6).

The graphical representation of the birth cohort and birth period effects using data from the Kampala and Harare registries before data interpolation for the incomplete years are shown in Appendix Figure 8 and Appendix Figure 9.

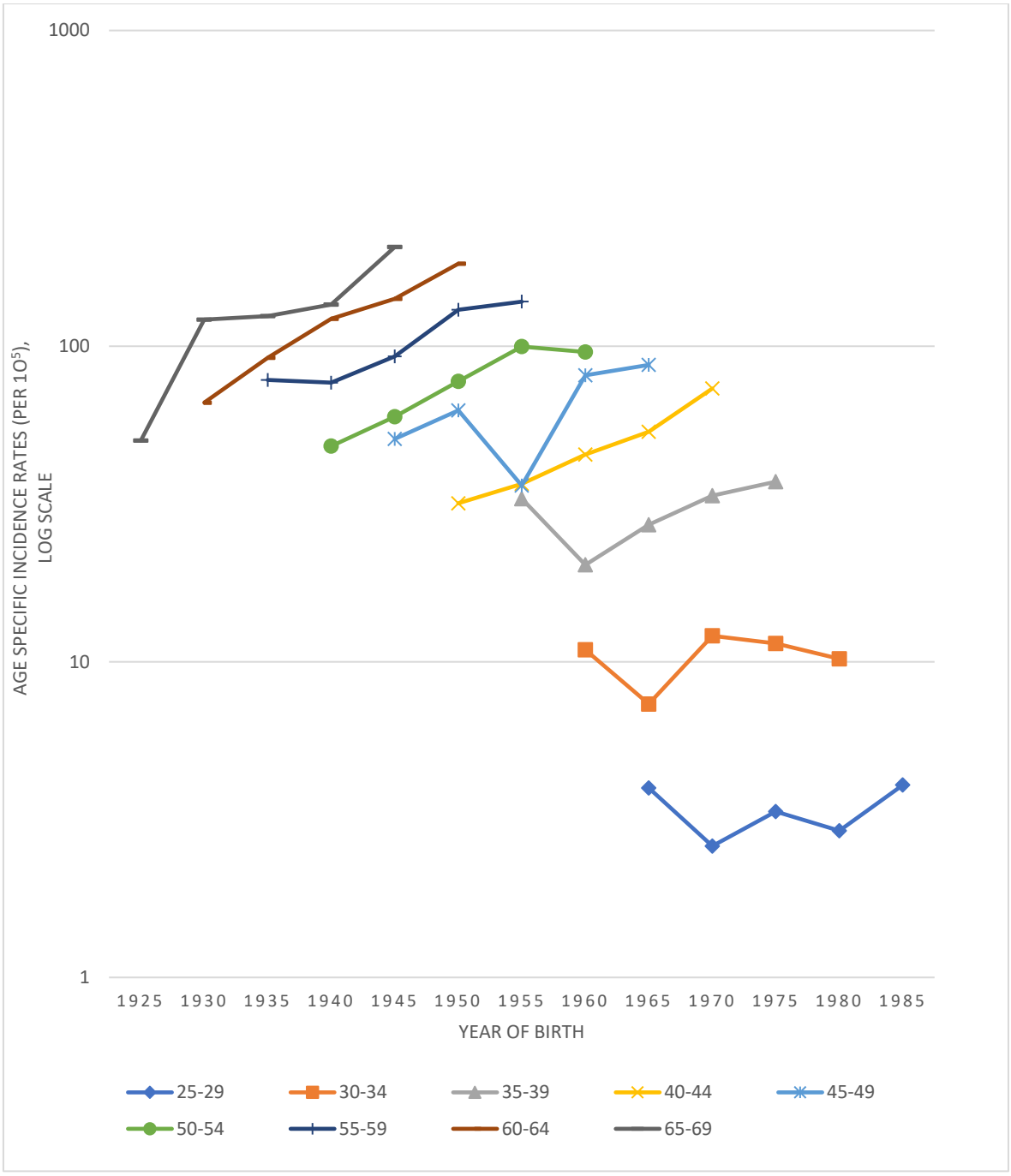


Figure 4.5: Breast cancer age-specific incidence trends by year of birth (birth cohort) and by age at diagnosis in Harare, Zimbabwe for the period 1990-2014.

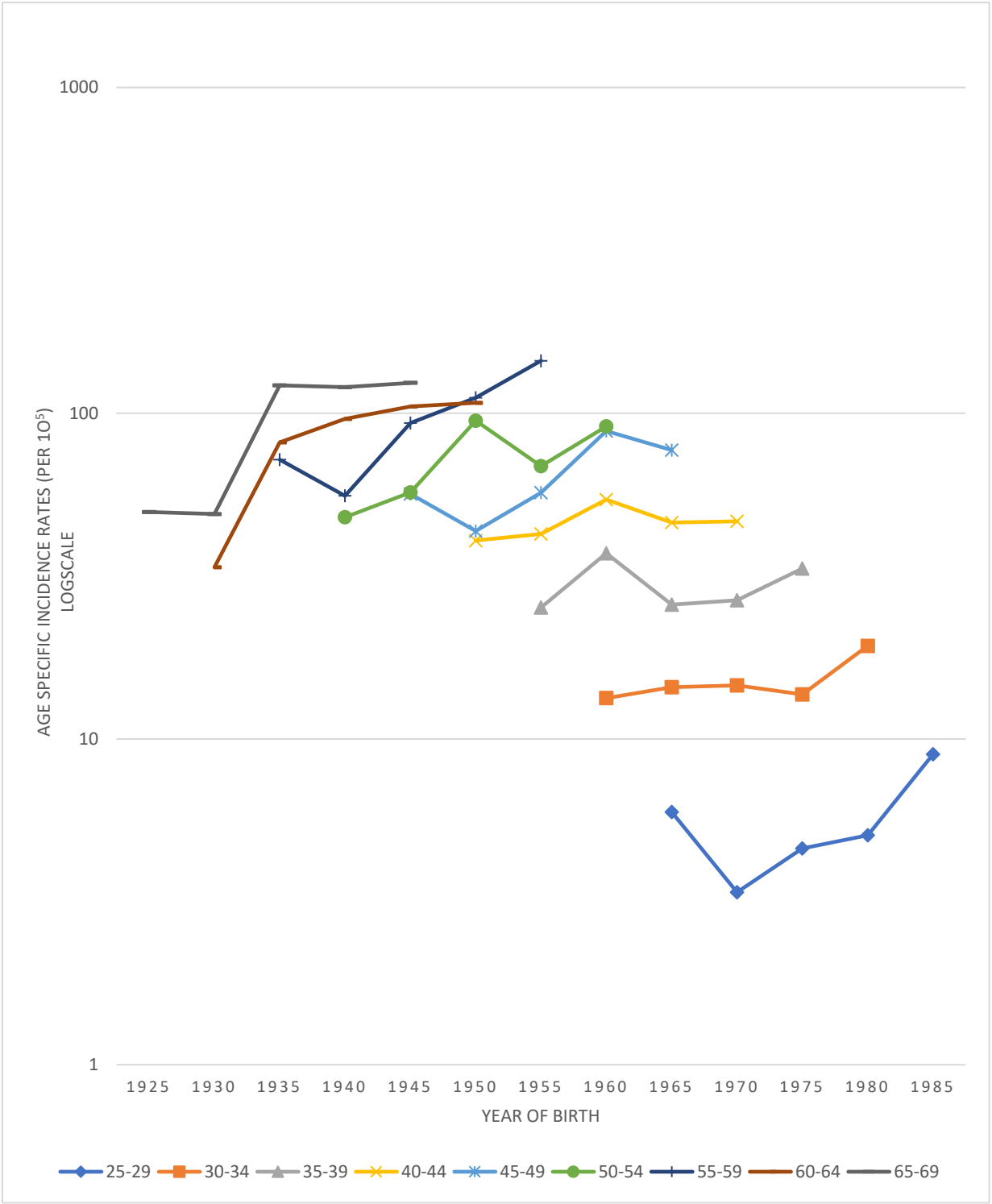


Figure 4.6: Breast cancer age-specific incidence trends by year of birth (birth cohort) and by age at diagnosis in Kampala, Uganda for the period 1990-2014.

4.5 Discussion

4.5.1 Main findings in the context of previous research

This chapter presents breast cancer incidence trends in the populations covered by 11 population-based registries of SSA. Although these registries vary in their coverage and completeness, they provide important insights on the variability in the breast cancer burden and incidence trends that exists within Africa.

Breast cancer incidence rates are increasing in almost all of these populations, from all four regions of SSA, in both rural (Eastern Cape – South Africa) and urban populations. The highest rates, however, are observed in urban, more affluent areas like Nairobi-Kenya, Mauritius, and Seychelles. Although age-specific and age-standardised rates are higher in older women (≥50 years) compared with younger women (<50 years), the younger demographic construct of African populations means that most breast cancer cases are diagnosed in women aged under 50, an observation made in many clinic-based studies[256–258]. It does not however imply a higher risk in younger women compared with older women, as has been noted previously.[259] Similarly, the relatively small increase in incidence with age in older women, evident in Figure 4.2 (compared with that observed in western populations) represents a cohort effect, with progressively higher incidence rates in more recent generations[259] – an effect visible in Figure 4.5 – most clearly for Harare. As a result, at any period of observation, older women will appear to have relatively lower rates, and there may even be an apparent decrease in risk with age (as in some of the curves in Figure 4.2).

For areas for which we have data as far back as the 1960s, a more than three-fold increase in the risk of breast cancer is observed over five decades in these countries. In CI5 Volume I,[100] the breast cancer ASIR in the period 1954-1960 in Kampala (Uganda) was estimated at 8.8 per 100,000 women, however, in 2005-2009 it was estimated at 29.2 per 100,000 women. In Bulawayo (Zimbabwe) the ASIR was estimated at 12.6 per 100,000 women in the period 1963-1972 while in the period 2011-2015, it is estimated at 39.4 per 100,000 women (Table

4.2). In Maputo (Mozambique), during the period 1956-1961, the breast cancer ASIR was 3.2 per 100,000 women[100,260] while by the period 2015-2017 it had reached 15.7 per 100,000 women.[54] These trends point towards increasing breast cancer rates across sub-Saharan African countries. Despite these increasing rates, observed particularly in post-menopausal women, they are lower than rates observed in more developed countries. In Appendix 4, data from GLOBOCAN 2020 was used to compare the ratio of the cumulative risk and ASIR of post-menopausal (aged 50+) to pre-menopausal (aged <50) using national-level estimates for different African regions, Europe, and North America. Rates of post-menopausal breast cancer are much higher than pre-menopausal in all world regions; although the ratios are lower in most regions of Africa where increases in generation-specific incidence rates appear to be continuing. This is partly due to the birth cohort effects seen in Figure 4.5, whereby rates increase within each age group among successive generations of women. However, the higher differential among post-menopausal women in developed countries may partly reflect the effects of population-level screening, with increases in recorded rates in women in screened age groups resulting from lead-time (earlier diagnosis than would have otherwise occurred in the screened group) and overdiagnosis effects. In the pre-screening era in Denmark, the cumulative risk of developing breast cancer was estimated at 8%,[261] and in 2018 the cumulative risk was estimated at 9.5%.[262] The lifetime risk of developing breast cancer in the United States. for all races in 2010-2012 was estimated at 12.3% (1 in 8 women).[111] In this study, in the most recent 5-year calendar period, the cumulative risk of developing breast cancer before age 75 ranged from 0.5% in The Gambia to 7.3% in Nairobi-Kenya (Table 4.2).

The influence of oestrogens on breast cancer pathogenesis is probably similar across regions of the world,[263] such that, the variability in the magnitude of recorded incidence is related to transitioning risk factor profiles in different SSA countries. Older age at first birth, reduced duration of breastfeeding, lower parity, and use of hormone-replacement therapy are all associated with increased breast cancer risks, as are low physical activity levels

(increased sedentarism) and increasing obesity rates.[263] The DHS provide insights on the prevalence and changes in some of these risk factors over time in Africa.[264] The DHS estimates that the prevalence of women with a body mass index (BMI) >25kg/m^2 has increased in Zimbabwe from 23% in 1994 to 34.9% in 2015, and from 8.4% in 1995 to 18.8% in 2011 in Uganda. Fertility rates are declining across SSA; for example, the average number of live births per woman decreased from 7.4 to 5.7 in Zimbabwe, and from 5.4 to 4.0 in Uganda from the 1980s to 2015. A greater proportion of African women are entering tertiary education, with corresponding delays in the age of marriage and first birth,[265] while greater numbers of women returning to work after maternity may limit the average duration of breastfeeding. Breast cancer risk is reduced by 4-7%[266,267] for every year of breastfeeding.

The increased risk conferred by these risk factors is more marked in older women. Obesity is associated with an increase in post-menopausal breast cancer.[268] Among African-American women, obesity is associated with an increased risk of oestrogen-receptor positive (ER-positive) breast cancer (more common in older women), and a decrease in the risk of TNBC.[269] In Ghana, Figueroa et al. showed that increased parity (≥3 births) was associated with a reduced risk of both ER-positive and ER-negative breast cancer among women aged 50+ but was associated with an increased risk of early-onset ER-negative tumours. Extended breastfeeding was also associated with a protective effect for both ER-positive and ER-negative breast cancer, although the protective effect was stronger for ER-positive tumours.[270] In a small Ugandan hospital-based study, no differences in the distribution of reproductive risk factors by ER status were found among breast cancer cases.[271]

The use of oral contraceptives has been shown to increase breast cancer risk in current and recent users. The use of modern contraceptives, amongst which are exogenous hormones, varies by sub-Saharan African region with the lowest use in Middle and Western Africa and the highest use in Southern Africa;[272] there is a greater uptake of contraceptive use among women of higher socioeconomic status.[273] The use of injectables and implants have

increased among sexually active women over time in SSA according to data from the DHS and the Performance Monitoring and Accountability Surveys 2020.[272] The use of injectable and/or oral contraceptives in South Africa was associated with significantly increased breast cancer risk, and this increased risk persists for about 5-10 years after cessation.[274] Reduced physical activity has been associated with increased breast cancer risk in SSA,[275] and physical activity during leisure in many SSA countries is relatively low.[276] There are also ongoing changes in diet with "westernisation" characterised by increased consumption of diets richer in calories and poorer in fruits and fibre. The increased use over time of animal over plant-based products in SSA correlates with increased breast cancer incidence rates.[217] Consumption of diets rich in fruits and cruciferous vegetables have been associated with a decreased breast cancer incidence rates in South Africa, while diets rich in calories and that are nutrient-poor conferred higher incidence rates.[216]A more complete review of these breast cancer risk factors will be presented in Chapter 5, as well as a summary of the trends in the population-level prevalence of these risk factors at ecological level in SSA.

These changing risk factor patterns across Africa surely account for much of the increase in breast cancer incidence rates, the larger increases observed in older (post-menopausal) women, as well as probably, explaining disparities in the magnitude of the breast cancer burden in different regions. However, incorporating all known risk factors in risk prediction models still underestimates risk among strata of the population.[277] In addition to the known modifiable risk factors, there are genetic predispositions and gene-environmental interactions for which more studies are needed on the African continent.[228,278] In Nigeria, Zheng and collaborators reported that, among women with breast cancer unselected for family history, 7.0% and 4.1% of them carried inherited genetic mutations in *BRCA1* and *BRCA2* genes respectively.[226] On the other hand, the prevalence is of these gene mutations is lower among Caucasians with breast cancer unselected for family history (2.9%), except for Ashkenazi Jews where approximately 10% of cases with breast cancer carry mutations in

BRCA1.[279] African Americans diagnosed with breast cancer before age 65 have a lower prevalence of *BRCA1* mutations compared with whites of a similar age group, however, among African Americans with early-onset breast cancer approximately 16.7% of cases have mutations in *BRCA1*.[280] Women with *BRCA1* gene mutations have a 65% (95% CI: 44%-78%) cumulative risk of developing breast cancer before age 70, while women with mutations in the *BRCA2* gene have a 45% (95% CI: 31%-56%) cumulative risk of developing breast cancer before age 70.[281]

Other less established risk factors which are more prevalent among African women, such as the use of hair relaxers and dyes,[242,243] skin lighteners[242] as well as exposure to DDT (an endocrine modulator used for malaria control in many SSA countries), require more comprehensive studies across different African settings.[109]

4.5.2 Limitations

Although the results in this chapter provide insights into the changing breast cancer incidence rates across different African countries, the estimates from these registries are not perfect, as maintaining completeness and constancy in registration activities within Africa depends on several socioeconomic factors as well as political stability in these countries. Caution is needed in interpreting these trends, as sometimes it may be challenging disintegrating data artefacts from real changes in the direction of the trends. Challenges in cancer registration were documented in the 2007-2009 period in Zimbabwe as a result of severe socioeconomic challenges in the country.[31] To minimise registration artefacts, only those registries with the most consistent registration activities were included, as evidenced by relatively constant numbers of registrations per year, as well as indicators such as MV% and DCO%, and several long-established registries for which such consistency was uncertain were excluded. Five of those included (Harare, Uganda, Blantyre, Seychelles, and Nairobi) have appeared in one of the last four volumes of CI5. In recent years, a drop in the completeness of registration activities was observed in Kampala (Uganda), as reported in

Appendix 3. This prompted active efforts by the AFCRN to support the registry in updating records for these last years. In Nairobi (Kenya), declining rates were also observed in recent years (2011-2014), which may be as a result of a lag in the completeness of cancer registration activities. The most recent iteration of Cancer Incidence in Five Continents (CI5) (volume XI) included cases from 2008-2012 from Nairobi (Kenya) and Kampala (Uganda).[51] The declining trends in recent years in these two registries will need to be explored and addressed actively in order to continually ensure robust estimates of the cancer incidence burden and trends in these registries. However, there have been relatively few independent external audits of the completeness of these cancer registration activities in recent years as described in section 2.2.1.4, thus, more objective studies of the quality and completeness of these registries would be necessary. Furthermore, the proportion of morphologically verified cases varies across registry areas, ranging from 58.2% in Kampala Uganda to 98.1% in Mauritius. This could reflect differences in access to pathologic diagnostic services in different countries.

Given the long time series available, and previously reported time trends of breast cancer incidence,[239] data from The Gambia was included. The fluctuations in the incidence rates observed in the Gambia are likely due to a deficit of cases in older age groups. This registry is known to suffer incompleteness of case finding – particularly in older subjects[45] - and this appears to be an increasing problem, which probably accounts for the observed results from this registry. In addition to potential problems of registry quality, calculation of rates relies upon interpolations of population censuses usually done at 10-year intervals, such that, the accuracy of the denominators will depend on the available census data.

4.6 Implications and conclusion

Despite these challenges and limitations, these results highlight the rising cancer burden in many SSA countries and the need for targeted actions across the cancer continuum. It will be necessary to raise breast cancer awareness in SSA, conduct more in-depth and context-

specific risk factor studies across Africa, and ensure the provision of adequate curative treatment and palliative care services to meet the demands of an increasing number of breast cancer patients. They also highlight the necessity of supporting the maintenance of good quality population-based cancer registration activities which are essential for the study of cancer trends at population-level. In the next chapter, I will explore further the breast cancer risk factors from sub-Saharan African studies and will report the results of a systematic review on the anthropometric, reproductive and lifestyle risk factors associated with breast cancer from sub-Saharan African studies.

Chapter 5. Breast Cancer Risk Factors in sub-Saharan Africa

5.1 Overview

The role of hormones on breast cancer pathogenesis has been studied extensively in Western populations. Patterns associated with an increased risk include an early age at menarche, low parity, a limited duration of breastfeeding, obesity in post-menopausal women, alcohol use, oral contraceptive use, menopausal hormone therapy (MHT) use, insufficient physical activity, and genetics.[179,181,188,195,197,263,282] Efforts have been made to study breast cancer risk among African American women in order to better understand risk factors of greatest relevance to women of African descent. However, there is insufficient breast cancer aetiologic research from the African continent.

In this chapter, I present an updated synthesis on breast cancer risk factors from sub-Saharan African studies and describe trends in the prevalence of measured risk factors at population-level in SSA. The aim is to summarise the available information on breast cancer risk from case-control or cohort studies in SSA, highlight research gaps, and summarise the available data on the trends in population-level risk factors in SSA. The chapter is presented in the following sub-sections:

1. A systematic review on breast cancer risk factors in SSA
2. Description of trends in the population-level risk factors for breast cancer in SSA
3. Discussion

5.2 Systematic review on breast cancer risk factors in sub-Saharan Africa

5.2.1 Background

Much of what we know about the aetiology of breast cancer are from studies carried out in more developed nations. Several collaborative groups have focused on the aetiologic research on breast cancer from mostly Western populations.[189,192,193,198,283,284] However relatively few collaborative groups have focused on the aetiologic research on breast cancer on the African continent.

Evidence from ethnic minority groups in England suggest that the role of these established risk factors is likely to be similar irrespective of ethnicity;[180] however, what may differ would be the distribution of these risk factors, as well as possible gene-environmental interactions, which may affect the strength of these associations.

Brinton et al. (2014)[109] and Kantelhardt et al.(2015)[285] published literature reviews on breast cancer in SSA. Brinton et al. presented a review on the breast cancer incidence and risk factors in SSA, while Kantelhardt et al.'s systematic review was primarily focused on breast cancer treatment and care in SSA. These reviews highlighted the paucity of and the need for more aetiological research on the African continent. In Chapter 3, section 3.7, I presented a brief overview of the aetiological research carried out in SSA.

In this section, an updated systematic review is carried out to synthesize the evidence on the association between breast cancer and anthropometric factors, reproductive patterns, alcohol use, and physical activity among women resident in SSA.

5.2.2 Methods

5.2.2.1 Literature search

The study protocol was registered in the International Registry of Prospectively Registered Systematic Reviews in health and social care (PROSPERO), registration number CRD42020226279 (https://www.crd.york.ac.uk/prospero/).

To guide the selection process of papers for inclusion and exclusion, the following framework was used:

- *Population:* Women with a breast cancer diagnosis (ICD10-50) living in SSA
- *Exposure:* Risk factor studies on anthropometry, reproductive factors, or lifestyle (alcohol and physical activity)
- Comparison: None
- *Outcomes:* Measures of association with breast cancer (ICD 10-50): (odds ratios, relative risk, risk differences)
- *Study designs:* Case-control or prospective cohort studies

I searched five databases – Ovid MEDLINE, Ovid Embase, Ovid Global Health, Scopus, and the Cumulative Index of Nursing and Allied Health Literature database (CINAHL) without any language restrictions. I searched all databases from inception until July 1st, 2020. The following search terms were used, adapted to the different databases:

[“breast cancer” or exp. Breast cancer/ or (breast or mammary) adj3 (neoplas* or carcinoma? or malign* or cancer? or sarcoma? or tumo?r?)] AND

[exp. Africa/ or Africa or Angola or Angolan or Benin or Beninese or Beninois or Botswana or Batswana or Burkina Faso or Burkinabe or Burundi or Burundian or Cameroon or Cameroonian or Cameroun or Camerounaise or Cape Verde or Cape Verdean or Cabo Verde or Central African Republic or Chad or Chadian or Comoros or Comoran or Congo or Congolese or Djibouti or Djiboutian or Equatorial Guinea or Equatoguinean or Eritrea or

Eritrean or Ethiopia or Ethiopian or Gabon or Gabonese or Gambia or Gambian or Ghana or Ghanaian or Guinea or Guinean or Guinea Bissau or Guinea-Bissau or Guinea-Bissauan or Ivory Coast or Ivorian or Cote d'Ivoire or Kenya or Kenyan or Lesotho or Basotho or Liberia or Liberian or Madagascar or Malagasy or Malawi or Malawian or Mali or Malian or Mauritius or Mauritian or Mozambique or Mozambican or Namibia or Namibian or Niger or Nigerien or Nigeria or Nigerian or Sao Tome or Sao Tomean or Rwanda or Rwandan or Rwandese or Senegal or Senegalese or Seychelles or Seychellois or Sierra Leone or Sierra Leonean or Somalia or Somali or South Africa or South African or Sudan or Sudanese or Swaziland or Swazi or Tanzania or Tanzanian or Togo or Togolese or Uganda or Ugandan or Zambia on Zambian or Zimbabwe or Zimbabwean or sub-Sahara* or subSahara*].

In addition, I searched the Open Science Framework platform (https://osf.io/) for preprints, the PROSPERO protocol database for any similar reviews on the subject, and reference lists of reviews on breast cancer in Africa.

The search results were compiled in EndNote for deduplication by a single researcher (YJ). Two reviewers independently screened the title and abstracts of included articles, using the Rayyan platform (https://rayyan.qcri.org/) with real-time annotations and recording of reasons for inclusion and exclusion. A total of 150 articles were considered to possibly be of relevance from the title and abstract screen.

Studies on black African women, resident in SSA were included. These were observational studies (case-control or prospective cohort studies), with primary data collected on breast cancer risk factors - anthropometric, reproductive, and lifestyle (alcohol and physical activity) factors.

Studies were excluded if they only included African women non-resident in SSA, if they were from North Africa (Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara), if they reported only molecular or genetic data, and if they included no primary data on

measures of association with breast cancer with either anthropometric factors, reproductive factors, alcohol, or physical activity.

5.2.2.2 Data extraction

The data were extracted into a pre-tested data extraction form in Google Forms. This permitted a second independent data extractor to enter the data for comparison and quality control purposes. The data entered in the Google Forms template was exported to Microsoft Excel for further analyses. Data were extracted on:

- Study characteristics: Author, country(ies) in which study was carried out, year of publication, study design, study duration, start and end date of the study, total sample size, number of cases, number of controls, sampling method.
- Details on risk factors: Risk factor(s) studied, the unadjusted measure of association, confidence interval or standard error, the adjusted estimate, confidence interval or standard error, factors adjusted for.
- Study limitation(s).

If several studies were published from the same cohort, reporting similar outcomes at different points in time, the last study or that with the largest study size was included. Multiple studies were included from the same cohort if the publication reported a specific outcome not reported in an earlier study.

5.2.2.3 Assessing for risk of bias and confounding

Assessment for confounding and bias was done at study level, using the "Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology" guidelines (COSMOS-E) proposed by Dekkers and colleagues.[286]

The key characteristics considered for quality assessment for each study were:

- Confounding: we independently documented what factors had been adjusted for, how they were measured, and if there were any known confounders not considered in the design or analysis stage of the study.
- Selection bias: we recorded if the controls were selected from the same population from which the cases arose and if the cases and controls were comparable in terms of their potential exposure to the risk factors being studied.
- Information bias: we evaluated and documented any systematic differences in the ascertainment of information on risk factors from cases or controls. Was the information on exposure (breast cancer risk factors) documented in the same way between cases and controls?

For each of these categories, we labelled a study to be of low, moderate, or high risk using the following template as a guide (Table 5.1):

Table 5.1: Guide used for risk of bias assessment.

	Risk of bias assessment guide.		
Category	**Low**	**Moderate**	**High**
Confounding	Potential risk of residual confounding with observational studies and of reverse causation for some of the associations observed. Thus, none of the case-control studies were evaluated as being of "low" risk for confounding.	If steps were taken by the researchers at the design and/or at the analysis stage to control for the effect of potential confounders	If only crude estimates were presented, or relevant confounders were not adjusted for
Selection bias	Study design ensured that cases and controls were comparable and from the same source population. Population-based y controls were generally considered as being of low risk of selection bias.	Hospital-based controls were considered to be of "moderate" risk of selection bias, given that most of the hospitals from which cases were recruited were referral hospitals for cancer management, and thus the cases would most likely come from all parts of the region or country, while controls who were either recruited from surgical wards, general outpatient clinics, or gynaecological wards, may not have had the same referral patterns as the cases.	If cases and controls were not comparable or not from the same population
Information bias	Potential risk of recall bias in all case-control studies. So, none were considered as being of "low" risk for information bias.	Given the risk of recall bias for all the self-reported risk factors, all the case-control studies with self-reported exposure variables were considered to be of "moderate" risk of information bias.	If in addition to the inherent risk of recall bias, that information ascertainment from cases differed with that from controls, or studies reported high proportions of missing data, then the study was considered to be of "high" risk of information bias.

This was adapted from the COSMOS-E "Conducting Systematic Reviews and Meta-analyses of Observational Studies of Etiology" guidelines.[286]

This assessment was done at study level by myself and independently by a second reviewer (OS). Any disagreements were evaluated and discussed with the supervisory team.

5.2.2.4 Data Synthesis and Analysis

A descriptive synthesis of the included studies was done. Results were presented by risk factor category (anthropometric, reproductive and lifestyle factors), by patient characteristics (pre-menopausal, post-menopausal), and by period.

- Data were pooled and analysed if there were risk factor groups with similar categorisation of risk factors or with categories that could be rescaled and homogenised.
- Meta-analyses were done in Stata 16 using the "metan" suite of commands if studies used similar categories for measurement of exposure. Depending on the characteristics of the included studies, a random or fixed meta-analysis was used. A fixed-effect model was used if the exposure and the outcomes measured were comparable across different studies, while a random-effects model was used if there was heterogeneity in the exposures and outcomes being measured. Rescaling of continuous variables to a common scale was done where it was possible to pool values using the formula: [287]

$$HR_y = (HR_x)^{\frac{y}{x}}$$

Where HR= Hazard ratio, *y*= desired scale, *x*=original scale

The 95% confidence intervals are obtained by: [287]

$$LCI_y = (LCI_x)^{\frac{y}{x}}$$

Where LCI = lower confidence interval, *y*= desired scale, *x*=original scale; and

$$UCI_y = (UCI_x)^{\frac{y}{x}}$$

Where UCI = upper confidence interval, *y*= desired scale, *x*=original scale.

5.2.3 Results

Thirty-eight publications from 27 independent study populations were eligible for inclusion (Figure 5.1).

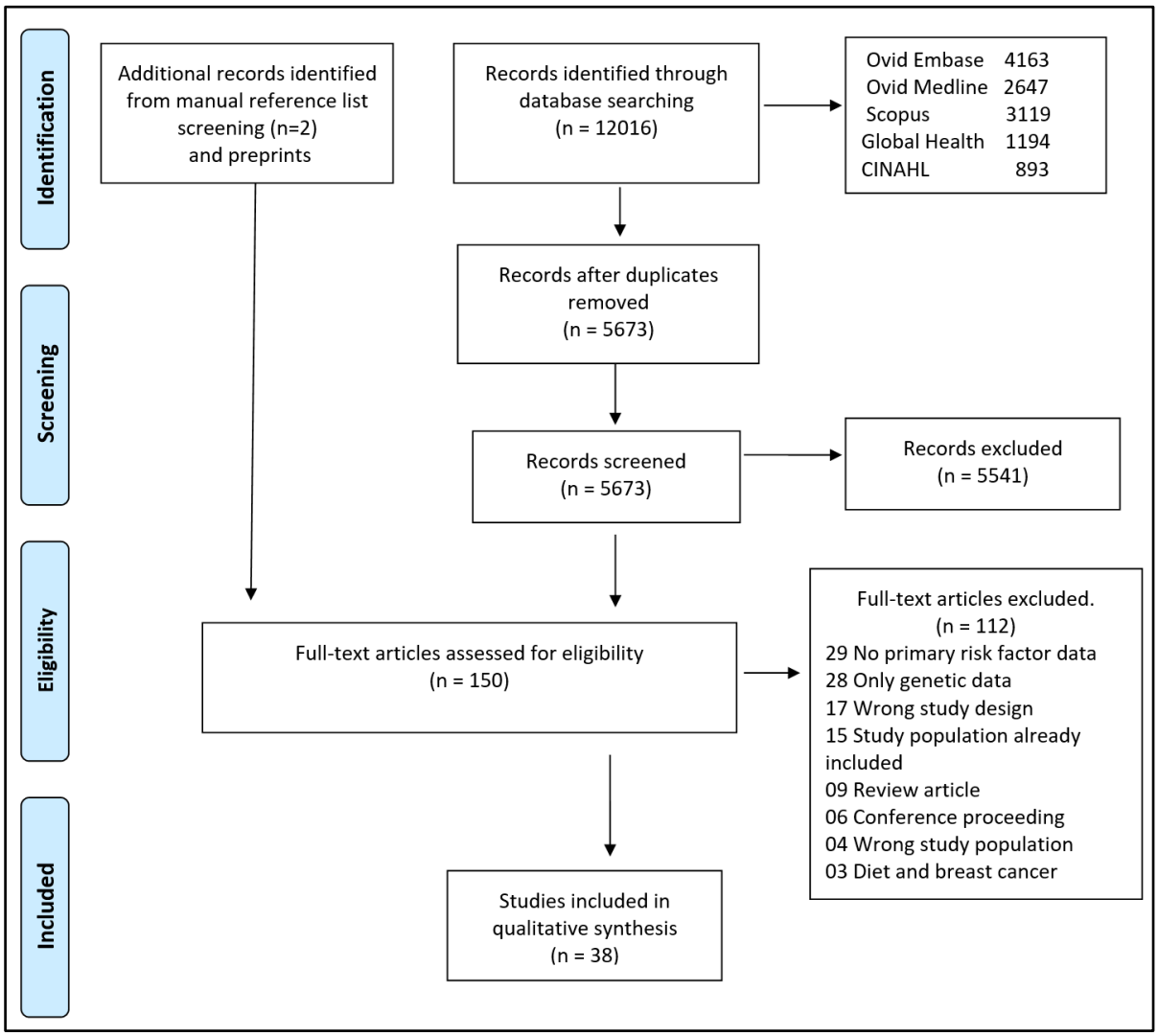


Figure 5.1: Study selection.

All the included studies were case-control studies. There were no cohort studies on the association between known risk factors and breast cancer risk in SSA.

Figure 5.2 shows the countries from where these studies were carried out. They were published between 1975 and 2020 and were conducted in only 10 of the 46 SSA countries.

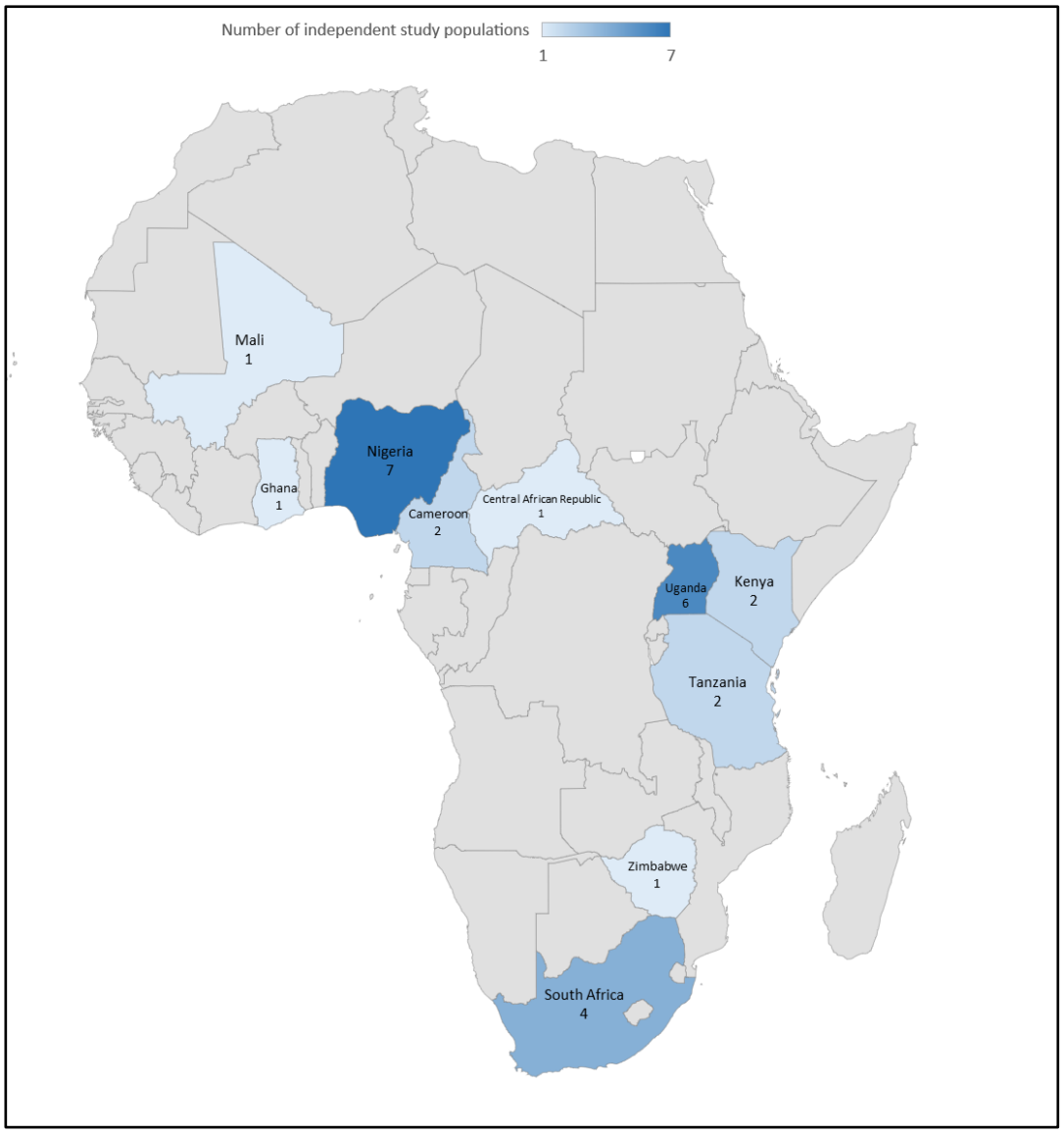


Figure 5.2: Map showing the number of independent study populations by country.

Table 5.2 summarizes the data on the included studies. Of these 38 studies, only two, Figueroa et al. (2020)[270] and Bigman et al. (2020)[288], presented risk factors by breast cancer hormone receptor status (HRS). Of the 38 studies, 13 presented results stratified by menopausal status.

Table 5.2: Included studies which reported on the association between reproductive, anthropometric, physical activity, or alcohol use and breast cancer risk in sub-Saharan Africa.

Authors	Start Year	End Year	Country	Year of publication	Total study size	Number of cases	Number of controls	Study site	Comments
Anderson et al.[289]	NA	NA	South Africa	1975	166	96	70	Multi-centre hospitals	
Walker et al.[290]	1986	1987	South Africa	1989	152	59	93	Single-centre hospital.	
Thomas and Noonan[291] **WHO collaborative study.**	1979	1986	Kenya	1991	800	49	751	Single-centre hospital	Focused on oral contraceptives. (Appendix 7)
Thomas and Noonan[292] **WHO collaborative study.**	1979	1986	Kenya, Nigeria	1993	826	62	764	Multi-centre hospitals	Focused on breastfeeding. (Appendix 7)
Parkin et al.[293]	1963	1977	Zimbabwe	1994	2691	344	2347	Population-based cancer registry setting	
Skegg et al.[294] **WHO collaborative study.**	1979	1986	Kenya	1995	801	49	752	Single-centre hospital	Focused on injectable contraceptives
Ssali et al.[295]	1990	1991	Uganda	1995	172	86	86	Multi-centre hospitals	
Amir et al.[296]	1996	1996	Tanzania	1998	101	50	51	Single-centre hospital	
Adebamowo and Adenkule[297]	1992	1995	Nigeria	1999	500	250	250	Single-centre hospital	
Coogan et al.[298]	1994	1997	South Africa	1999	1917	446	1471	Multi-centre hospitals	Focused on lactation
Shapiro et al.[299]	1994	1997	South Africa	2000	2109	484	1625	Multi-centre hospitals	Same population as Coogan et al, 1999 (Focused on contraceptives)
Rosenberg et al.[222]	1994	1997	South Africa	2002	288	65	223	Multi-centre hospitals	Black only population of Shapiro, 2000 and Coogan, 1999
Adebamowo et al.[300]	1998	2000	Nigeria	2003	507	234	273	Single-centre hospital	Nigerian Breast Cancer Study (NBCS)
Okobia et al.[223]	2002	2004	Nigeria	2006	500	250	250	Multi-centre hospitals	

Table 5.1 continued

Authors	Start Year	End Year	Country	Year of publication	Total study size	Number of cases	Number of controls	Study site	Comments
Okobia et al.[301]	2002	2004	Nigeria	2006	500	250	250	Multi-centre hospitals	Same population as Okobia et al.,2006 (Focused on anthropometry by menopausal status)
Huo et al.[267]	1998	2006	Nigeria	2008	1388	819	569	Single-centre hospital	NBCS (Focused on parity and breastfeeding)
Ogundiran et al.[210]	1998	2009	Nigeria	2010	2334	1233	1101	Single-centre hospital	NBCS (Focused on body size)
Sule[302]	NA	NA	Nigeria	2011	142	71	71	Multi-centre hospitals	
Awio et al.[303]	NA	NA	Uganda	2012	140	70	70	Single-centre hospital	
Ogundiran et al.[304]	1998	2009	Nigeria	2012	2334	1233	1101	Single-centre hospital	NBCS (Focused on body fat distribution)
Urban et al.[305]	1995	2006	South Africa	2012	3156	1664	1492	Multi-centre hospitals	
Jordan et al.[306]	2004	2007	Tanzania	2013	345	115	230	Single-centre hospital	
Mukasa et al.[307]	2011	2012	Uganda	2013	183	90	93	Single-centre hospital	
Hou et al.[308]	1998	2011	Nigeria	2013	1715	718	997	Single-centre hospital	NBCS (Focused on pregnancy-associated breast cancer)
Sighoko et al.[239]	2005	NA	Mali	2013	502	253	249	Multi-centre hospitals	
Hou et al.[275]	2011	2013	Nigeria, Cameroon, Uganda	2014	1572	558	1014	Multi-centre hospitals	Includes data from the NBCS. (Focused on physical activity)
Qian et al.[309]	1998	2013	Nigeria, Cameroon, Uganda	2014	4727	2138	2589	Multi-centre hospitals	Includes data from the NBCS. (Focused on alcohol)
łOthieno-Abinya et al.[310]	2011	2012	Kenya	2015	694	339	355	Multi-centre hospitals	

Table 5.1 continued

Authors	Start Year	End Year	Country	Year of publication	Total study size	Number of cases	Number of controls	Study site	Comments
Rukundo et al.[311]	2012	2012	Uganda	2014	145	72	73	Single-centre hospital	
Sighoko et al.[312]	1998	2013	Nigeria, Cameroon, Uganda	2015	4626	1995	2631	Multi-centre hospitals	Includes data from the NBCS. (Focused on risk after first-full term pregnancy)
Kana et al.[313]	2009	2010	Nigeria	2015	172	29	143	Single-centre hospital	
Galukande et al.[314]	2011	2012	Uganda	2016	350	113	237	Multi-centre hospitals	
ǂEssiben et al.[214]	2015	2015	Cameroon	2016	315	105	210	Multi-centre hospitals	
Balekouzou et al.[315]	2003	2015	Central African Republic	2017	522	174	348	Multi-centre hospitals	Focused on reproductive risk factors
Balekouzou et al.[215]	2003	2015	Central African Republic	2017	522	174	348	Multi-centre hospitals	Same study population as Balekouzou et al.,2017 (Focused on behavioural risk factors)
Brinton et al.[224]	2013	2015	Ghana	2017	3363	1201	2161	Multi-centre hospitals	Focused on study design considerations.
Figueroa et al.[270]	2013	2015	Ghana	2020	3232	1126	2106	Multi-centre hospitals	Same study cohort as Brinton et al.,2017
Bigman et al.[288]	2014	2016	Nigeria	2020 (preprint)	944	472	472	Multi-centre hospitals	

ǂ Did not specify baseline categories against which comparisons were made, so not included in subsequent tables. NA= Not available NBCS = Nigerian Breast Cancer Study

5.2.3.1 Reproductive Factors

Data were extracted from studies that reported on the association between breast cancer and any of the following: age at menarche, age at menopause, parity, age at first full-term pregnancy, breastfeeding, or contraceptive use. No attempts were made at abstracting data on surgical menopause since, although it is a procedure that is associated with reduced breast cancer risk (particularly if both ovaries are removed), it is an operation that has a low prevalence in SSA.

5.2.3.1.1 Age at menarche

Fifteen studies reported on the association between age at menarche and breast cancer in SSA (Table 5.3). In eight of these studies, an older age at menarche was associated with a reduction in breast cancer risk, although in seven of these eight studies, this association was not statistically significant. Although these studies used different cut-offs to define an older age at menarche, in all these studies women with an age at menarche of age 12 or later were categorized as being of an older age at menarche (Table 5.3). In the study by Walker et al. 1989, the odds of getting breast cancer was not related to the age at menarche (OR=1.0 (95% CI: 0.4-3.1)). In five studies (Ssali et al. 1995, Amir et al. 1998, Sule et al. 2011, Galukande et al. 2016, and Figueroa et al. 2020), contrary to the literature, an older age-at-menarche was associated with an increased breast cancer risk, although for three of these studies (Sule et al. 2011, Galukande et al. 2016, and Figueroa et al. 2020), this association was non-significant. Figueroa et al. 2020 was the largest of the included studies (Table 5.3).

Of the 15 included studies, five reported on the association with age at menarche by menopausal status. One of them reported on the association between pregnancy-associated breast cancer and age at menarche among pre-menopausal women. A later age-at-menarche was associated with a decrease in risk among Nigerian pre-menopausal women who develop breast cancer more than 5 years post-partum (OR=0.40 (95% CI: 0.16-0.98)).[308]

Among pre-menopausal or younger women, of the four other included studies, a later age at menarche was associated with an increased risk of breast cancer in three of them, although none of these were statistically significant. Jordan et al. 2013 reported a 26% reduced risk per year later at menarche (OR=0.74 (95% CI: 0.56 – 1.00)).[306]

Among older women, a later age at menarche was associated with a non-significant decreased breast cancer risk in two out of the four included studies.

Only one study presented findings according to ER status. Among women aged less than 50 years with ER-positive disease, Figueroa et al. 2020, report a non-significant increased risk of breast cancer with a later age at menarche (OR=1.61 (95% CI: 1.00-2.58)).[270] For women aged 50+ with ER-positive disease, there was a decreased risk with later age-at-menarche. However, none of these observed associations were statistically significant. We observe a reversal of the direction of association among women with ER-negative disease, with a non-significant decrease in risk among women less than 50 with a later age-at-menarche (0.97 (95% CI: 0.61-1.55)) and a non-significant increased risk among women older than 50. (Table 5.3)

Table 5.3: Case-control studies which reported on the association between age at menarche (AAM) and breast cancer risk.

Authors	Year	Country	Group	No. Cases	No. controls	Data type	Unit of change if continuous	Baseline variable (years)	Highest category (years)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comments
Walker et al.[290]	1989	South Africa	All cases	59	93	Categorical		≥13	<13	1.00 (0.40 – 3.10)	NA	-	
Thomas and Noonan[292]	1993	Kenya	All cases	49	751	Categorical		<14	16+	NA	0.78 (0.28-2.22)	A, E, P, C, BF	Re-analyses of primary data (Appendix 7)
Parkin et al.[293]	1994	Zimbabwe	All cases	246	977	Categorical		<14	>14	0.90	0.80 (0.50 – 1.20)	A, E, P, AFFP, Alc, Res	
Ssali et al.[295]	1995	Uganda	All cases	86	86	Continuous	Difference in the mean age at menarche (AAM)	Mean age among controls= 13.80	Mean age among cases= 14.47	NA	NA	-	Significant difference in means p=0.0148
Amir et al.[296]	1998	Tanzania	All cases	50	51	Both	Difference in the mean age at menarche	≥15	<15	0.50 (-)	NA	-	p=0.45 Mean age among cases (14.0), among controls (13.8)
Rosenberg et al.[222]	2002	South Africa	All cases	65	222	Categorical		17+	≤12	NA	1.90 (0.50 -7.40)	A, E	
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Categorical		≥12	<12	1.11 (0.98–1.26)	1.47 (0.87 - 2.47)	A, E, AFFP, WHR, FH	
Huo et al.[267]	2008	Nigeria	All cases	735	548	Both	per 2-year delay in AAM Adj. OR 0.92 (0.81-1.03)	10-14	≥19	0.56 (0.35-0.91)	0.71 (0.42 – 1.2)	A, E, P, AFFP, BF, Meno, C, Alc, Ht, BMI, FH, Eth, BBD	*p* for trend=0.04
Sule[302]	2011	Nigeria	All cases	66	70	Categorical		≤13	>13	1.30 (0.91-1.84)	NA	-	Reported relative risks
Awio et al.[303]	2012	Uganda	All cases	70	70	Categorical		<12	≥12	0.68 (0.52-0.90)	NA	-	
Jordan et al.[306]	2013	Tanzania	All cases	111	230	Continuous	per year increase			NA	0.84 (0.69 – 1.01)	A, AFFP, BF, BMI, Res, Meno	
Galukande et al.[314]	2016	Uganda	All cases	104	231	Categorical		≤14	≥17	1.58 (0.68-3.68)	NA	-	

Table 5.3 continued

Authors	Year	Country	Group	No. Cases	No. controls	Data type	Unit of change if continuous	Baseline variable (years)	Highest category (years)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comments
Balekouzou et al.[315]	2017	Central African Republic	All cases	174	348	Categorical		<12	≥12	0.22 (0.10-0.47)	0.18 (0.07 – 0.44)	A, P, BF, C	
Figueroa et al.[270]	2020	Ghana	All cases	1122	2096	Categorical		<15	≥17	NA	1.08 (0.85 – 1.37)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.30
Breast cancer in pre-menopausal women													
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤14.27	>14.27	NA	1.08 (0.93 – 1.26)	A	
Jordan et al.[306]	2013	Tanzania	Pre-menopausal	NA	NA	Continuous	Per year increase			NA	0.74 (0.56 – 1.0)	A, AFFP, BF, BMI, Res	
Hou et al.[308]	2013	Nigeria	Pre-menopausal	148	279	Categorical		10-14	≥19	NA	0.32 (0.09 – 1.13)	A, E, P, AFFP, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC ≤ 2yearrs post-partum. Includes data from Huo 2008. *p* for trend=0.2
Hou et al.[308]	2013	Nigeria	Pre-menopausal	142	183	Categorical		10-14	≥19	NA	0.49 (0.13 – 1.82)	A, E, P, AFFP, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC 3-5 years post-partum. Includes data from Huo 2008. *p* for trend=0.05
Hou et al.[308]	2013	Nigeria	Pre-menopausal	395	512	Categorical		10-14	≥19	NA	0.40 (0.16 – 0.98)	A, E, P, AFFP, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC > 5years post-partum. Includes data from Huo 2008. *p* for trend=0.06
Sighoko et al.[239]	2013	Mali	Pre-menopausal	84	123	Categorical		≤14	>14	NA	2.02 (1.08 - 3.78)	A, P, AFFP, BF	
Figueroa et al.[270]	2020	Ghana	Women <50	500	1201	Categorical		<15	≥17	NA	1.08 (0.79 – 1.48)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.46

Table 5.3 continued

Authors	Year	Country	Group	No. Cases	No. controls	Data type	Unit of change if continuous	Baseline variable (years)	Highest category (years)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comments
Figueroa et al.[270]	2020	Ghana	Women <50, ER negative	172	1201	Categorical		<15	≥17	NA	0.97 (0.61 – 1.55)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.81
Figueroa et al.[270]	2020	Ghana	Women <50, ER positive	168	1201	Categorical		<15	≥17	NA	1.61 (1.00 – 2.58)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.05
						Breast cancer in post-menopausal women							
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤14.81	>14.81	NA	1.16 (0.93 – 1.45)	A	
Jordan et al.[306]	2013	Tanzania	Post-menopausal	NA	NA	Continuous	Per year increase			NA	0.95 (0.72- 1.24)	A, AFFP, BF, BMI, Res	
Sighoko et al.[239]	2013	Mali	Post-menopausal	68	100	Categorical		≤14	>14	NA	0.61 (0.29 - 1.29)	A, P, AFFP, BF	
Figueroa et al.[270]	2020	Ghana	Women ≥50	471	688	Categorical		<15	≥17	NA	1.6 (0.66 – 1.42)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.34
Figueroa et al.[270]	2020	Ghana	Women≥ 50, ER negative	155	693	Categorical		<15	≥17	NA	1.13 (0.67 – 1.92)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.77
Figueroa et al.[270]	2020	Ghana	Women≥ 50, ER positive	180	693	Categorical		<15	≥17	NA	0.84 (0.50 – 1.13)	A, E, P, AFFP, BF, Meno, BMI, FH, Res	*p* for trend=0.74

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; NA, Not available; P, parity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.1.2 Age at menopause

Six studies reported on the association between menopause and the risk of breast cancer (Table 5.4). Three studies presented only crude estimates for the association between menopause and breast cancer risk (Walker et al. 1989, Amir et al. 1998, and Awio et al. 2012). In all these three studies, the breast cancer risk was not associated with menopausal status or with age at menopause.

Of the other three studies that presented adjusted odds ratios, none of the estimates were statistically significant. A later age at menopause was associated with a non-significant increased risk in two of these three studies. However, different studies used different baseline categories for these comparisons, and none of the results were statistically significant. None of the included studies assessed the influence of age at menopause by ER status.

Table 5.4: Case-control studies that reported on the association between age at menopause and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:
Walker et al.[290]	1989	South Africa	All cases	59	93	Categorical		No	Yes, menopausal	0.90 (0.40 – 1.80)	NA	-
Parkin et al.[293]	1994	Zimbabwe	All cases	109	421	Categorical		<48 years	>52 years	1.30 (-)	1.40 (0.70 – 3.10)	A, E, P, AFFP, Alc, Res
Amir et al.[296]	1998	Tanzania	All cases	50	51	Continuous	Difference in mean age at menopause among cases and controls p=0.12	Mean age among controls (43.5)	Mean age among cases (45.6)	NA	NA	-
Okobia et al.[223]	2006	Nigeria	All cases	108	108	Categorical		≤50 years	>50	1.06 (0.66 – 1.72)	1.06 (0.62 – 1.81)	A, E, AFFP, WHR, FH
Awio et al.[303]	2012	Uganda	All cases	70	70	Categorical		≤55 years	>55 years	1.15 (0.8 – 1.64)	NA	-
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical		≤55 years	>55 years	0.30 (0.10 – 1.30)	0.16 (0.10 – 1.50)	AFFP, Alc, S, BF, C, FH, BMI

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; P, parity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.1.3 Age at first full-term pregnancy

Fourteen studies reported on the association between the age at first full-term pregnancy (AFFP) and breast cancer for women of all ages, irrespective of menopausal status (Table 5.5). Of these 14 studies, there were 12 independent study populations. Rosenberg et al. 2002 reported on the black population only of Coogan et al. 1999, who presented combined estimates by race. Huo et al. 2008 present data from the Nigerian Breast Cancer study, while Sighoko et al. 2015 investigate if there is a transient change in risk after the first full-term pregnancy from the African Breast Cancer study using combined data from Cameroon, Uganda, and Nigeria.

For all ages combined, a later AFFP was associated with an increased risk of breast cancer in 9 out of 12 independent study populations, although these results were statistically significant in only one of these studies (Okobia et al. 2006).

From the African Breast Cancer Study, we observe a 24% reduction in risk after first birth at age 20 (OR=0.76 (95% CI: 0.57-0.99)) in comparison with nulliparous women. This risk reduction with first full-term pregnancy was observed irrespective of AFFP, with similar risk reduction observed at age 25 and age 30, and with an overall risk reduction of 27% (OR= 0.73 (95% CI: 0.56-0.97) after a first full-term pregnancy as compared with nulliparous women.[312]

Six studies presented these results stratified by age at menopause. All of these studies reported an increased risk with a later AFFP among pre- and post-menopausal women apart from Sighoko et al. 2013 in Mali, who reported a decreased breast cancer risk with later AFFP among pre- and post-menopausal women and Huo et al. 2013 who reported a non-significant decreased risk with later AFFP among pre-menopausal women who were more than five years post-partum. This increased risk was significant among post-menopausal women in the study by Okobia et al. 2006 and Jordan et al. 2013. Figueroa et al. 2020 who presented their findings

by ER status, report a non-significant increased breast cancer risk with later AFFP irrespective of ER status or age at diagnosis.

Table 5.5: Case-control studies that reported on age at first full-term pregnancy (AFFP) and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Walker et al.[290]	1989	South Africa	All cases	59	93	Categorical		≤20	>20	0.80 (0.3-2.3)	NA	-	
Parkin et al.[293]	1994	Zimbabwe	All cases	230	924	Categorical		<18	>20	1.20 (-)	1.10 (0.70 – 1.70)	A, E, P, Alc, Res	
Ssali et al.[295]	1995	Uganda	All cases	80	81	Categorical		≤21	>21	4.30 (1.70 – 10.80)	NA	-	Predominantly pre-menopausal women
Coogan et al.[298]	1999	South Africa	All cases	369	1253	Categorical		≤18	≥30	NA	1.70	A, E, P, Eth	Included "blacks" and "coloureds"
Rosenberg et al.[222]	2002	South Africa	All cases	63	215	Categorical		<17	25-29	NA	1.30 (0.40 – 4.80)	A, E, P	Black only population of Shapiro, 2000 and Coogan, 1999
Okobia et al.[223]	2006	Nigeria	All cases	210	209	Categorical		≤20	>20	1.48 (1.16-1.88)	1.48 (1.16-1.88)	A, E, WHR, FH	
Huo et al.[267]	2008	Nigeria	All cases	738	454	Both	Per 5-year increase AOR=0.87 (0.73-1.04)	<20	≥30	0.94 (0.57-1.57)	0.80 (0.44 – 1.47)	A, E, P, BF, Mena, C, Alc, Ht, BMI, FH, Eth, BBD, Meno	*p* for trend=0.16
Sule[8]	2011	Nigeria	All cases	70	70	Categorical		≤20	>20	1.03 (0.74 – 1.40)	NA	-	Reported relative risks
Awio et al.[303]	2012	Uganda	All cases	70	70	Continuous	Per unit increase in AFFP			1.01 (0.98 – 1.04)	NA	-	
Jordan et al.[306]	2013	Tanzania	All cases	106	217	Categorical		≤20	>20	NA	1.52 (0.86 – 2.69)	A, BF, Mena, BMI, Meno, Res	
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical		≤25	>25	0.80 (0.30 – 2.30)	0.30 (0.10 – 2.43)	BF, Meno, C, Alc, S, BMI, FH	

Table 5.4 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Sighoko et al.[312]	2015	Nigeria, Cameroon, Uganda	All cases	1771	2336	Continuous	Change in risk level after the first birth			NA	0.73 (0.56-0.97)	A, P, Mena, Meno, C, Alc, BMI, FH, BBD	
Galukande et al.[314]	2016	Uganda	All cases	89	224	Categorical		<20	≥25	1.83 (0.91 -3.67)	1.27 (0.58- 2.81)	A, P, BF, Mena, C, Alc, BMI, Res	
Figueroa et al.[270]	2020	Ghana	All cases	1122	2096	Categorical		<19	≥26	NA	1.18 (0.91 – 1.54)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.135
							Breast cancer in pre-menopausal women						
Parkin et al.[293]	1994	Zimbabwe	Pre-menopausal	NA	NA	Categorical		≤18	19+	NA	1.07 (0.66 – 1.74)	A	
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤22.77	>22.77	NA	1.26 (0.94 – 1.71)	A	
Jordan et al.[306]	2013	Tanzania	Pre-menopausal	NA	NA	Categorical		≤20	>20	NA	1.05 (0.44-2.49)	A, BF, Mena, BMI, Res	
Hou ,et al.[308]	2013	Nigeria	Pre-menopausal	152	282	Categorical		<25	≥30	NA	1.06 (0.42 – 2.69)	A, E, P, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC ≤ 2years post-partum Includes data from Huo 2008. *p* for trend=0.9
Hou et al.[308]	2013	Nigeria	Pre-menopausal	145	188	Categorical		<25	≥30	NA	1.18 (0.4 – 3.51)	A, E, P, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC 3-5 years post-partum Includes data from Huo 2008. *p* for trend=0.8
Hou et al.[308]	2013	Nigeria	Pre-menopausal	388	483	Categorical		<25	≥30	NA	0.79 (0.36 – 1.73)	A, E, P, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC > 5years post-partum Includes data from Huo 2008. *p* for trend=0.4
Sighoko et al.[239]	2013	Mali	Pre-menopausal	96	130	Categorical		≤20	>20	NA	0.41 (0.18 – 0.89)	A, P, BF, Mena	

Table 5.4 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Figueroa et al.[270]	2020	Ghana	Women <50	472	1051	Categorical		<19	≥26	NA	1.40 (0.97 – 2.01)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.05
Figueroa et al.[270]	2020	Ghana	Women <50, ER negative	164	1051	Categorical		<19	≥26	NA	1.15 (0.66 – 1.99)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.30
Figueroa et al.[270]	2020	Ghana	Women <50, ER positive	158	1051	Categorical		<19	≥26	NA	1.72 (0.99 – 2.97)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.08
						Breast cancer in post-menopausal women							
Parkin et al.[293]	1994	Zimbabwe	Post-menopausal	NA	NA	Categorical		≤18	19+	NA	1.32 (0.9 – 1.95)	A	
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤20.91	>20.91	NA	1.71 (1.16-2.53)	A	
Jordan et al.[306]	2013	Tanzania	Post-menopausal	NA	NA	Categorical		≤20	>20	NA	2.40 (1.03 – 5.6)	A, BF, Mena, BMI, Res	
Sighoko et al.[239]	2013	Mali	Post-menopausal	80	102	Categorical		≤20	>20	NA	0.87 (0.36 – 2.12)	A, P, BF, Mena	
Figueroa et al.[270]	2020	Ghana	Women≥ 50	484	743	Categorical		<19	≥26	NA	1.03 (0.68 – 1.56)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.74
Figueroa et al.[270]	2020	Ghana	Women≥ 50, ER negative	172	748	Categorical		<19	≥26	NA	1.02 (0.57 – 1.84)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.95
Figueroa et al.[270]	2020	Ghana	Women≥ 50, ER positive	175	748	Categorical		<19	≥26	NA	1.09 (0.61 – 1.93)	A, E, P, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.72

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; NA, Not available; P, parity; Res, residence; S, smoking; SES, socio-economic status; TNBC, Triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.1.4 Parity

Sixteen studies reported on the association between parity and breast cancer risk (Table 5.6). These studies used different baseline categories, with some studies using nulliparous women as the baseline, while others used a single child, or fewer than 4 children, amongst other categorizations used. Of the16 included studies, 12 reported a reduced breast cancer risk with increasing parity. In 2 studies that reported increased risk with parity (Amir et al. 1998 and Sule et al. 2011), the estimates were not age-adjusted. In South Africa, Anderson et al. 1975 reported a non-significant difference in parity among cases and controls and Rosenberg et al. 2002 reported a non-significant increased breast cancer risk among South African blacks when comparing women with five or more children to women with a single child.

In the largest of these studies, Sighoko et al. 2015, data from the African Breast Cancer Study showed that, compared with a nulliparous woman, having one child was associated with a 31% reduction in breast cancer risk (OR=0.69 (95% CI: 0.49-0.96)), while having seven or more children was associated with a 46% reduced risk (OR=0.54 (95% CI: 0.38-0.75)). This risk reduction with parity was observed irrespective of AFFP.[312]

When stratified by menopausal status, among the six studies that included results for pre-menopausal women, all the studies showed a reduced breast cancer risk with increasing parity apart from Parkin et al. 1994 who showed a non-significant increased risk with parity and Huo et al. 2012, who studied this association in relation to pregnancy-associated breast cancer and they report a non-significant increased risk within five years post-partum among pre-menopausal women. Among post-menopausal women, there is a consistent report of risk reduction with increasing parity.

Figueroa et al. 2020 present these findings by ER status and by age group. Among women aged <50 years with ER-negative tumours, higher parity was associated with a non-significant increased breast cancer risk, and this association became protective among women aged ≥50

years with ER-negative breast cancer. However, for women with ER-positive tumours, higher parity was associated with a non-significant decrease in breast cancer risk irrespective of age at diagnosis.

Table 5.6: Case-control studies that reported on the association between parity and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline category: (No of children)	Highest category: (No. of children)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Anderson et al.[289]	1975	South Africa	All cases	96	70	Continuous	Difference in the mean number of births among cases and controls	-	-	NA	NA	-	No significant difference in parity
Walker et al.[290]	1989	South Africa	All cases	59	93	Categorical		Parous	Nulliparous	2.40 (0.90-6.10)	NA	-	
Parkin et al.[293]	1994	Zimbabwe	All cases	241	997	Categorical		<3	>6	0.80 (-)	0.80 (0.50-1.30)	A, E, AFFP, Alc, Res	
Ssali et al.[295]	1995	Uganda	All cases	86	86	Categorical		1-3	7+	0.10 (-)	NA	-	Predominantly pre-menopausal women
Amir et al.[296]	1998	Tanzania	All cases	50	51	Categorical		Nulliparous	7+	11.00 (-)	NA	-	Cases were older than controls.
Rosenberg et al.[222]	2002	South Africa	All cases	65	223	Categorical		1	5+	NA	1.60 (0.50-4.50)	A, E, AFFP	
Okobia et al.[223]	2006	Nigeria	All cases	210	209	Categorical		≤4	>4	0.79 (0.64-0.99)	0.8 (0.53 – 1.2)	A, E, AFFP, WHR, FH	
Huo et al.[267]	2008	Nigeria	All cases	817	559	Both	Each additional live birth AOR 0.95(0.88-1.02)	0	≥7	0.52 (0.30-0.89)	0.52 (0.28-0.94)	A, E, BF, Mena, C, Alc, Ht, BMI, FH, Eth, BBD, Meno	*p* for trend=0.02
Sule[302]	2011	Nigeria	All cases	72	72	Categorical		≤2	>2	1.42 (1.03-1.96)	NA	-	Reported relative risks
Awio et al.[303]	2012	Uganda	All cases	70	70	Continuous				0.99 (0.96-1.02)	NA	-	
Rukundo et al.[311]	2014	Uganda	All cases	72	73	Categorical		nulliparous	>4	0.30 (0.1-2.5)	NA	-	
Sighoko et al.[312]	2015	Nigeria, Cameroon, Uganda	All cases	1983	2626	Categorical		nulliparous	7	NA	0.54 (0.38—0.75)	A, AFFP, Mena, Meno, C, Alc, BMI, FH, BBD	*Includes data from Huo 2008

Table 5.6 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline category: (No of children)	Highest category: (No. of children)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Kana et al.[313]	2015	Nigeria	All cases	29	143	Categorical		1-4	Nulliparous	NA	3.44 (0.68-17.54)	Not specified	
Galukande et al.[314]	2016	Uganda	All cases	89	211	Categorical		1	≥ 5	0.59 (0.25-1.35)	NA	-	
Balekouzou et al.[315]	2017	Central African Republic	All cases	173	348	Categorical		≥ 3	nulliparous	1.76 (1.02-3.04)	1.98 (1.12-3.49)	A, BF, Mena, C	
Figueroa et al.[270]	2020	Ghana	All cases	1122	2096	Categorical		nulliparous	≥5	NA	0.73 (0.50-1.07)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.005
Breast cancer in pre-menopausal women													
Parkin et al.[293]	1994	Zimbabwe	Pre-menopausal	NA	NA	Categorical		≤2	≥6	NA	1.05 (0.53-2.08)	A	
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤4	>4	NA	0.89 (0.76 – 1.03)	A	Rounded to the nearest integer
Hou et al.[308]	2013	Nigeria	Pre-menopausal	152	282	Both	per child	1-2	≥ 6	NA	2.12 (0.5-9.04)	A, E, AFFP, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC ≤ 2yrs post-partum. Includes data from Huo 2008. *p* for trend=0.2
Hou et al.[308]	2013	Nigeria	Pre-menopausal	145	188	Both	per birth	1-2	≥6	NA	1.87 (0.39-9.00)	A, E, AFFP, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC 3-5 years post-partum. Includes data from Huo 2008. *p* for trend=0.4
Hou et al.[308]	2013	Nigeria	Pre-menopausal	418	525	Both	per birth	1-2	≥6	NA	0.66 (0.26-1.66)	A, E, AFFP, Mena, BF, C, Alc, Ht, BMI, FH, Eth, BBD	BC > 5years post-partum. Includes data from Huo 2008. *p* for trend=0.4

Table 5.6 continued overleaf

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline category: (No of children)	Highest category: (No. of children)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comments
Sighoko et al.[239]	2013	Mali	Pre-menopausal	110	135	Categorical		1-4	10+	NA	0.57 (0.13-2.36)	A, AFFP, BF, Mena	*p* for trend>0.05
Kana et al.[313]	2015	Nigeria	Women ≤ 45 years	29	143	Categorical		1-4	Nulliparous	NA	1.43 (0.11-18.22)	Not specified	
Figueroa et al.[270]	2020	Ghana	Women <50	563	1290	Categorical		Nulliparous	≥5	NA	0.70 (0.42-1.18)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.06
Figueroa et al.[270]	2020	Ghana	Women <50 ER negative	193	1290	Categorical		Nulliparous	≥5	NA	1.80 (0.82-3.95)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.32
Figueroa et al.[270]	2020	Ghana	Women <50 ER positive	185	1290	Categorical		Nulliparous	≥5	NA	0.46 (0.20-1.06)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.19
Breast cancer in post-menopausal women													
Parkin et al.[293]	1994	Zimbabwe	Post-menopausal	NA	NA	Categorical		≤2	≥6	NA	0.70 (0.41-1.18)	A	
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤6	>6	NA	0.90 (0.75-1.08)	A	Rounded to the nearest integer
Sighoko et al.[239]	2013	Mali	Post-menopausal	98	104	Categorical		1-4	10+	NA	0.38 (0.14-1.01)	A, AFFP, BF, Mena	*p* for trend<0.05
Kana et al.[313]	2015	Nigeria	Women > 45 years	29	143	Categorical		1-4	Nulliparous	NA	12.07 (0.62-233.0)	Not specified	
Figueroa et al.[270]	2020	Ghana	Women ≥ 50	555	798	Categorical		Nulliparous	≥5	NA	0.40 (0.20-0.83)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.01
Figueroa et al.[270]	2020	Ghana	Women ≥ 50 ER negative	194	808	Categorical		Nulliparous	≥5	NA	0.28 (0.11-0.70)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.004

Table 5.6 continued overleaf

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline category: (No of children)	Highest category: (No. of children)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	
Figueroa et al.[270]	2020	Ghana	Women ≥ 50 ER positive	208	808	Categorical		Nulliparous	≥5	NA	0.49 (0.19-1.26)	A, E, AFFP, BF, Mena, Meno, BMI, FH, Res	*p* for trend=0.24

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; NA, Not available; P, parity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.1.5 Breastfeeding

Fourteen studies reported on the association between breastfeeding and breast cancer risk among women of all ages irrespective of menopausal status at diagnosis (Table 5.7). Of these 14 studies, all but two reported a decreased breast cancer risk with lactation. The two studies that do not report a decreased risk with breastfeeding reported only unadjusted estimates.

Seven studies presented results stratified by menopausal status at the time of diagnosis. Among pre-menopausal women, breastfeeding was protective of breast cancer in five of these, although many of the associations observed were non-significant. Anderson et al. 1975 reported a non-significant difference in the duration of breastfeeding among black cases and controls in South Africa, while Huo et al., 2013 reported a non-significant increased risk with breastfeeding among pre-menopausal women with pregnancy-associated breast cancer and Figueroa et al. 2020 reported a non-significant increased risk with breastfeeding among women under age 50 in Ghana.

All but one of the included studies that presented this association among post-menopausal women reported a decreased risk with breastfeeding, but not all were statistically significant.

Figueroa et al, 2020 presented results by ER status. They report a non-significant decrease in breast cancer risk among women with ER-negative disease, irrespective of age at diagnosis. Among women with ER-positive disease, a significant protective effect of breastfeeding is seen among women aged 50+ who had a median duration of breastfeeding per pregnancy of 19 months and above compared with women with a median duration of breastfeeding of fewer than 13 months (OR=0.54 (95% CI: 0.34-0.85), *p*-value for trend=0.01). A non-significant increased risk is observed among younger women with ER-positive breast cancer with a longer median duration of breastfeeding (OR=1.39 (95% CI: 0.83-2.34), *p*-value for trend=0.29).

Table 5.7: Case-control studies that reported on the association between breastfeeding and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Thomas and Noonan[292]	1993	Kenya, Nigeria	All cases	62	764	Categorical		<24months total lifetime BF	>72 months total lifetime BF	1.96 (0.97-3.92)	0.64 (0.22-1.79)	A, AFFP, P, SC	Primary data re-analysis (Appendix 7)
Ssali et al.[295]	1995	Uganda	All cases	85	86	Categorical		Never breastfed	Ever breastfed	0.21 (-)	NA	-	Predominantly premenopausal women
Amir et al.[296]	1998	Tanzania	All cases	50	51	Categorical		"Lactating"	"Not lactating"	0.60 (-)	NA	-	
Adebamowo and Adenkule[297]	1999	Nigeria	All cases	217	250	Categorical		NA	NA	0.00 (0.00-0.10)	NA	-	
Coogan et al.[298]	1999	South Africa	All cases	403	1377	Categorical		Never breastfed	≥7 years total lifetime BF	NA	0.70 (0.40-1.30)	A, E, P, AFFP, Eth, SES	Included "blacks" and "coloureds". *p* for trend=0.3
Okobia et al.[223]	2006	Nigeria	All cases	209	208	Both	Per additional month of BF AOR=0.99(0.98-0.99)	≤ 60 months	>60 months	0.75 (0.62-0.91)	0.88 (0.7-1.1)	A, E, AFFP, WHR, FH	
Huo et al.[267]	2008	Nigeria	All cases	742	456	Both	Per 12 months increase in total BF AOR 0.93(0.87-1.00)	≤ 24 months	>96 months	0.54 (0.34-0.85)	0.36 (0.17-0.75)	A, E, P, AFFP, Mena, C, Alc, Ht, BMI, FH, Eth, BBD, Meno	*p* for trend=0.005
Sule[302]	2011	Nigeria	All cases	72	72	Categorical		>2 years of cumulative breastfeeding	≤2 years	1.28 (0.93-1.77)	NA	-	Reported relative risks

Table 5.7 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Awio et al.[303]	2012	Uganda	All cases	70	70	Continuous	Per year			1.00 (0.97-1.01)	NA	-	Baseline not clearly specified
Jordan et al.[306]	2013	Tanzania	All cases	114	230	Both	Per month of lifelong lactation AOR= 0.99 (0.98-1.0)	≤54 months	>131 months	NA	0.37 (0.14-0.97)	A, AFFP, BMI, Mena, Meno, Res	
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical		<24 months	>96 months	1.50 (0.60-3.50)	0.30 (0.1-1.5)	AFFP, C, Meno, FH, Alc, S, BMI	
Galukande et al.[314]	2016	Uganda	All cases	111	237	Categorical		no - did not breastfeed	yes - breastfed	0.06 (0.02-0.20)	0.04 (0.01-0.18)	A, P, BF, AFFP, Mena, C, Alc, BMI, Res	
Balekouzou et al.[315]	2017	Central African Republic	All cases	143	317	Categorical		mixed feeding	Natural breastfeeding	0.20 (0.04-0.85)	0.33 (0.02-1.15)	A, Mena, P, C	Assessed mixed vs natural BF
Figueroa et al.[270]	2020	Ghana	All cases	1122	2096	Categorical		<13 median months BF/pregnancy among parous women	≥19 months	NA	0.84 (0.67-1.05)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.159

Table 5.7 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Breast cancer in pre-menopausal women													
Anderson et al.[289]	1975	South Africa	Pre-menopausal	35	40	Continuous	Measured the mean duration of BF/pregnancy among cases (16.6months) and controls (20.2 months)			NA	NA	-	Non-significant difference in means
Coogan et al.[298]	1999	South Africa	Pre-menopausal	313	1056	Categorical		Never breastfed	≥7 years total lifetime BF	NA	0.80 (0.40-1.40)	A, E, P, AFFP, Eth, SES	All participants were <55yrs. *p* for trend=0.2
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤59.45 months	>59.45 months	NA	0.84 (0.67-1.06)	A	
Hou et al.[308]	2013	Nigeria	Pre-menopausal	147	280	Categorical		≤24 of total lifetime breastfeeding	>96 months	NA	1.03 (0.16-6.85)	A, E, P, AFFP, Mena, C, Alc, Ht, BMI, FH, Eth, BBD	BC ≤ 2yrs post-partum. Includes data from Huo 2008 *p* for trend=0.4
Hou et al.[308]	2013	Nigeria	Pre-menopausal	145	186	Categorical		≤24 months	>96 months	NA	1.37 (0.2-9.42)	A, E, P, AFFP, Mena, C, Alc, Ht, BMI, FH, Eth, BBD	BC 3-5 yrs post-partum. Includes data from Huo 2008 *p* for trend=0.5
Hou et al.[308]	2013	Nigeria	Pre-menopausal	325	524	Categorical		≤24 months	>96 months	NA	0.97 (0.33-2.82)	A, E, P, AFFP, Mena, C, Alc, Ht, BMI, FH, Eth, BBD	BC > 5yrs post-partum. Includes data from Huo 2008 *p* for trend=0.9

Table 5.7 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Jordan et al.[306]	2013	Tanzania	Pre-menopausal	NA	NA	Continuous	Per month of lifelong lactation			NA	0.98 (0.97-0.99)	A, AFFP, BMI, Mena, Res	
Sighoko et al.[239]	2013	Mali	Pre-menopausal	65	94	Categorical		≤2 years	>2 years	NA	0.97 (0.24-3.92)	A, P, AFFP, Mena	*p* for trend>0.05
Figueroa et al.[270]	2020	Ghana	Women <50	455	1039	Categorical		<13 median months of BF/pregnancy	≥19 months	NA	1.04 (0.75-1.44)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.77
Figueroa et al.[270]	2020	Ghana	Women <50 ER negative	157	1039	Categorical		<13 median months BF/pregnancy	≥19 months	NA	0.71 (0.45-1.12)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.25
Figueroa et al.[270]	2020	Ghana	Women <50 ER positive	153	1039	Categorical		<13 median months BF/pregnancy	≥19 months	NA	1.39 (0.83-2.34)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.29

Table 5.7 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Breast cancer in post-menopausal women													
Anderson et al.[289]	1975	South Africa	Post-menopausal	48	28	Continuous	Measured the mean duration of BF/pregnancy among cases (19.1 months) and controls (23.5 months)			NA	NA	-	Non-significant difference in means
Coogan et al.[298]	1999	South Africa	Post-menopausal	75	295	Categorical		Never breastfed	≥7 years total lifetime BF	NA	1.00 (0.40-2.40)	A, E, P, AFFP, Eth, SES	All participants were <55yrs *p* for trend=0.7
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤104.18 months	>104.18 months	NA	0.67 (0.48-0.92)	A	
Jordan et al.[306]	2013	Tanzania	Post-menopausal	NA	NA	Continuous	Per month of lifelong lactation			NA	0.99 (0.98-1.0)	A, AFFP, BMI, Mena, Res	
Sighoko et al.[239]	2013	Mali	Post-menopausal	69	78	Categorical		≤2 years of maternal BF	>2 years	NA	0.49 (0.1-2.55)	A, P, AFFP, Mena	*p* for trend<0.05
Figueroa et al.[270]	2020	Ghana	Women ≥ 50	468	743	Categorical		<13 median months BF/pregnancy	≥19 months	NA	0.71 (0.51-0.98)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.05
Figueroa et al.[270]	2020	Ghana	Women ≥ 50 ER negative	161	752	Categorical		<13 median months BF/pregnancy	≥19 months	NA	0.89 (0.56-1.42)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.82

Table 5.7 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Figueroa et al.[270]	2020	Ghana	Women ≥ 50 ER positive	173	752	Categorical		<13 median months BF/pregnancy	≥19 months	NA	0.54 (0.34-0.85)	A, E, P, AFFP, Mena, Meno, BMI, FH, Res	*p* for trend=0.01

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; NA, Not available; P, parity; Res, residence; RR, risk ratio; S, smoking; SC, Study centre; SES, socio-economic status; TNBC, Triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.1.6 Contraceptive use

Studies were categorised into those which reported on the use of mainly oral contraceptives, and those which reported on the use of injectable contraceptives only (Table 5.8). The first category was more heterogeneous, as some studies did not clearly specify the type of contraceptive used. In this first category, of the 12 studies which reported on the association between contraceptive use and breast cancer, six studies report a protective effect for women who ever used contraceptives, compared with never users. This protective effect was significant in two studies, one of which was the largest included (Sighoko et al. 2015), who reported an OR of 0.79 (95% CI: 0.63-0.94) for ever vs never users. When stratified by menopausal status, none of the associations observed were significant for ever vs never users (Table 5.8).

Three studies reported on the association between breast cancer risk and the use of injectable contraceptives (Table 5.8). Doing a pooled analysis of these studies, ever use vs never use of injectable contraceptives was associated with a non-significant increased risk (OR=1.05 (0.74-1.48)) (Figure 5.3). More granular analyses on the duration of injectable contraceptive use and whether this involved current vs past users was specified by Shapiro et al. (2000) who reported a stronger association among current users (OR=1.6 (95% CI: 1.1-2.3)) compared with never users in South Africa.

Urban et al., 2012 report a 66% increased breast cancer risk among women who used either oral or injectable contraceptives in the last 10 years (OR=1.66 (95% CI: 1.28-2.16)); however, this increased risk declines and becomes non-significant more than 10 years after cessation of contraceptive use (OR=1.11 (95% CI: 0.91-1.36)).

Table 5.8: Case-control studies that reported on the association between contraceptive use and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Type of contraceptive	Baseline: Ever used?	Highest category: Ever used?	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comment
Mainly Oral contraceptives and breast cancer risk													
Thomas and Noonan[292]	1993	Kenya	All cases	49	751	Categorical	Oral contraceptives	No	Yes, used	1.03 (0.54-1.96)	1.22 (0.58-2.56)	A, no. of pregnancies, IUD use, E, Meno	Primary data re-analysis
Adebamowo and Adenkule[297]	1999	Nigeria	All cases	250	250	Categorical	Oestrogen-containing contraceptives	No	Yes, used	5.17 (1.08-48.85)	NA	-	Baseline not clearly specified
Shapiro et al.[299]	2000	South Africa	All cases	220	633	Categorical	Combined oestrogen/progestogen oral contraceptives	No	Yes, used	NA	1.2 (1.00-1.50)	A, C, SES, Eth	
Okobia et al.[223]	2006	Nigeria	All cases	249	249	Categorical	Hormonal contraceptives	No	Yes, used	1.4 (0.84-2.34)	0.99 (0.53-1.87)	A, E, AFFP, WHR, FH	
Sule[302]	2011	Nigeria	All cases	72	69	Categorical	Oral contraceptives	No	Yes, used	0.82 (0.53-1.27)	NA	-	
Awio et al.[303]	2012	Uganda	All cases	70	70	Categorical	Not specified	No	Yes, used	0.95 (0.80-1.12)	NA	-	Baseline not specified clearly
Urban et al.[305]	2012	South Africa	All cases	256	156	Categorical	Oral contraceptives ever/never injectables	No	Yes, used	NA	1.28 (1.00-1.64)	A, E, P, AFFP, Alc, S, Res	Oral and/or injectable contraceptives AOR=1.26(1.05-1.52)
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical	Oral contraceptives	Yes	No	8.20 (3.70-18.3)	16.70 (1.20-226.0)	A, AFFP, BF, Meno, Alc, S, BMI, FH	
Rukundo et al.[311]	2014	Uganda	All cases	89	53	Categorical	Oral contraceptives	No	Yes, used	1.0 (0.50-2.10)	NA	-	

Table 5.8 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Type of contraceptive	Baseline: Ever used?	Highest category: Ever used?	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comment
Sighoko et al.[312]	2015	Nigeria, Cameroon, Uganda	All cases	1964	2602	Categorical	Oestrogen-containing oral contraceptives	No	Yes, used	NA	0.79 (0.63-0.94)	A, P, AFFP, Mena, Meno, Alc, BMI, FH	Includes data from Adebamowo 2003
Galukande et al.[314]	2016	Uganda	All cases	110	222	Categorical	Combined oral contraceptives	No	Yes, used	0.1 (0.04-0.22)	0.30 (0.07-1.27)	A, P, AFFP, BF, Mena, Alc, BMI	
Balekouzou et al.[315]	2017	Central African Republic	All cases	173	348	Categorical		No	Yes, used	0.58 (0.39-0.86)	0.62 (0.41-0.93)	A, E, P, BF, Mena	
Breast cancer in pre-menopausal women													
Adebamowo et al.[300]	2003	Nigeria	Pre-menopausal	120	180	Categorical	Estrogen-containing oral contraceptives	No	Yes, used	NA	0.84 (0.51-1.39)	A	
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical	Hormonal contraceptives	No	Yes, used	NA	1.00 (0.53-1.89)	A	
Hou et al.[308]	2013	Nigeria	Pre-menopausal	152	281	Categorical	Hormonal contraceptives	No	Yes, used	NA	0.87 (0.49-1.53)	A, E, P, AFFP, BF, Alc, Ht, BMI, FH	BC ≤2years post-partum. Includes data from Adebamowo 2003.
Hou et al.[308]	2013	Nigeria	Pre-menopausal	144	188	Categorical	Hormonal contraceptives	No	Yes, used	NA	0.96 (0.53-1.73)	A, E, P, AFFP, BF, Alc, Ht, BMI, FH	BC 3-5 years post-partum. Includes data from Adebamowo 2003.

Table 5.8 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Type of contraceptive	Baseline: Ever used?	Highest category: Ever used?	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted for:	Comment
Hou et al.[308]	2013	Nigeria	Pre-menopausal	421	524	Categorical	Hormonal contraceptives	No	Yes, used	NA	0.92 (0.65-1.30)	A, E, P, AFFP, BF, Alc, Ht, BMI, FH	BC >5years post-partum. Includes data from Adebamowo 2003.
							Breast cancer in post-menopausal women						
Adebamowo et al.[300]	2003	Nigeria	Post-menopausal	104	89	Categorical	Estrogen-containing oral contraceptives	No	Yes, used	NA	0.96 (0.50-1.84)	A	
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical	Hormonal contraceptives	No	Yes, used	NA	2.67 (1.04-6.82)	A	
							Injectable contraceptives and breast cancer risk						
Skegg et al.[294]	1995	Kenya	All cases	49	752	Categorical	Depot medroxyprogesterone acetate (DMPA)	No	Yes, used	NA	0.62 (0.18-2.10)	A, AFFP	
Shapiro et al.[299]	2000	South Africa	All cases	318	1161	Categorical	Injectable Progesterone Contraceptives (IPC), mainly DMPA and recently norethisterone enanthate	No	Yes, used	NA	0.90 (0.70-1.20)	A, C	Current user 1.6 (1.1-2.3) vs never user
Urban et al.[305]	2012	South Africa	All cases	344	249	Categorical	Injectable contraceptives, never oral	No	Yes, used	NA	1.31 (1.03-1.65)	A, E, P, AFFP, S	

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BC, breast cancer; BBD, benign breast disease; BF, breastfeeding; BMI, body mass index; C, contraceptive use; DMPA, Depot medroxyprogesterone acetate; E, education; Eth, ethnicity; FH, family history; Ht, height; IUD, Intra-uterine device; Mena, Menarche; Meno, Menopause; No., Number; P, parity; Res, residence; S, smoking; SES, socio-economic status; TNBC, Triple-negative breast cancer; WHR, waist-to-hip ratio

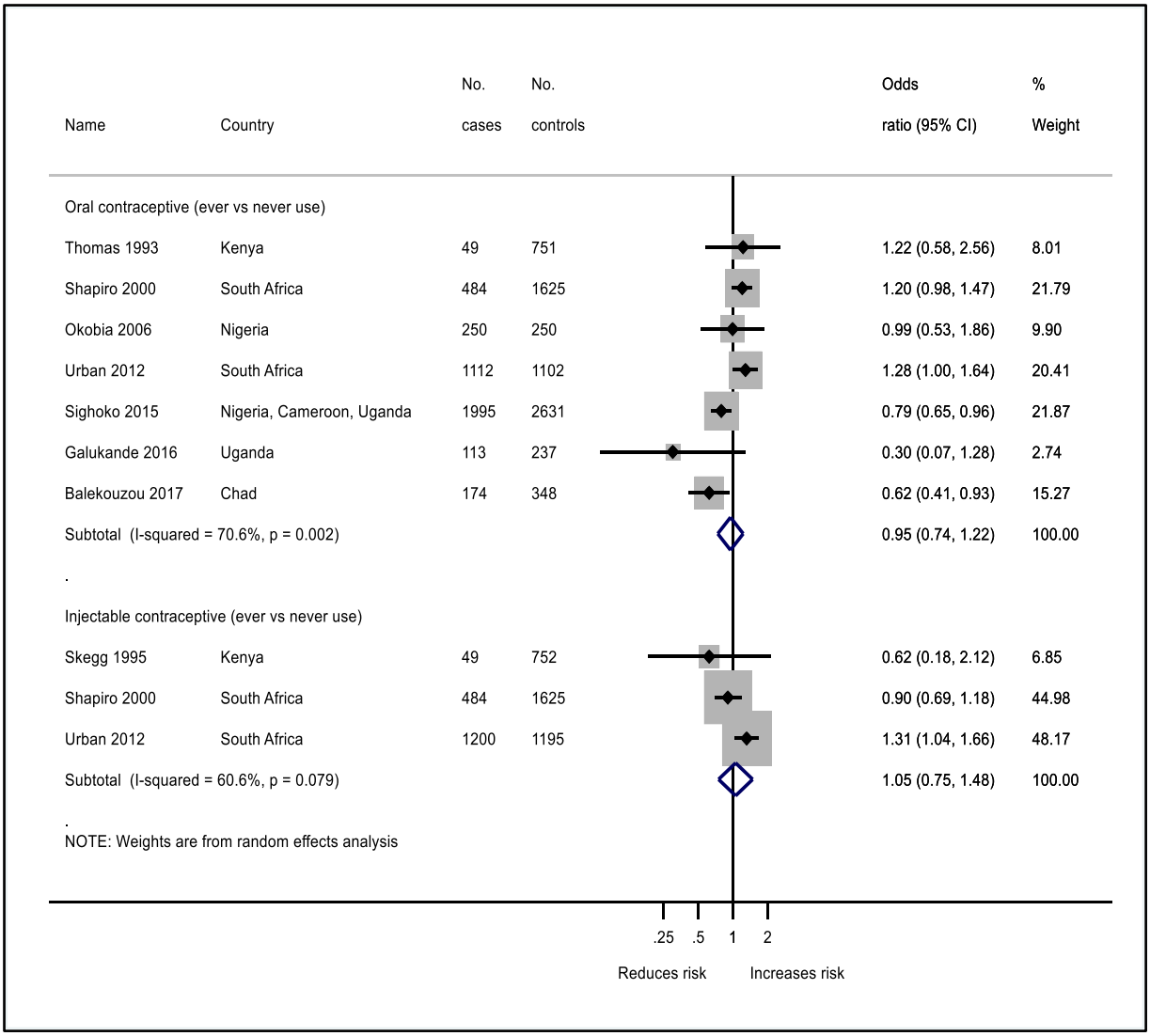


Figure 5.3: Meta-analysis of the association between ever use of contraceptives and breast cancer risk among all women irrespective of menopausal status at diagnosis.

Studies by Sule et al. (2011), Awio et al. (2012) and Rukundo et al. (2014). which did not adjust for any confounders are not included.

5.2.3.2 Anthropometric factors

The anthropometric factors we considered for the review were: height at diagnosis, weight at diagnosis, BMI, and the waist-to-hip-ratio.

5.2.3.2.1 Height

Three studies from two independent study populations reported on the association between height and breast cancer risk (Table 5.9). All studies were from Nigeria. Ogundiran et al. 2010 and Hou et al. 2013 were both from the Nigerian Breast Cancer cohort. Hou et al 2013 reported on the association between height and breast cancer risk in relation to time since pregnancy among pre-menopausal women only, while Ogundiran et al. 2010 presented data for all women, and stratified by menopausal status.

Analysis of the two independent populations suggests that a 5cm increase in height is associated with an 18% increase in risk (OR=1.18 (95% CI: 1.11-1.27)) (Figure 5.4).

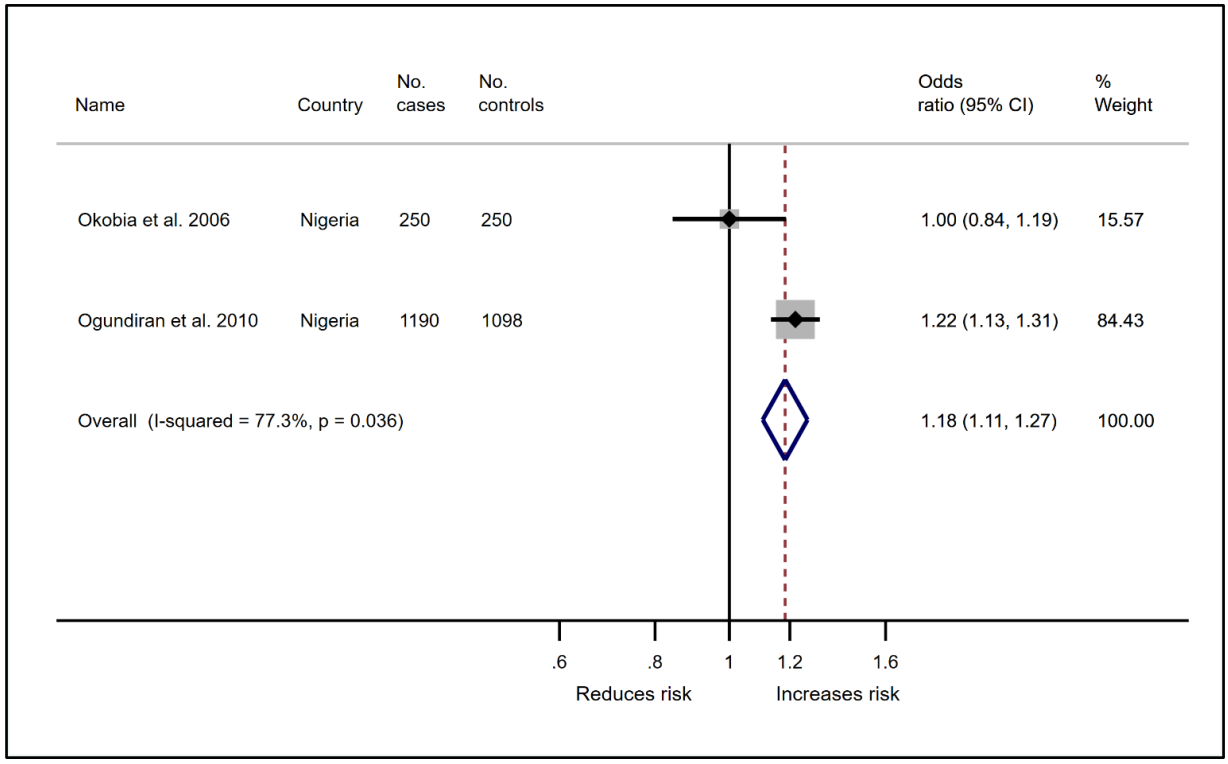


Figure 5.4: Meta-analysis of the association between height and breast cancer risk for all women.

When stratified by menopausal status, this increased risk with height was observed in both pre- and post-menopausal women. From the largest of the included studies, Ogundiran et al. 2010, a 5cm increase in height among pre-menopausal women was associated with a 23% increase in breast cancer risk (OR=1.23 (95% CI: 1.13-1.35)). Among post-menopausal women, this was associated with a 20% increased risk (OR=1.20 (95% CI: 1.07-1.36)) (Table 5.9).

Table 5.9: Case-control studies that reported on the association between height and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Continuous	per 1cm increase			1.01 (0.98-1.04)	1.0 (0.97-1.04)	A, E, AFFP, WHR, FH	*Scaling up: per 5cm increase 1.0(0.86-1.21)
Ogundiran	2010	Nigeria	All cases	1190	1098	Both	per 5 cm increase AOR=1.22 (1.14-1.32)	<155cm	≥165cm	1.98 (1.51-2.59)	2.03 (1.51-2.72)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend<0.001
Breast cancer in pre-menopuasal women													
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤164.25 cm	>164.25 cm	NA	1.59 (0.98-2.58)	A	
Ogundiran et al.[210]	2010	Nigeria	Pre-menopausal	684	820	Both	per 5cm increase AOR=1.23 (1.13-1.35)	<155cm	≥165cm	2.16 (1.55-3.02)	2.11 (1.46-3.05)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend<0.001
Hou et al.[308]	2013	Nigeria	Pre-menopausal	152	282	Continuous	per 5cm increase			NA	1.07 (0.89-1.28)	A, E, P, AFFP, BF, Mena, C, Alc, BMI, FH, Eth, BBD	BC ≤ 2yrs post-partum. Includes data from Ogundiran 2010
Hou et al.[308]	2013	Nigeria	Pre-menopausal	145	188	Continuous	per 5cm increase			NA	1.32 (1.07-1.62)	A, E, P, AFFP, BF, Mena, C, Alc, BMI, FH, Eth, BBD	BC 3-5 yrs post-partum. Includes data from Ogundiran 2010
Hou et al.[308]	2013	Nigeria	Pre-menopausal	421	525	Continuous	per 5cm increase			NA	1.11 (0.99-1.26)	A, E, P, AFFP, BF, Mena, C, Alc, BMI, FH, Eth, BBD	BC > 5yrs post-partum. Includes data from Ogundiran 2010
Breast cancer in post-menopausal women													
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤161.3 cm	>161.3 cm	NA	1.08 (0.62-1.89)	A	
Ogundiran et al.[210]	2010	Nigeria	Post-menopausal	506	278	Both	per 5cm increase AOR=1.20 (1.07-1.36)	<155cm	≥165cm	1.60 (1.00-2.55)	1.75 (1.06-2.88)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend=0.002

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; P, parity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.2.2 Weight

Three studies measured the association between weight and breast cancer risk (Table 5.10). Two studies measured weight in kilograms and one study used a body pictogram. The two studies that reported the weight using the metric scale were both from Nigeria and both reported risk reduction with increasing weight. Pooling the estimates from these two studies, for all women irrespective of menopausal status, being 10kg heavier at time of diagnosis was associated with a non-significant 4% decrease in risk (OR=0.96 (95% CI: 0.90-1.03) (Figure 5.5).

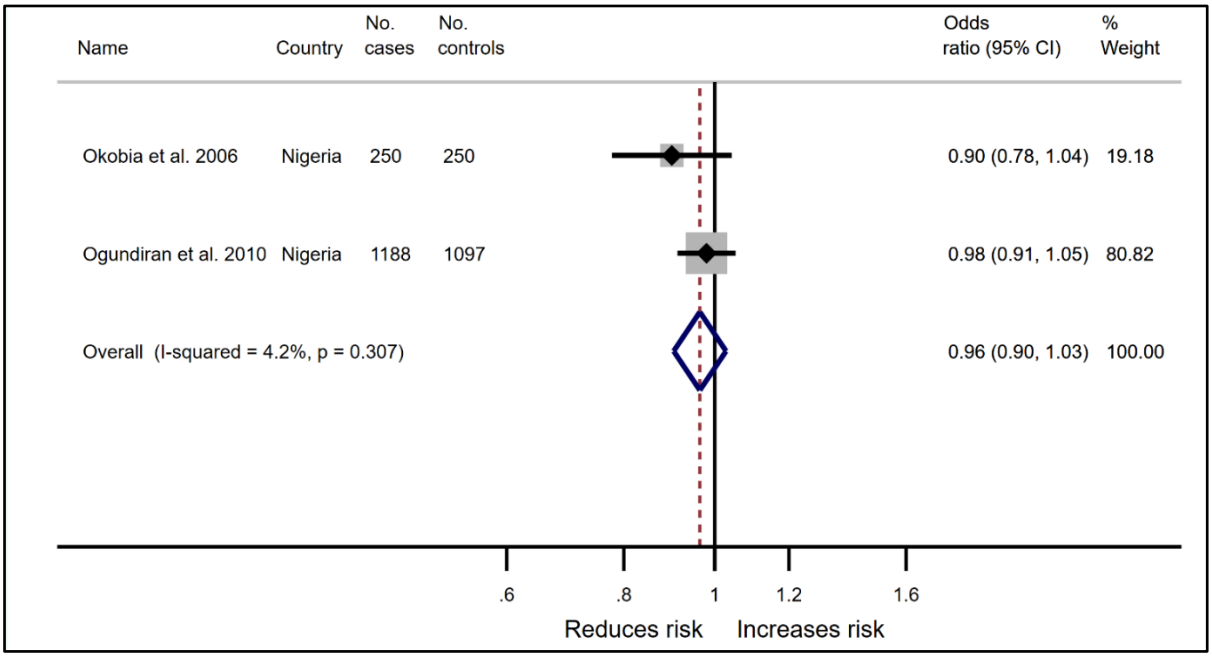


Figure 5.5: Pooled analyses of the association between a 10kg increase in weight and breast cancer risk.

Brinton et al. (2017) used a body-scale pictogram to assess weight and breast cancer risk among Ghanaian women. In this study, being heavier compared with being slight, was associated with a 50% increase in breast cancer risk (OR=1.50 (95% CI: 1.11-2.02)) (Table 5.10).

Ogundiran et al. (2010) stratified their findings by menopausal status, reporting a non-significant protective effect per 10kg increase in weight among pre-menopausal women

(OR=0.95 (95% CI: 0.87-1.04)) and non-significant increased risk among post-menopausal women (OR=1.02 (95% CI: 0.91-1.13)). (Table 5.10).

Table 5.10: Case-control studies on the association between body weight and breast cancer risk.

Author	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Continuous	per kg increase			0.99 (0.98-1.01)	0.99 (0.98-1.01)	A, E, AFFP, WHR, FH	Rescale - per 10kg AOR=0.90 (0.82-1.1)
Ogundiran et al.[210]	2010	Nigeria	All cases	1188	1097	Both	per 10kg increase AOR=0.98 (0.91-1.05)	<55kg	≥75kg	1.08 (0.84-1.39)	0.82 (0.62-1.1)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Ht, Eth	*p* for trend=0.20
Brinton et al.[224]	2017	Ghana	All cases	1201	2161	Categorical		Slight	Heavy	NA	1.50 (1.11-2.02)	A, E, P, Mena, FH, Res	Used a 9-scale body size pictogram
Breast cancer in pre-menopausal women													
Ogundiran et al.[210]	2010	Nigeria	Pre-menopausal	683	819	Both	per 10kg increase AOR=0.95 (0.87-1.04)	<55kg	≥75kg	1.18 (0.86-1.62)	0.78 (0.55-1.12)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Ht, Eth	*p* for trend=0.27
Breast cancer in post-menopausal women													
Ogundiran et al.[210]	2010	Nigeria	Post-menopausal	505	278	Both	per 10kg increase AOR=1.02 (0.91-1.13)	<55kg	≥75kg	0.95 (0.62-1.45)	0.90 (0.57-1.44)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Ht, Eth	*p* for trend=0.48

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; P, parity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.2.3 Body Mass Index

Eleven studies from nine independent cohorts reported on the association between BMI at time of diagnosis and breast cancer risk (Table 5.11). Among all women, irrespective of menopausal status, an increase in BMI was associated with an increase in risk in four of the included studies (Rosenberg et al. 2002, Awio et al. 2012, Rukundo et al.2014, and Balekouzou et al. 2017), while the others reported a decrease in risk. The largest of the included studies (Sighoko et al. 2015) which included data from three countries, reported a 3% decreased breast cancer risk per unit increase in BMI (OR=0.97 (95% CI: 0.95-0.99)).

When stratified by menopausal status, among pre-menopausal women, a higher BMI was associated with a protective effect. Ogundiran et al. 2010, the largest of the included studies, report an 11% decrease in risk per 5kg/m^2 increase in BMI among pre-menopausal women (OR=0.89 (95% CI: 0.79-0.99)). Among post-menopausal women, this protective effect with increasing BMI was observed in all included studies, although these effects were not statistically significant (Table 5.11).

Jordan et al. 2013 was the only study to report the association between BMI estimated at an earlier time point (at age 20) and breast cancer risk. They reported a non-significant increase in risk per unit increase in BMI at age-20 among all women (OR=1.31 (95% CI: 0.87-1.02), and in pre- (OR=1.41 (95% CI: 1.1-1.81)) and post-menopausal (OR=1.38 (95% CI: 1.06-1.8)) women in Tanzania.

No studies reported on the association between BMI and breast cancer risk by ER status.

Table 5.11: Case-control studies which reported on the association between Body Mass Index and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable (kg/m^2)	Highest category (kg/m^2)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Walker et al.[290]	1989	South Africa	All cases	59	93	Categorical		<30	≥30	1.70 (0.8-3.6)	NA	-	
Rosenberg et al.[222]	2002	South Africa	All cases	58	92	Categorical		<20	≥30	NA	2.70 (0.5-14)	A, E	
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Categorical		≤30	> 30	0.59 (0.34-1.02)	0.90 (0.57-1.44)	A, E, AFFP, WHR, FH	
Ogundiran et al.[210]	2010	Nigeria	All cases	1187	1097	Both	per 5kg/m^2 AOR=0.93 (0.85-1.01)	<21	≥28	0.81 (0.63-1.04)	0.72 (0.54-0.94)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend=0.009
Awio et al.[303]	2012	Uganda	All cases	70	70	Continuous	per unit increase in BMI (kg/m^2)	-	-	1.02 (1.01-1.04)	NA	-	
Jordan et al.[306]	2013	Tanzania	All cases	114	227	Continuous	per unit increase in BMI (kg/m^2)	-	-	NA	0.94 (0.87-1.02)	A, AFFP, BF, Mena, Meno, Res	At age 20 AOR=1.31(0. 87-1.02)
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical		normal	obese	0.30 (0.10-0.70)	0.30 (0.1-1.9)	AFFP, BF, Meno, C, Alc, S, FH	
Rukundo et al.[311]	2014	Uganda	All cases	90	53	Categorical		less than 18.5 kg/m^2	≥30 kg/m^2	4.0 (0.4-40.1)	NA	-	
Sighoko et al.[312]	2015	Nigeria, Cameroon, Uganda	All cases	1906	2583	Continuous	per unit increase in BMI (kg/m^2)	-	-	NA	0.97 (0.95-0.99)	A, P, AFFP, Mena, Meno, C, Alc, FH, BBD	Includes data from Ogundiran 2010
Balekouzou et al.[215]	2017	Central African Republic	All cases	169	344	Categorical		<25	≥30	2.58 (1.45-19.37)	3.11 (2.39-20.42)	A, Alc, PA	*p* for trend=0.01
Breast cancer in pre-menopausal women													
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤ 24.83	>24.83	NA	0.82 (0.49-1.36)	A	
Ogundiran et al.[210]	2010	Nigeria	Pre-menopausal	682	819	Both	per 5kg/m^2 AOR=0.89 (0.79-0.99)	<21	≥28	0.88 (0.64-1.2)	0.70 (0.5-0.98)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend=0.027

Table 5.11 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable (kg/m^2)	Highest category (kg/m^2)	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Jordan et al.[306]	2013	Tanzania	Pre-menopausal	NA	NA	Continuous	per unit increase in BMI (kg/m^2)	-	-	NA	0.94 (0.84-1.06)	A, AFFP, BF, Mena, Res	At age 20 AOR=1.41 (1.1-1.81)
Hou et al.[308]	2013	Nigeria	Pre-menopausal	152	282	Continuous	per 5kg/m^2 increase	-	-	NA	0.73 (0.56-0.95)	A, E, P, AFFP, BF, Mena, C, Alc, Ht, FH, Eth, BBD	BC ≤ 2yrs post-partum. Includes data from Ogundiran 2010
Hou et al.[308]	2013	Nigeria	Pre-menopausal	145	188	Continuous	per 5kg/m^2 increase	-	-	NA	0.75 (0.56-1.01)	A, E, P, AFFP, BF, Mena, C, Alc, Ht, FH, Eth, BBD	BC 3-5yrs post-partum. Includes data from Ogundiran 2010
Hou et al.[308]	2013	Nigeria	Pre-menopausal	421	525	Continuous	per 5kg/m^2 increase	-	-	NA	0.82 (0.7-0.95)	A, E, P, AFFP, BF, Mena, C, Alc, Ht, FH, Eth, BBD	BC > 5yrs post-partum. Includes data from Ogundiran 2010
Breast cancer in post-menopausal women													
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤25.03	>25.03	NA	0.76 (0.44-1.32)	A	
Ogundiran et al.[210]	2010	Nigeria	Post-menopausal	505	278	Both	per 5kg/m^2 increase AOR=0.98 (0.86-1.12)	<21	≥28	0.71 (0.46-1.09)	0.76 (0.48-1.21)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, FH, BBD, Eth	*p* for trend=0.15
Jordan et al.[306]	2013	Tanzania	Post-menopausal	NA	NA	Continuous	per unit increase in BMI (kg/m^2)	-	-	NA	0.92 (0.82-1.03)	A, AFFP, BF, Mena, Res	At age 20 AOR=1.38 (1.06-1.8)

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; NA, Not available; P, parity; PA, physical activity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.2.4 Waist-to-hip-ratio (WHR) and breast cancer risk

There were two studies, both from Nigeria, which reported on the association between WHR and breast cancer risk. Both studies showed a strong association between a higher WHR and breast cancer risk. This relationship was shown for all women, and among pre- and post-menopausal women (Table 5.12). A 0.1 unit increase in WHR was associated with a 45% increased breast cancer risk among all women, irrespective of menopausal status in the largest of these studies (OR=1.45 (95% CI: 1.28-1.65)).

Table 5.12: Case-control studies which reported on the association between waist-to-hip ratio and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Categorical		≤0.90	> 0.90	2.00 (1.39-2.87)	1.98 (1.27-3.10)	A, E, AFFP, FH	
Ogundiran et al.[304]	2012	Nigeria	All cases	1220	1097	Both	per 0.1-unit increase AOR=1.45 (1.28-1.65)	<0.77	≥0.87	1.90 (1.47-2.44)	2.15 (1.61-2.85)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, Ht, BMI, FH, BBD, Eth	*p* for trend<0.001
Breast cancer in pre-menopausal women													
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		≤ 0.88	>0.88	NA	2.56 (1.48-4.41)	A	
Ogundiran et al.[304]	2012	Nigeria	Pre-menopausal	702	819	Both	per 0.1-unit increase AOR=1.44 (1.22-1.69)	<0.77	≥0.87	1.88 (1.38-2.56)	2.12 (1.49-2.99)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, Ht, BMI, FH, BBD, Eth	*p* for trend<0.001
Breast cancer in post-menopausal women													
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		≤ 0.90	>0.90	NA	2.00 (1.10-3.64)	A	
Ogundiran et al.[304]	2012	Nigeria	Post-menopausal	518	278	Both	per 0.1 unit increase AOR=1.47 (1.21-1.80)	<0.77	≥0.87	2.02 (1.28-3.17)	2.26 (1.39-3.68)	A, E, P, AFFP, BF, Mena, Meno, C, Alc, Ht, BMI, FH, BBD, Eth	*p* for trend<0.001

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; P, parity; Res, residence; S, smoking; SES, socio-economic status; TNBC, Triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.3 Lifestyle factors

Studies that reported on the association between physical activity or alcohol use and breast cancer were included. Studies on diet were not included because of the heterogeneity of the comparison groups.

5.2.3.3.1 Alcohol and breast cancer risk

The association between alcohol use and breast cancer risk was reported in seven study populations (Table 5.13). Four studies reported an increase in breast cancer risk for women who ever drank alcohol compared with women who never drank. The largest study, Qian et al. 2014, reported a 39% increase in risk per 10g of average daily alcohol consumption (OR=1.39 (95% CI: 1.09-1.76)) (Table 5.13). Three studies, all from Uganda, contrary to the literature, reported a decrease in risk with alcohol use (Awio et al. 2012, Mukasa et al. 2013, and Galukande et al. 2016). However, these three studies did not quantify or describe the duration of alcohol use.

When stratified by menopausal status, alcohol use was associated with a non-significant increased breast cancer risk among both pre- and post-menopausal women, in all but one sub-population. Hou et al. 2013 studied this association between alcohol and breast cancer risk among Nigerian pre-menopausal women stratified by time since giving birth. They observed non-significant associations of alcohol use with breast cancer risk. Qian et al. 2014, reported a 64% increased risk among pre-menopausal (OR=1.64 (95% CI: 1.26–2.12)) and an 82% increased risk among post-menopausal women when comparing ever vs never users (OR=1.82 (95% CI: 1.32-2.52)) (Table 5.13).

Table 5.13: Case-control studies that reported on the association between alcohol use and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change: Alcohol usage	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Okobia et al.[223]	2006	Nigeria	All cases	250	250	Categorical		No	Yes	1.29 (0.87-1.9)	1.41 (0.86-2.3)	A, E, AFFP, WHR, FH	
Awio et al.[303]	2012	Uganda	All cases	70	70	Categorical		No	Yes	0.73 (0.55-0.96)	NA	-	
Mukasa et al.[307]	2013	Uganda	All cases	90	93	Categorical		Yes	No	0.91 (0.5-1.7)	1.6 (0.4-5.6)	AFFP, BF, Meno, C, S, BMI, FH	
Qian et al.[309]	2014	Nigeria, Cameroon, Uganda	All cases	2138	2589	Both	per 10g of average daily consumption AOR=1.39(1.09-1.76)	Non-drinker	Ever-drinker	NA	1.62 (1.33-1.97)	A, E, P, AFFP, Mena, Meno, C, Ht, BMI, FH, BBD, Res, Eth	
Rukundo et al.[311]	2014	Uganda	All cases	90	53	Categorical		No	Yes	2.10 (1.1-4.1)	NA	-	
Galukande et al.[314]	2016	Uganda	All cases	108	235	Categorical		No	Yes	0.42 (0.86-2.35)	0.57 (0.29-1.11)	A, P, AFFP, BF, Mena, C, BMI, Res	
Balekouzou et al.[215]	2017	Central African Republic	All cases	174	348	Categorical		No	Yes	3.14 (1.84-5.29)	2.53 (1.39-4.6)	A, BMI, PA	

Table 5.13 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change: Alcohol usage	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Breast cancer in pre-menopausal women													
Okobia et al.[301]	2006	Nigeria	Pre-menopausal	142	142	Categorical		No	Yes	NA	1.15 (0.69-1.92)	A	
Hou et al.[308]	2013	Nigeria	Pre-menopausal	150	281	Categorical		No	Yes	NA	1.14 (0.27-4.84)	A, E, P, AFFP, BF, Mena, C, Ht, BMI, FH, Eth, BBD	BC ≤ 2yrs post-partum
Hou et al.[308]	2013	Nigeria	Pre-menopausal	140	188	Categorical		No	Yes	NA	0.96 (0.32-2.89)	A, E, P, AFFP, BF, Mena, C, Ht, BMI, FH, Eth, BBD	BC 3-5 yrs post-partum
Hou et al.[308]	2013	Nigeria	Pre-menopausal	410	521	Categorical		No	Yes	NA	1.76 (0.99-3.13)	A, E, P, AFFP, BF, Mena, C, Ht, BMI, FH, Eth, BBD	BC > 5yrs post-partum
Qian et al.[309]	2014	Nigeria, Cameroon, Uganda	Pre-menopausal	1166	1782	Categorical		non-drinkers	ever-drinkers	NA	1.64 (1.26-2.12)	A, P, AFFP, Mena, C, Ht, BMI, FH, BBD, Res, Eth	Includes data from Hou et al. 2013.

Table 5.13 continued

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change: Alcohol usage	Baseline	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
						Breast cancer in post-menopausal women							
Okobia et al.[301]	2006	Nigeria	Post-menopausal	108	108	Categorical		No	Yes	NA	1.56 (0.83-2.93)	A	
Qian et al.[309]	2014	Nigeria, Cameroon, Uganda	Post-menopausal	848	730	Categorical		non-drinkers	ever-drinkers	NA	1.82 (1.32-2.52)	A, P, AFFP, Mena, C, Ht, BMI, FH, BBD, Res, Eth	

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BC, breast cancer; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; Mena, Menarche; Meno, Menopause; P, parity; PA, physical activity; Res, residence; S, smoking; SES, socioeconomic status; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.3.2 Physical activity and breast cancer risk

Three studies reported on the association between physical activity and breast cancer risk (Table 5.14). In all three studies, increasing physical activity was associated with a decrease in breast cancer risk. The largest of these studies, Huo et al. 2014, reported a 2% decreased breast cancer risk per unit increase in the metabolic equivalents (METs) expressed in hours/day (OR=0.98 (95% CI: 0.97-0.99)). Bigman et al. 2020 reported a greater than 50% risk reduction for the most active compared with the least active women for all women irrespective of HRS (Table 5.14).

Table 5.14: Case-control studies that reported on the association between physical activity and breast cancer risk.

Authors	Year	Country	Group	No. cases	No. controls	Data type	Unit of change	Baseline variable	Highest category	Unadjusted OR (95% C.I.)	Adjusted OR (95% C.I)	Adjusted for:	Comment
Hou et al.[275]	2014	Nigeria, Cameroon, Uganda	All cases	639	1011	Both	per MET (h/d) unit increase AOR=0.98 (0.97-0.99)	<5.3 MET h/d Total PA	>25.0 MET h/d Total PA	NA	0.39 (0.27-0.58)	A, E, Meno, BMI, Res	For Leisure time PA Yes: AOR=0.26 (0.18-0.37) vs No *p* for trend<0.001
Balekouzou et al.[215]	2017	Central African Republic	All cases	174	348	Categorical		No, does not do PA	Yes	0.91 (0.21-0.98)	0.71 (0.14-0.84)	A, Alc, BMI,	
Bigman et al.[288]	2020	Nigeria	All cases	439	457	Categorical		<3.00 MET h/week	≥11.5 MET h/week	0.41 (0.28-0.6)	0.49 (0.32-0.74)	A, E, Meno, Alc, BMI, WHR	*Leisure-time physical activity *p* for trend<0.001
Bigman et al.[288]	2020	Nigeria	HR+/HER2-	94		Categorical		<3.00 MET h/week	≥11.5 MET h/week	0.40 (0.21-0.75)	0.49 (0.24-0.97)	A, E, Meno, Alc, BMI, WHR	*Leisure-time physical activity *p* for trend=0.004
Bigman et al.[288]	2020	Nigeria	TNBC	123		Categorical		<3.00 MET h/week	≥11.5 MET h/week	0.28 (0.16-0.51)	0.35 (0.18-0.67)	A, E, Meno, Alc, BMI, WHR	*Leisure-time physical activity *p* for trend=0.001

A, age; AFFP, age at first full-term pregnancy; Alc, alcohol; BBD, benign breast disease; BF, breastfeeding; BMI, body mass index; C, contraceptive use; E, education; Eth, ethnicity; FH, family history; Ht, height; HER2-, Human Epidermal Growth Factor-2 negative; HR+, hormone-receptor positive; h/d, hours/day; h/week, hours/week; Mena, Menarche; Meno, Menopause; MET, metabolic equivalent; P, parity; PA, physical activity; Res, residence; S, smoking; TNBC, triple-negative breast cancer; WHR, waist-to-hip ratio

5.2.3.4 Risk of bias assessment

The COSMOS-E recommendations were used as a guide for the risk of bias assessment. We evaluated for confounding, risk of selection bias, and risk of information bias. All included studies were case-control studies, and all depended on self-report and were thus prone to recall bias. As with all observational studies, although some investigators, aimed to control for confounding either at the design stage (by matching), or at the analyses stage, there would still be the risk of residual confounding, either from unmeasured confounders or from incompletely measured confounders. An additional problem in case-control studies is the risk of reverse causation for some of the risk factors studied, for example, the effect of weight and BMI on breast cancer risk. Table 5.15 summarizes the risk of bias assessment for the included studies.

Table 5.15: Risk of bias assessment.

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Anderson et al.[289]	1975	Statistical analyses were not adjusted. Included women of two ethnic groupings (black and "coloureds") in the same category, following the social classification of the South African apartheid era, however, without reporting if there were any differences between the two groups. HIGH	Controls were hospital-based admitted for other diseases. Each cancer case could not be paired with a control. Consequently, the investigators compared the two series of patients. MODERATE.	Information collection did not differ between cases and controls. Risk of recall bias for self-reported exposures. MODERATE.	There were relatively few cases in each category when results were presented by menopausal status.
Walker et al.[290]	1989	Statistical analyses not adjusted. HIGH.	Controls were hospital-based. Controls were matched by age and residence. Cases and controls are most likely from the same population, but referral patterns may differ. MODERATE.	Information collected did not differ between cases and controls. Risk of recall bias for self-reported exposures. MODERATE.	

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Parkin et al.[293]	1994	Statistical analyses were adjusted but did not adjust for breastfeeding and anthropometric factors. Risk of residual confounding. MODERATE.	Controls were selected from the PBCR.Excluded cancers of the uterus. Controls and cases from the same population. MODERATE.	Some information bias if questionnaires were filled by next of kin or family member, but this would most likely not be differential by cases or controls. The proportion of questionnaires filled by next of kin was not reported. Risk of recall bias for self-reported exposures. MODERATE.	Controls were patients with other cancers selected from the population-based registry, excluding cancers of the uterus.
Skegg et al.[294]	1995	Controls were on average younger than cases, although estimates were age-adjusted at the analyses stage. Risk of residual confounding with observational studies. MODERATE.	Controls were hospital-based. Controls were women from non-obstetric or gynaecological wards. Referral patterns may differ between cases and controls. MODERATE.	Information collection did not differ between cases and controls. Data on injectable contraceptive use was cross-checked against medical records for both cases and controls. Risk of recall bias for self-reported exposures among. MODERATE.	Included women aged 52 and below. Older women were not included in the study. (Population from the WHO Collaborative studies used-Thomas and Noonan[292],1993) Relatively small number of cases, with less than 50 cases from Kenya.
Ssali et al.[295]	1995	Statistical analyses were adjusted. Risk of residual confounding. MODERATE.	Controls were selected from the surgical wards and were matched by age and residence. Referral patterns may differ between cases and controls. MODERATE.	Information collection did not differ between cases and controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	Due to the small sample size, there were relatively few patients in some risk factor strata.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Amir et al.[296]	1998	Cases were on average older than controls. The median age of cases was 48 and of controls was 36 years. Controls were thus younger women, and still in their reproductive years. The association reported of increasing risk with parity was confounded by age, as this was not controlled for. Other factors such as duration of lactation were not reported or controlled for, as well as anthropometric factors. HIGH.	Controls were hospital-based. Controls were selected from the surgical wards and were not matched by age. Cases and controls most likely from the same population. MODERATE.	Information collection did not differ between cases and controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	Relatively small sample size (50 cases).
Adebamowo and Adenkule[297]	1999	Measures of association were not adjusted for any confounders. HIGH.	Controls were hospital-based and were selected among women admitted at the surgical unit during the same period the cases were seen, with non-endocrine and non-malignant diseases. MODERATE.	Information collection did not differ between cases and controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	Very few cases in some risk factor strata. Baseline categories not stated.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Coogan et al.[298]	1999	Statistical analyses adjusted for confounders. Lacked information about details of breastfeeding. Risk of residual confounding. MODERATE.	Cases and controls are hospital-based and from the same area, controls were excluded if they were admitted to the hospital for conditions related to breast cancer risk, with very few refusals among cases and controls. Cases and controls were recruited from 1994 to October 1997 from two public hospitals (Groote Schuur and Tygerberg). After 1996, treatment became available elsewhere to women with comprehensive medical insurance. Thus, a small number of cases may have been missed from the two major hospitals. This may have been differential by socioeconomic status after 1996. MODERATE.	Information collection did not differ between cases and controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	This study combined data for blacks (13%) and “coloured” South Africans. Included mostly younger women < 55 years, as it was designed to study the role of contraceptives. Same cohort as Shapiro et al. 2000. and Rosenberg et al. 2002. Presented results on lactation and BC risk.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Shapiro et al.[299]	2000	Statistical analyses adjusted for confounders. MODERATE.	Controls were hospital-based who were admitted for conditions not related to breast cancer or contraceptive use. Selection bias if women on contraceptives were checked more often for breast cancer resulting in breast cancer being diagnosed earlier or more frequently among women on contraceptives than among their unexposed counterparts. There was a statistically higher proportion of cases on contraceptives diagnosed at early stages. MODERATE.	Information collection did not differ between cases and controls. Cases could have reported their contraceptive exposures more fully than controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	Same study population as Coogan et al. 1999. Shapiro focused on contraception use and BC risk. Multivariable regression analyses controlled for confounding. With no large differences in magnitude or direction of effect between unadjusted and adjusted values.
Rosenberg et al.[222]	2002	Statistical analyses were adjusted for confounders but estimates were not adjusted for duration of breastfeeding. Risk of residual confounding. MODERATE.	Controls were hospital-based who were admitted for conditions not related to breast cancer or contraceptive use. MODERATE.	Information collection did not differ between cases and controls. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	Presented results separately for black and “coloured” women. Same population as Shapiro et al. 2000 and Coogan et al.1999. This study included a relatively small number of black women (65 women).

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Okobia et al.[223]	2006	Statistical analyses were adjusted however, data on breastfeeding, contraceptive, and alcohol use were dichotomised. No information on the duration of exposures. Risk of residual confounding. MODERATE.	Cases and controls are hospital-based, controls were admitted for non-malignant, non-hormonal disorders, unclear if cases and controls are from the same area, missing data were reviewed. MODERATE.	Anthropometric factors such as BMI, waist-to-hip ratio and weight were measured at the time of diagnosis, and this may be influenced by recent changes in health as a result of the disease process. No earlier measurements of these anthropometric factors were used. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	This second paper by Okobia et al.[301] is based on the same study population, but the second paper focuses on anthropometric risk factors stratified by menopausal status. Menopause was defined as the cessation of menstruation for the past 12 months in an otherwise healthy woman.
Huo et al.[267]	2008	Statistical analyses were adjusted for measured confounders, hormonal contraceptive use was only assessed as dichotomous ('ever', 'never'). Cases and controls were not age-matched. Cases were older and taller than controls. However, this was controlled for at the analyses stage. MODERATE.	Controls were randomly selected from a community of the catchment area of the hospital and from the clinics of the University College Hospital Ibadan. Hospital controls were matched for age and ethnicity. Not reported if any differences in characteristics between community and hospital controls. MODERATE.	Information collection did not differ between cases and controls. Some missing data for age at menarche (proportion not reported), although multiple imputation was used to impute the missing values. The BMI was measured at the time of diagnosis, and this may be influenced by changes in health as a result of the disease process. No earlier measurements of BMI were available. Some risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	A publication of the Nigerian Breast Cancer Study which is part of the African Breast Cancer Study.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Ogundiran et al.[210]	2010	Statistical analyses were adjusted. Risk of residual confounding. Not adjusted for physical activity levels. Changes in body size and composition as a result of disease progression could bias the results of the study. MODERATE.	Controls were randomly selected from a community of the catchment area of the hospital and from the clinics of the University College Hospital Ibadan. Hospital controls were matched for age and ethnicity. Not reported if any differences in characteristics between community and hospital controls. MODERATE.	Information collection did not differ between cases and controls. Risk of recall bias among cases and controls. MODERATE.	A publication of the Nigerian Breast Cancer Study which is part of the African Breast Cancer Study. Similar limitations in the follow-up study Ogundiran 2012.
Sule[302]	2011	Statistical analyses were not adjusted, presentation of statistical analysis was equivocal, contraceptive use was dichotomised. HIGH.	Cases and controls are hospital-based. MODERATE.	Information collection did not differ between cases and controls however, the baseline characteristics of cases and controls were not described. Risk of recall bias. MODERATE.	
Awio et al.[303]	2012	Not specified if the reported odds values were adjusted for any other covariates or confounding factors. use of contraceptives was an exclusion criterion for controls but is presented in the analysis. HIGH.	Cases and controls were selected from women who came for screening and breast health care. Most likely from the same population. MODERATE.	Information collection most likely did not differ between cases and controls. Risk of recall bias among cases and controls. MODERATE.	The study was powered to study differences in oestradiol levels and breast cancer risk. It was not clearly defined which categories were the referent against which comparisons were made.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Urban et al.[305]	2012	Statistical analyses were adjusted for measured confounders. Cases and controls were included from 1995 to 2006, a period of 11 years over which there might have been changes in type or dosage of contraceptives routinely used. Risk of residual confounding. MODERATE.	Controls were patients with cancers not known to be associated with contraceptive use. However, knowledge on cancer risk is not yet fully known, and some cancers used as controls could have an unknown association with contraceptives. MODERATE.	Information collection did not differ between cases and controls. "Although the vast majority of the oral contraceptives investigated here are likely to be combined oral contraceptives, we cannot exclude the possibility that a small proportion comprises progestogen-only preparations. Similarly, a small proportion of the injectable contraceptives may be combined oestrogen-progestagen preparations." Could result in misclassification. Self-reported exposures could be affected by recall bias. MODERATE.	This study is part of the Johannesburg Cancer Case-Control study. Controls were other patients with cancers that were unrelated to the exposures being studied. Cancers of the liver and biliary tract, other genital cancers, placenta, and Kaposi sarcoma were excluded as controls. As well as cancers of the cervix, ovaries, and endometrium for this study on breast cancer.
Hou et al.[308]	2013	Statistical analyses were adjusted for measured confounders, hormonal contraceptive use was only assessed as dichotomous ('ever', 'never'). MODERATE.	Controls were randomly selected from a community of the catchment area of the hospital and from the clinics of the University College Hospital Ibadan. Hospital controls were matched for age and ethnicity. Not reported if any differences in characteristics between community and hospital controls. MODERATE.	Information collection did not differ between cases and controls. There are higher rates of delayed breast cancer diagnosis in sub-Saharan African populations in the absence of screening programmes, such that pregnancy-associated breast cancers may be diagnosed later and could thus be misclassified. MODERATE.	See Huo, 2008. This study is part of the NBCS (reported in Huo 2008), but this study reports data on pregnancy-associated cancers among pre-menopausal women only.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Jordan et al.[306]	2013	Statistical analyses were adjusted for measured confounders. Family history was not adjusted for. Risk of residual confounding. MODERATE.	Controls were hospital- and visitor-based and were matched by district. A higher proportion of cases were illiterate or attended less than 3 years of schooling as compared with controls. And the property level of cases was lower than that of controls. Both differences were significant. MODERATE.	Used a Stunkard et al.'s pictogram modified to the African setting to estimate BMI at age 20. This could result in a non-differential misclassification of BMI at age 20. These pictogram estimates could not be compared against any objective measures of weight at age 20, as this information would most likely be more difficult to obtain. However, any risk of misclassification would most likely not be differential by case or control status. Risk of recall bias for self-reported risk factors. MODERATE.	Comparisons made between the current BMI at interview estimated from the pictogram, and the actual BMI had a Spearman rho's correlation coefficient of 0.75.
Mukasa et al.[307]	2013	Analyses were adjusted. But did not adjust for any anthropometric factors. Duration of contraceptive use not recorded and controlled for. Risk of residual confounding. MODERATE.	Cases and controls are hospital-based, cases are referred from all over the country, unclear if the same applies to controls, controls were, inter alia, patients of the endocrine/breast clinic and surgical outpatients' clinic. MODERATE.	Information collection most likely did not differ between cases and controls. Baseline categories were not clearly defined. Risk factors were self-reported with risk of recall bias among cases and controls. MODERATE.	

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Sighoko et al.[239]	2013	Statistical analyses were adjusted but were not adjusted for anthropometric, lifestyle factors, or family history. Risk of residual confounding. MODERATE.	Cases and controls are hospital-based, no information if cases and controls are from the same areas of residence. MODERATE.	Information collection did not differ between cases and controls. Proportion of cases with missing data on age at menarche was not specified). Results were presented by menopausal status and menopausal status was "self-reported" by participants. No uniform definition of menopause was mentioned to have been used by investigators in the manuscript, which may introduce some misclassification. MODERATE.	Included parous women only.
Hou et al.[275]	2014	Statistical analyses were adjusted for confounders. Cases were older on average than controls, but this was adjusted for in the analysis stage. Risk of residual confounding with observational studies. MODERATE.	Control recruitment was not the same for all 3 study centres. Hospital-based controls may have a different physical activity profile compared with cases. Community and hospital-based controls were recruited in Ibadan while in Yaoundé and Kampala, only age-matched hospital-based controls were used. It was not mentioned if the characteristics of controls used in Ibadan were similar for community and hospital controls. MODERATE.	Information collection did not differ between cases and controls. The study relied on self-reported physical activity, and this was not validated against any objective measures of physical activity such as accelerometery. The investigators enquired about the cases and controls' physical activity in the year before the interview, and this may be subject to recall bias. Furthermore, patients' activities may have been different from normal in the period before diagnosis, particularly for patients diagnosed at advanced stages. MODERATE.	This study focused on physical activity and breast cancer risk. Results from the African Breast Cancer Study.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Qian et al.[309]	2014	Statistical analyses were adjusted for confounders. Cases were older on average than controls, but this was adjusted for at the analysis stage. Risk of residual confounding with observational studies. MODERATE.	Controls were not recruited in the same way in all three study sites. Controls were randomly selected from communities in Nigeria and hospital-based in Cameroon and Uganda. The low proportion of refusals. Controls were selected from the general outpatient and surgical, ophthalmologic and gynaecologic and obstetric units. Hospital-based controls may have a different pattern of alcohol use than community-based controls. MODERATE.	Information collection did not differ between cases and controls. There were missing data on the age at first drink and the duration and quantity of alcohol consumed. The investigators used multiple imputation to impute missing values and conducted sensitivity analyses to assess differences in results. Results could be affected by recall bias, and this could be differential by age, and case/control status. Participants could underreport their alcohol intake, introducing social desirability bias. MODERATE.	This study focused on alcohol consumption and breast cancer risk. Included results from the Nigerian Breast Cancer Study which is part of the African Breast Cancer Study.
Othieno-Abinya et al.[310]	2014	Did not adjust for confounders such as parity, breastfeeding, or anthropometric factors. HIGH.	Cases and controls were hospital-based. Controls were matched by age but not by residence. MODERATE.	Information collection did not differ between cases and controls. Risk of recall bias for self-reported exposures among both cases and controls. MODERATE.	Baseline categories not specified. So, it was not clear what the comparisons were being made against.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Rukundo et al.[311]	2014	Only crude odds ratios were reported. Statistical analyses not adjusted. HIGH.	Cases and controls are hospital-based, no information if cases and controls are from the same areas of residence. MODERATE.	Information collection did not differ between cases and controls. Risk of recall bias for self-reported exposures among both cases and controls. MODERATE.	The study was designed to evaluate the association between red blood cell folate concentration and breast cancer risk.
Kana et al.[313]	2015	Models were not fully adjusted, as data on some potential confounders were not available in the dataset. Factors that were adjusted for were not fully reported in the manuscript. HIGH.	Cases and controls were selected among women who presented for breast and cervical cancer screening following an awareness campaign. MODERATE.	Little information on the data collection process. HIGH.	Small sample size, with only 29 cases included. 6 controls were selected per case.
Sighoko et al.[312]	2015	Statistical analyses were adjusted, contraceptive use was dichotomised. Community controls in Ibadan were not age-matched although this was adjusted for at the analysis stage. MODERATE.	Community and hospital-based controls were used in Ibadan while in Yaoundé and Kampala, age-matched hospital-based controls were used. It was not mentioned if the characteristics of controls used in Ibadan were similar for community and hospital controls. MODERATE.	Information collection did not differ between cases and controls. Slightly different versions of the study questionnaire were used at different times in Nigeria, and the final version was used in Yaoundé and Kampala. Not mentioned what questions had changed in different versions of the questionnaire. Risk of recall bias for self-reported exposures among both cases and controls. MODERATE.	Part of the African Breast Cancer Study.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Essiben et al.[214]	2016	Duration, type, and quantity of alcohol use was not controlled for. Physical activity was dichotomised. Risk of residual confounding. MODERATE.	Cases and controls were hospital-based. Controls not matched for age or residence. MODERATE.	Information collection did not differ between cases and controls. Risk of recall bias for self-reported exposures among both cases and controls. MODERATE.	No baseline variables were specified for the odds ratios from the multi-variable regression analysis. Not stated what were the reference categories.
Galukande et al.[314]	2016	Analyses were adjusted, but the multivariable analyses, did not adjust for duration of breastfeeding and duration of contraceptive use. Risk of residual confounding. MODERATE.	Cases and controls are hospital-based and not all from the same area of residence, no information on missing data, no cases but few controls refused to participate. MODERATE.	Information collection did not differ between cases and controls. Recall bias could affect the accuracy of reported risk factors such as age at menarche. MODERATE.	

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Balekouzou et al.[315]	2017	Statistical analyses were partially adjusted. Did not adjusted for duration of breastfeeding, or age at first full-term pregnancy. MODERATE.	Cases and controls are hospital-based, both from the same catchment area, cases (n=174) were recruited over 12 years, unclear whether controls were recruited over the same period MODERATE.	When cases had died, the information on risk factors was obtained from the next of kin. And this would increase the risk of misclassification errors, missing data, and loss of accuracy on some risk factors studied such as duration of breastfeeding, age at menarche, contraception use, etc. The proportion of cases who had died and for whom risk factors were obtained from a next-of-kin was not reported. The case-control design and the self-reporting of risk factors could result in recall bias and risk of misclassification. HIGH.	Same study population like their second paper Balekouzou et al., 2017[215]
Figueroa et al.[270]	2020	Statistical analyses were adjusted, potential confounders were addressed. Risk of residual confounding with observational studies. MODERATE.	Controls were randomly selected from the residence area of the cases. Used a census-based population-level selection of controls. LOW.	Information collection did not differ between cases and controls. A substantial number of women could not recall their age at menarche which could lead to misclassification. MODERATE.	Same study population like Brinton et al. 2017, in which body size was assessed with a pictogram, however, information was not available if this was validated against actual weight or BMI.

Table 5.15 continued

Authors	Year	Confounding	Selection bias (Selection of cases and controls)	Information bias (Exposure/outcome assessment + Missing data)	Comment
Bigman et al.[288]	2020	Statistical analyses were adjusted. Did not adjust for family history of breast cancer, and calorie intake. Alcohol use was dichotomised (yes/no). Risk of residual confounding. MODERATE.	Controls were hospital-based. Low proportion of refusals. Hospital controls could have different physical activity levels from the general population. Controls were age-matched, without cancer or endocrine conditions and enrolled within 2.5months in the same hospital as the cases. MODERATE.	Information collection did not differ between cases and controls. The study relied on self-reported physical activity, and this was not validated against any objective measures of physical activity such as accelerometery. Leisure-time physical activity levels could have been impacted in the year prior to diagnosis especially if cases presented at advanced stages. MODERATE.	This study focused on physical activity and breast cancer risk. Pre-print. Not peer reviewed.

NBCS=Nigerian Breast Cancer Study, BC=Breast cancer, PBCR = Population-based cancer registry

5.3 Population-level trends in risk factors

Data on trends in the population-level measures of the above studied risk factors were obtained from population-level surveys, published reports, and peer-reviewed papers. In this section, I focused on countries included in Chapter 4, for which we have data on trends in breast cancer incidence rates from the sub-national or national population-based registries. These were Congo-Brazzaville, Gambia, Kenya, Malawi, Mauritius, Nigeria Seychelles, South Africa, Uganda, and Zimbabwe.

The population-based registries of Gambia, Mauritius, and Seychelles cover the national territory, while all the others cover urban areas, except for the Eastern Cape registry of South Africa, which covers a rural population.

5.3.1 Reproductive Factors

5.3.1.1 Age at Menarche

Two recent studies mapped the available data on trends in the age at menarche (AAM) in low-and-middle-income countries using data from the DHS and the World Fertility Surveys (WFS).[316,317]The WFS were population-level surveys conducted from 1977-1983 and included data from Nigeria and Kenya.

Of the 10 countries included in the chapter on breast cancer incidence trends, data on trends in age at menarche were available for three- Nigeria, Kenya, and Uganda from both of these population-level surveys.[316]

Using data from the WFS, for women of the 1935-1965 birth cohort, it was estimated that the AAM decreased by 0.35 years in Kenya, and by 0.64 years in Nigeria over a 30-year period; with overall lower AAM for women in North Africa (13.5 years), compared with women in SSA (14.5 years) in this period.[317] Using recent data from the DHS and historic data from the WFS, Garenne reports that the mean AAM has decreased from 15.02 years for the 1933 birth cohort

to 13.78 years for the 2003 birth cohort, among Nigerian women and this decline is correlated with increases in per capita income. [318]

Leone and Brown's research on age at menarche in LMIC also indicates a decline in age at menarche with later birth cohorts; with average AAM declining from 14.66 years (95%CI: 14.34–14.98) for women of the 1932 birth cohort to 12.86 years (95%CI: 12.64–13.07) for women of the 2002 birth cohort.[316]

Using cross-sectional studies from a 40-year period, Cameron et al.,1991 presented trends in the AAM among black South Africans in rural and urban areas. They reported a decline in the AAM of 0.34 years and 0.64 years per decade among black women in rural and urban areas respectively.[319] Using more recent data from South Africa, a similar trend from cross-sectional studies is reported with a decrease of 0.50 years per decade; from an AAM of 14.9 years (95% CI: 14.8-15.0) in 1956 to 12.4 years (95% CI: 12.2-12.6) in 2004 among black Urban South African girls.[320] In rural Gambia, a 0.65 year decline in the median AAM per decade was reported ($p < 0.00001$) from cross-sectional studies, with a median AAM of 16.06 (95% CI: 15.67–16.45) in 1989, 15.03 (95% CI: 14.76–15.30) in 2000, and 14.90 (95% CI: 14.52–15.28) in 2008.[321]

5.3.1.2 Menopause

There are no reports or available data on trends in age at menopause at population-level among sub-Saharan African women. The DHS reports data on the percentage of women aged 30-49 who are menopausal. It defines menopausal as "women who are not pregnant and not postpartum amenorrhoeic whose last menstrual period occurred 6 or more months preceding the survey", which differs from WHO definition of menopause as the age of cessation of menses plus 12 months of spontaneous amenorrhoea.[322]

From cross-sectional studies of variable size and variable representativeness, the mean age at menopause (MAM) was estimated at 49.2 (SD=4.2) in 1960 among a small sample of black

urban Zulu South Africans, with a median of 48.2.[323] In 1984, Walker et al. reported on a cross-sectional population sample from 1255 urban and 1850 rural South African women, and the MAM was estimated at 48.9 (SD=4.2) and 49.5 (SD=4.7) respectively. This difference in the MAM was not statistically significant between women residing in urban and rural areas.[324] In 2005, among rural Xhosa women from the Eastern Cape Province of South Africa, the MAM was 50.2 years (range 45-57).[325]

In 1990, in a sample of 563 Nigerian women, Okonofua et al. reported a MAM of 48.4 years (SD 5.0).[326] In 2009, in a cross-sectional community-based study on 1189 women in Ibadan - Nigeria, the MAM was estimated at 48.5 years (SD 4.6), with a median of 49 years.[327] In 2012, Ogwumike et al. reported a MAM of 49.2 (SD 5.2) from a cross-sectional population survey in three urban states in Nigeria.[328] In rural communities of Orlu, Nigeria, the MAM was estimated at 47 years (SD 4.2) in 2012.[329] In 1997, in a rural population of 1078 Western Kenyan women, the median age at menopause was estimated at 48.3 years.[330]

The WHO Collaborative Study of Neoplasia and Steroid contraception conducted from 1979-1986 which included data from Nigeria and Kenya, showed that there was less variability in the age at menopause across centres, with a mean of 50 years (range 49-52) in comparison to the age at menarche and age at first birth, which showed more variability for the 13 centres included. However, the sample mainly consisted of younger women, age range 15-64, with a median of 40, from which they modelled the age at which natural menopause would occur.[331]

5.3.1.3 Age at first birth

Data on the age at first birth was obtained from the DHS for the countries included in chapter 4, which had more than one data point from the DHS. There were modest changes in the overall median age at first birth among women aged 45-49. When stratified by educational status, the data shows consistently higher median age at first birth among the women with higher levels of education in these countries (Figure 5.6).

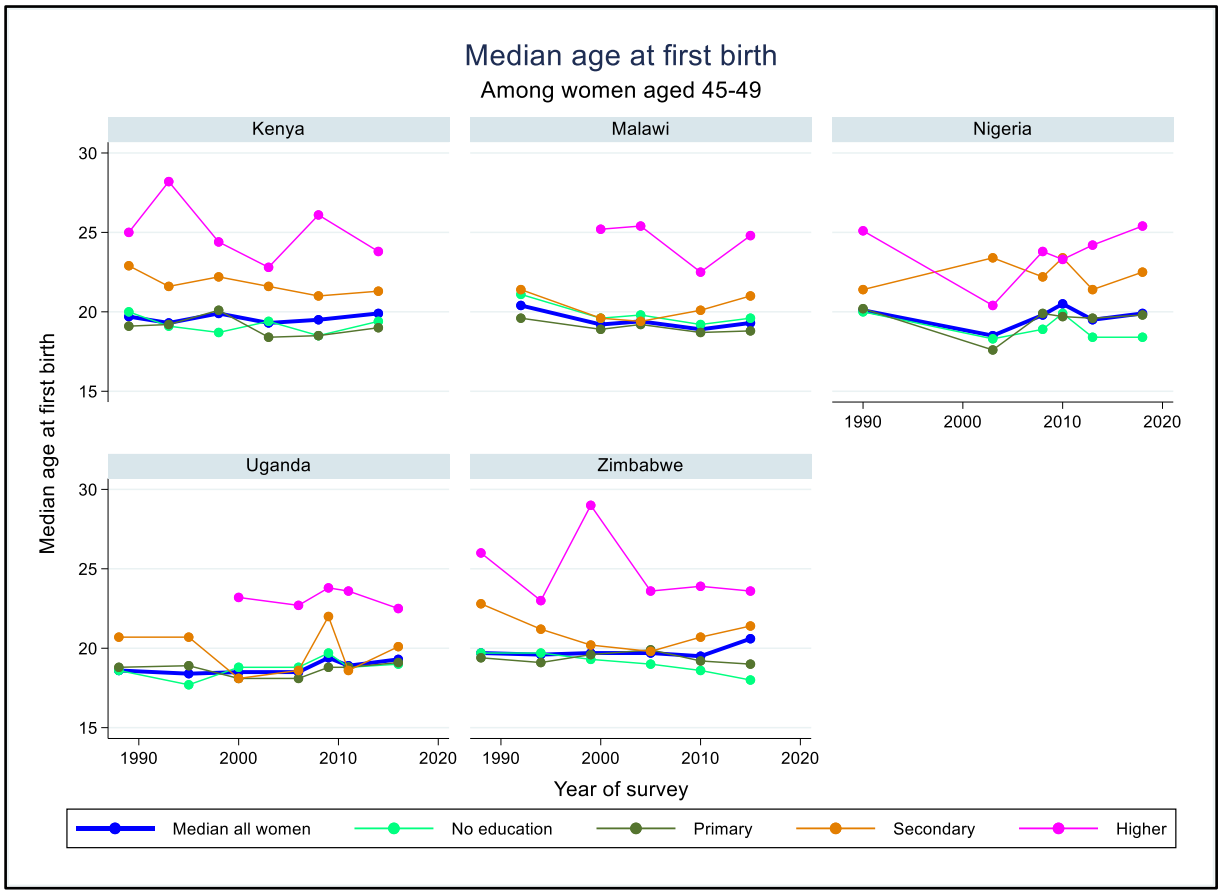


Figure 5.6: Trends in the median age at first birth from the Demographic and Health Surveys (DHS).

5.3.1.4 Trends in total fertility rates (parity)

Publicly available population-level survey data on the total fertility rates were obtained from the United Nations World Population Prospects 2019 database[332] for the 10 countries included in Chapter 4. The total fertility rate is the average number of children born per woman i.e. the total number of children that would be born per woman if she were to live to the end of her childbearing years (usually taken as 15-49) and give birth to children in alignment with the prevailing age-specific fertility rates.[333] The available data in the World Population Prospects is obtained from birth histories data from population-level surveys including

theWFS, the DHS and the Performance Monitoring and Accountability surveys.[332] These data show declining fertility rates in all 10 nations (Figure 5.7).

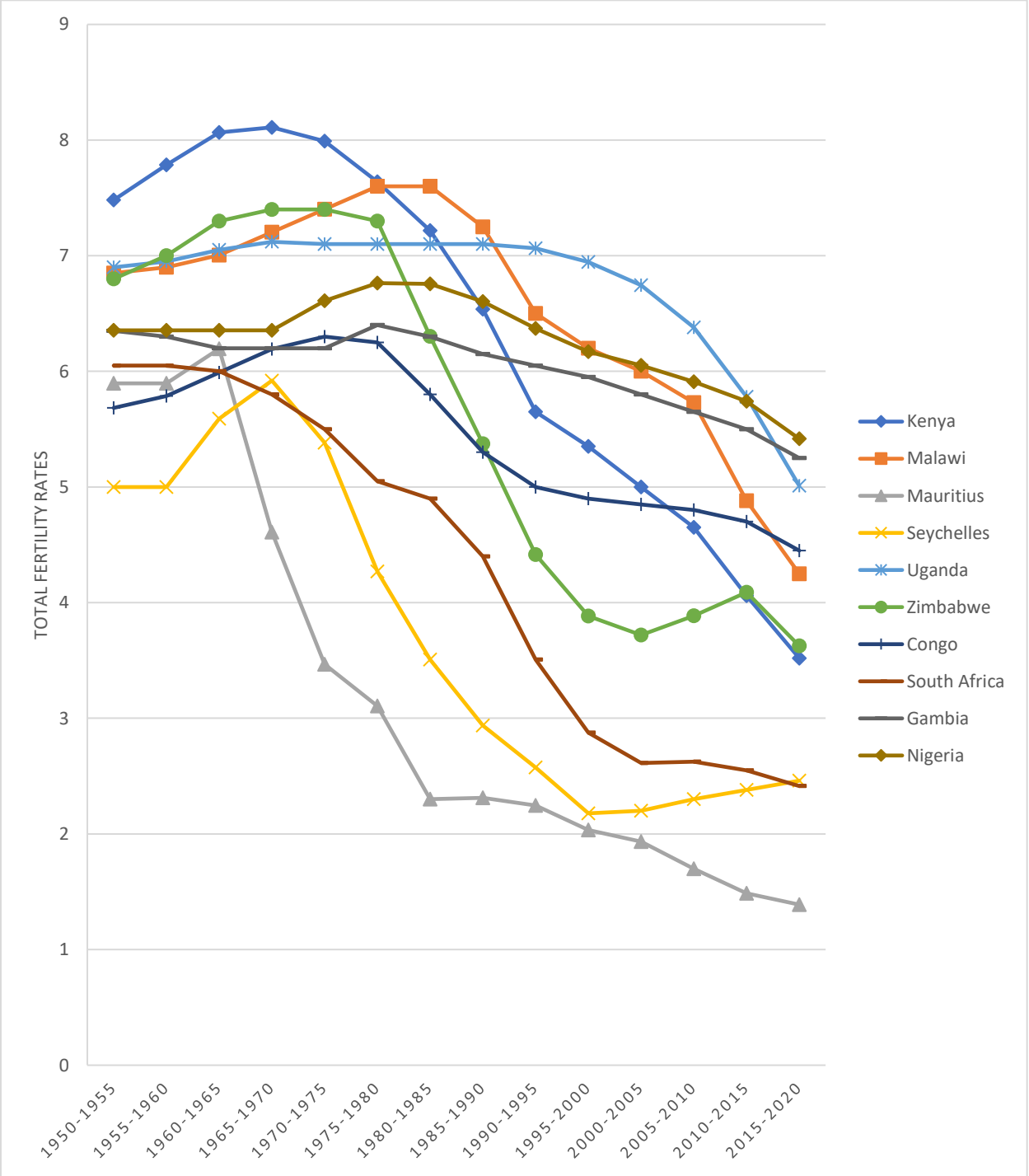


Figure 5.7: Trends in total fertility rates from population-level surveys.

The World Fertility Report predicts even further declines in the fertility rates in SSA (Table 5.16), with a corresponding increase in the prevalence of contraception use.[334]

Table 5.16: Trends in Total Fertility Rates by Region, sub-Saharan Africa.

	Total Fertility Rates (children per woman)		
Region	**1990**	**2019**	**2030**
Eastern Africa	6.6	4.3	3.6
Middle Africa	6.7	5.4	4.5
Southern Africa	4.1	2.5	2.2
Western Africa	6.5	5.1	4.4

Data source: World Fertility and Family Planning 2020: Highlights

5.3.1.5 Trends in breastfeeding

Data were obtained from the DHS database on the median duration of any breastfeeding for children born in the three years preceding the survey. Countries in chapter 4 with more than two DHS data points were included. These data suggest modest changes in the median duration of breastfeeding for all women over time. Women with higher levels of education breastfed, on average, for shorter durations compared with women with fewer years of formal education (Figure 5.8).

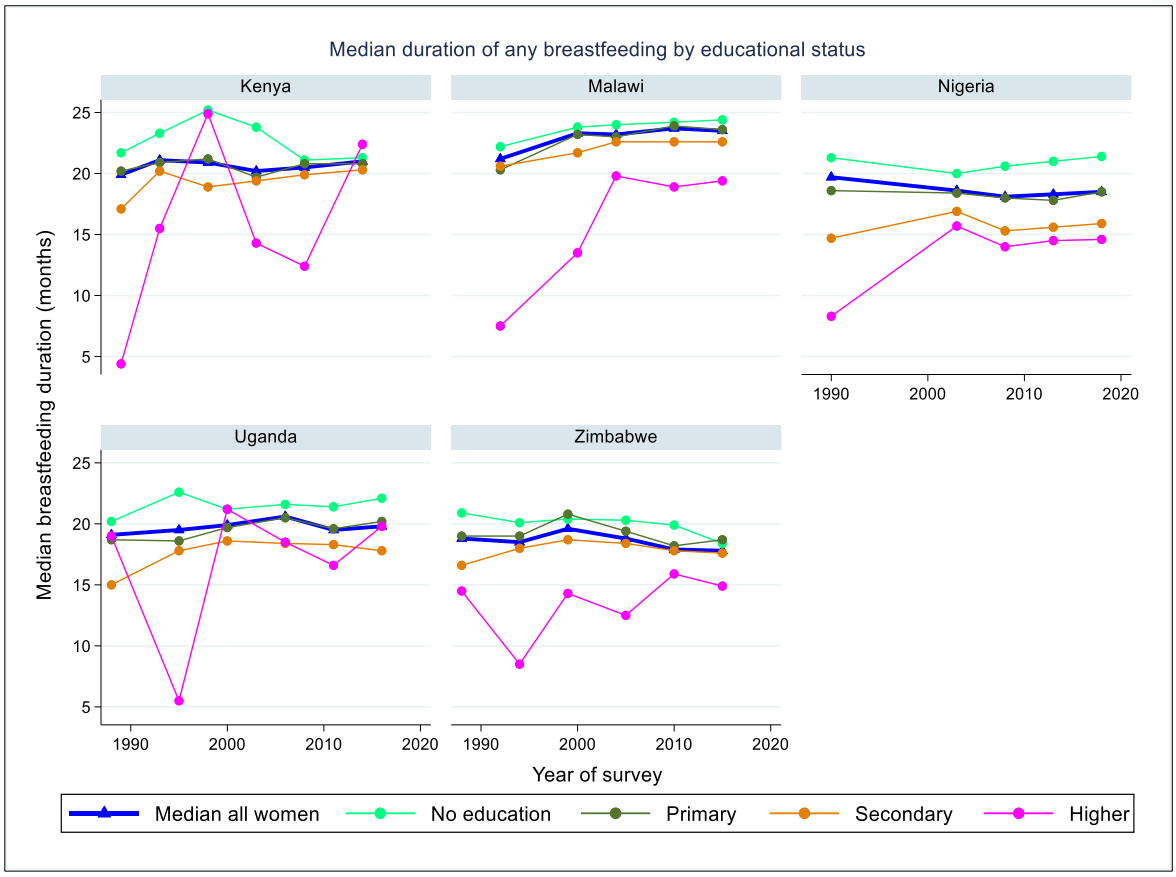


Figure 5.8: Median duration of any breastfeeding (in months) over time and by educational status, DHS.

5.3.1.6 Trends in the use of contraception

Population-level data were obtained from the United Nation Population Division World Contraceptive Use 2020 database, on trends in the proportion of women aged 15-49 who used pills and injectable contraceptives.[335] It revealed country-level differences in the proportion of women who ever used contraceptives. There are relatively lower rates of ever use of contraceptives in Congo, Gambia, Mali, and Nigeria compared with Kenya, Malawi, South Africa, and Zimbabwe (Figure 5.9). The prevalence of oral or injectable contraceptive use varies across these countries. Over the last four decades, the proportion of women who use injectable contraceptives has increased in Kenya, Malawi, and Uganda; while the proportion of women who use oral contraceptives has doubled in Zimbabwe. The proportion

of women who use oral and injectable contraceptives have declined among women in Mauritius and South Africa in recent years (Figure 5.9).

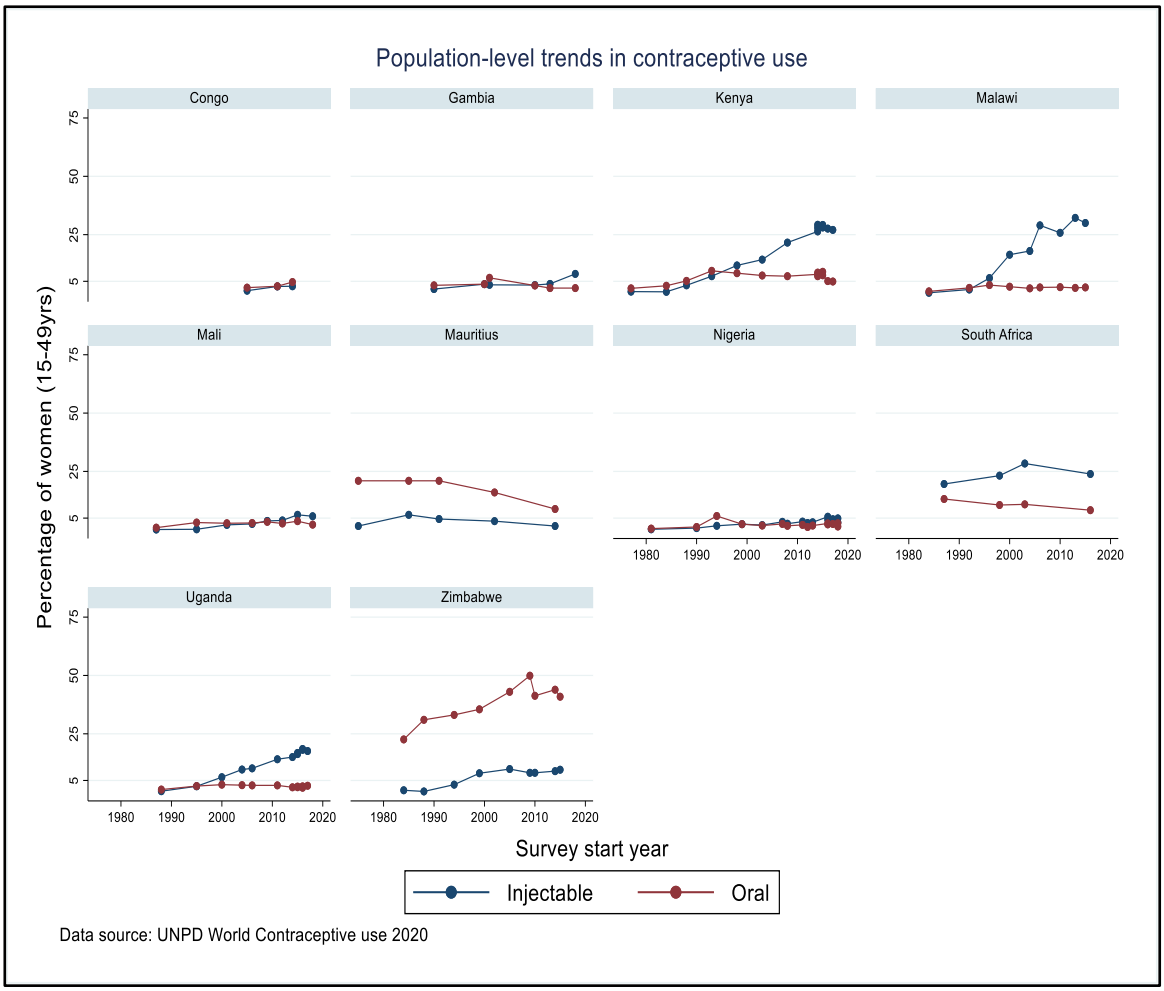
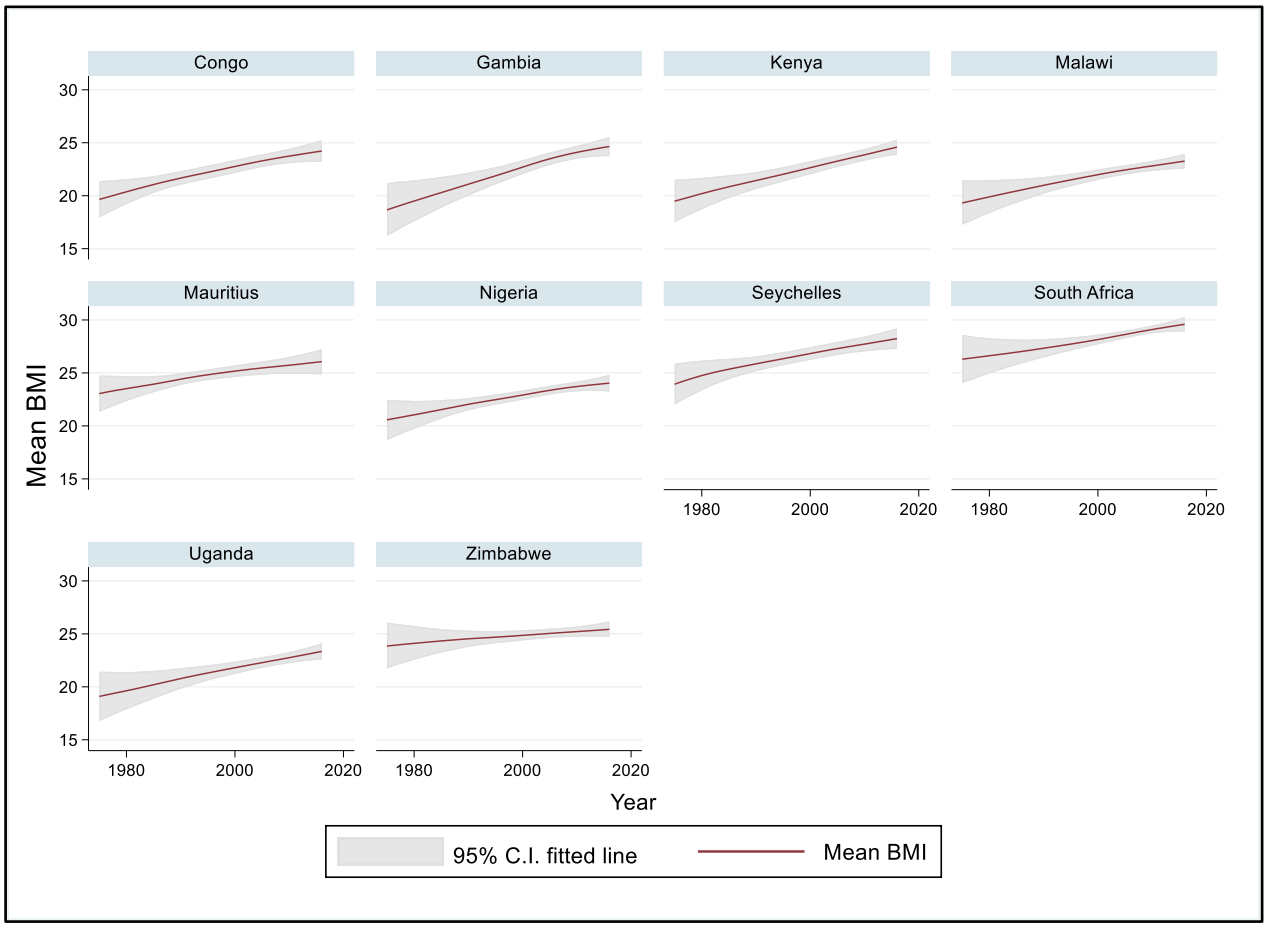


Figure 5.9: Trends in the proportion of women who use contraceptives.

5.3.2 Anthropometric Factors

Data were obtained on trends in BMI for sub-Saharan African populations from the Non-Communicable Diseases Risk Factor Collaboration group (NCD-RisC).[336] The NCD-RisC group used data from all available population-level datasets to estimate trends in BMI over this period. The graphic below shows trends in mean BMI for adult women for all countries included in chapter 4 (Figure 5.10). There are rapid increases in BMI in a majority of these

nations, and with higher mean BMI in countries with higher HDI such as Seychelles, South Africa, and Mauritius (Figure 5.10). However, within these countries, there would be disparities in BMI by socio-economic status, age, and ethnicity, for which we do not have sufficiently granular data.



Data source: NCD-Risk Factor Collaboration Group.

Figure 5.10: Trends in BMI among adult females over time.

Analyses of individual-level data on height from the DHS for adult women aged 20-49, was reported in the DHS comparative report on trends in nutritional status of adult women in SSA.[337] This showed increases in height in birth cohorts born before 1965, correlated with increases in country-per capita income. However, a decline in the average height of adult SSA women was observed for birth cohorts between 1965 and 1990 which correlated with a

decrease in per capita income as a result of the economic downturn faced in many of these countries. The average adult height is influenced by the nutrient availability in childhood and adolescence.[337]

5.3.3 Trends in alcohol consumption and trends in physical activity

Population-level data on the proportion of alcohol use and physical activity were obtained from the reports of the WHO's STEPwise Approach to NCD Risk Factor Surveillance (STEPS) surveys.[338] These surveys were initiated in 2000 to support LMIC in collecting data on trends in non-communicable disease (NCD) risk factors. The proportion of women who currently drink alcohol or binge drink is low in SSA compared with proportions observed in men, with some countries like the Gambia recording very low proportions of alcohol consumption among women (less than 0.5%) (Table 5.17). Different definitions for "binge drinking" was used in the different countries, with the highest proportion recorded in Congo (Table 5.17).

The percentage of women with insufficient physical activity levels ranged from 1.8% in Malawi to 26.5% in the Gambia (Table 5.17). Data from these surveys show that more than 50% of women do not engage in vigorous physical activity in almost all of these countries. However, within these large categories, there would be differences by age, socio-economic status, and health levels.

Table 5.17: Population-level proportions of alcohol use, and physical activity levels, results from the WHO STEPS surveys.

Country	Year	Age group	% Who currently drink[1]	% Who binge drink[2]	Percentage with insufficient Physical Activity[3] (PA)	Percentage not engaging in vigorous activity
Congo	2004	25-64	3.8 (-)	7.1 (-)	NA	NA
Gambia	2010	25-64	0.4 (0.2-0.7)	0.3 (0.1- 0.6)	26.5 (18.6-34.5)	66.0 (58.8-73.3)
Kenya	2015	18-69	5.4 (3.6-7.2)	2.7 (1.2-4.1)	6.8 (5.1-8.4)	52.9 (48.5-57.3)
Malawi	2009	25-64	4.2 (3.2-5.2)	2.3 (1.6-3.1)	12.6 (10.6-14.7)	22.3 (19.3-25.3)
Malawi	2017	18-69	2.8 (1.6-3.9)	NA	1.8 (1.0-2.5)	NA
Seychelles	2004	25-64	NA	NA	20.1 (16.9-23.3)	91.1 (88.8-93.4)
Uganda	2014	18-69	17.9 (15.3-20.5)	7.9 (6.3-9.6)	4.9 (3.8-6.0)	58.4 (54.7-62.1)

[1] Currently drink was defined as haven drank alcohol in the past 30 days except for Congo 2004 where it was defined as drank alcohol on 4 or more days in the last week.
[2] For Uganda, Kenya the definition for binge drinking: drank 6 or more drinks in the last 30days. For Congo, Seychelles: Binge drinking was defined as having 4 or more drinks on any day in the last week. For the Gambia and Malawi, 2009 it was defined as women who had 4 or more drinks on any day in the past 30 days.
[3] < 150 minutes/week of moderate-intensity activity, or equivalent.
NA: Not available.

Martinez et al. 2011 described differences in the pattern of alcohol consumption in Africa using population-level data from the World Health Surveys (WHS).[339] The WHS were carried out between 2002 and 2004 and included 20 African countries.[340] Of the 10 countries included for the study of trends, data were available from five of these: Kenya, Mali, Malawi, South Africa, and Zimbabwe. In 2002-2004, the proportion of women who currently drank alcohol (drank at least one standard drink in the last seven days) was 4.1% in Kenya, 1.0% in Malawi, 2.5% in Mali, 13.5% in South Africa, and 3.4% in Zimbabwe. Of the 20 countries included in the WHS, the highest proportion of lifetime abstainers was observed in predominantly Muslim/Arab nations such as Morocco, Tunisia, and Comoros where more than 99.5% of women were lifetime abstainers. In Mali, 95.8% of women were lifetime abstainers.[339]

Guthold et al. 2018 estimated worldwide trends in insufficient activity worldwide in 2016, using all available data from population-level surveys. They estimated that the proportion of insufficient physical activity among women in SSA in 2016 was 24·8% (95% CI: 21·8–27·2), with lowest rates observed in Uganda (5·5% (95% CI: 4·0–7·6)) and highest rates observed in Mali (40·4% (95% CI: 33·6–47·3)), and with higher rates of insufficient physical activity in women compared with men.[276]

5.4 Discussion

There is considerable amount of research on breast cancer aetiology in Western countries, but relatively few high-quality studies from SSA. Although the knowledge gained from these Western studies is invaluable; context-specific studies are needed on the African continent. This is because of the complex interplay of hormonal, environmental, and genetic factors in any given eco-system.

There are as yet, no cohort studies investigating breast cancer aetiology in SSA. Although cohort studies have the drawback of being more resource intensive and require a longer duration of time to generate enough events (i.e., if a prospective cohort is set up), they provide a stronger evidence-base for most of these associations studied; given that, the temporality of the exposure and outcome may not be clearly established from case-control studies. Moving forward, the ability to set up reliable electronic records and surveillance systems will be pivotal for generating good quality evidence from SSA.

In spite of the volume of aetiologic research on breast cancer, only about half of breast cancer cases can be attributed to known risk factors.[134] So, for almost half of the cases, the aetiologic pathway is not fully understood. Thus, aetiologic research is still important and especially from previously under-studied communities with rising trends.

In the review of the literature described in this chapter, we focused on aetiologic research from SSA on reproductive, anthropometric, and lifestyle factors (alcohol and physical

activity). We synthesized the available information on population-level trends in these risk factors, to provide further insight for future breast cancer trend studies.

5.4.1 Association between reproductive factors and breast cancer risk

Menarche:

The age at menarche marks the onset of ovarian activity, and a later age at menarche (AAM) has been associated with a decreased risk of breast cancer.[183] Results from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) estimate that breast cancer risk increases by 5% per year younger at menarche.[183] There were 15 studies from SSA that reported on this association. Given the diverse categorization of age at menarche, and without individual-level data for the studies included in our review, a pooled analysis of the study findings could not be performed. The majority of these studies were of relatively small sample size, with weak associations observed, and with an inherent risk of recall bias. This recall bias may have been differential by age, with some authors reporting a higher proportion of missing data on age at menarche among older women. The largest of the studies included were by Figueroa et al. 2020 from Ghana and Hou et al. 2008 from Nigeria. Hou et al. 2008 reported an 8% decreased breast cancer risk per 2-year delay in AAM (OR=0.92 (95% CI: 0.81-1.03)) among Nigerian women, while Jordan et al. 2013 in Tanzania report a 16% decreased risk per year later at menarche (OR=0.84 (95% CI: 0.69-1.01)).

There are insufficient data on trends in AAM from population-level surveys in SSA. From what is available, these surveys show that the mean AAM is on the decline in LMIC.[316] The AAM is correlated with increased caloric intake in adolescence and childhood, and with body size.[341,342] This gradual decline in the AAM which is observed in SSA, was also observed in Western countries in earlier decades. This declining trend in the AAM, will increase the duration of exposure to endogenous oestrogens among females in many African communities. In the UK, AAM declined from 13.5 years in the 1908–19 cohort to 12.6 years in the 1945–49 birth cohort. The decline in the AAM stabilized among women born between

1949 and 1989 , however, further declines in AAM are being observed among women born after 1990.[343]

Figueroa et al. 2020 presented their findings by ER status. In this study, a later age at menarche was correlated with a non-significant increased breast cancer risk among women <50 years with ER-positive disease (OR=1.61 (95% CI: 1.00-2.58)). Results from the CGHFBC and the AMBER (African American Breast Cancer Epidemiology and Risk) consortium report decreased breast cancer risk with later AAM, irrespective of ER status.[183,344] However, in the CGHFBC study, the effect of AAM was attenuated by BMI especially among postmenopausal women.[183] Results from the Black Women Health's Study (BWHS) show decreased breast cancer risk with later AAM, irrespective of ER-status and age at diagnosis (among women aged <45years and ≥45 years).[345]

Menopause:

Six studies reported on the association between age at menopause and breast cancer risk. Three of these studies were of high risk of bias, as they did not adjust for covariates. Of the three studies that presented adjusted estimates, none showed statistically significant results. Findings from the CGHFBC showed that, among post-menopausal women, for every year older at menopause, the breast cancer risk increased by 2.9% (OR=1·029 (95% CI: 1·025–1·032); p<0·0001).[183] This increased risk with older age at menopause was stronger among women with ER-positive disease. The association of age at menopause and breast cancer risk was attenuated by BMI: lean women had a lower risk after the menopause compared with overweight and obese women.[183]

At a population-level, there are inadequate data on trends in the age at menopause from sub-Saharan countries. Data from Western countries reveal an increase in the age at natural menopause (ANM) in some countries; a Norwegian retrospective population-level cohort reported a 3-year increase in the ANM from 50.31 years in the 1936-1939 cohort to 52.73

years in the1960-1964 birth cohort.[185] It is unknown whether similar trends are occurring at a population-level in SSA. Data from the U.K. Women's Cohort Study suggest that diets rich in red meat and animal proteins are associated with a later ANM.[346]

Age at first birth:

For the majority of studies included, a later age at first full-term pregnancy or birth was associated with a non-significant increased breast cancer risk. Some of these studies had a small sample size, and the studies used different categories for comparison. Sighoko et al. 2015 one of the largest of the included studies report a 27% risk reduction after first birth irrespective of age at first birth (AFB) (OR=0.73 (95% CI: 0.56-0.97)).[312] Huo et al. 2008 using data from Nigerian women only, did not find that an early age at first live birth was associated with a decreased risk of breast cancer. They reported a non-significant 13% risk reduction per 5-year older at first birth (OR=0.87(0.73-1.04)). Earlier seminal work by McMahon et al. showed that women who had a first birth before age 18 had a third of the breast cancer risk as women whose first birth occurred after age 35.[347] Lambe et al.1996, using data from the Swedish Cancer Registry showed that a 5-year increase in the age at first birth was associated with a 13% increase in breast cancer risk (OR = 1.13 (95% CI: 1.08-1.19).[348] However, the risk factor profile could differ by breast cancer sub-type, but this has not been sufficiently explored in SSA. It is suggested that the increased breast cancer risk with later age at first birth is stronger for younger women with ER-positive/PR-positive breast cancer of some ethnicities, but this stronger association was not shown among African American women in the US.[349]

Figueroa et al. 2020 studied Ghanaian women aged <50 and ≥50, and by ER status. They observed a non-significant increased breast cancer risk with later AFFP, irrespective of ER status; however, there were higher point estimates among women aged <50 years, and weaker associations among women aged ≥50 years.[270] The loss of power from the stratification of the study cohort may have made these findings less discriminatory.

Population-level trends in the median age at first birth among women aged 45-49 from the DHS show higher median age at first birth among women with a higher educational status, compared with women with non or primary education only. Increased access to higher education, may shift the median AFB upwards in these countries, especially among younger cohorts of women.

Parity:

There is conflicting evidence on the association between parity and breast cancer risk from the included studies. These studies used different baseline categories for evaluating the association between parity and breast cancer risk. Twelve of the 16 included studies reported a lower breast cancer risk with increased parity. The largest of the studies included, Sighoko et al. 2015, reported a 46% risk reduction for women with seven children compared with nulliparous women (OR=0.54 (95% CI: 0.38-0.75)), with the largest reduction in risk occurring soon after the first birth.[312] In many African settings, results from the DHS show that the median age at first birth is under age 22.

Huo et al. 2013 presented the association between pregnancy-associated breast cancer and parity. They reported a non-significant increased breast cancer risk with higher parity in the first five years post-partum, and a decrease in the risk five years post-partum. This relationship described by Huo et al. 2013 was fully explored in the pooled analysis of prospective studies by Nichols et al. 2019, which showed a transient increase in breast cancer risk with parity. This transient increases peaks about five years after birth followed by a decline. This was observed only if the AFB occurred after age 25. Nichols et al. reported a persistently protective effect of parity, if age at first birth occurred before age 25, when compared with nulliparous women.[350] However, this contrasts with Sighoko et al. 2015, who used data from the Nigerian Breast Cancer Study (Huo et al. 2013) as well as data from Cameroon and Uganda. They found no transient increase in breast cancer risk in the larger cohort, irrespective of age at first birth.[312]

Figueroa et al. 2020, presented results on parity stratified by age and by ER status. They report a non-significant increased risk among women aged <50 with ER-negative disease (OR=1.80 (95% CI: 0.82-3.95)), but a protective effect with parity in women aged >50 (OR = 0.28 (95% CI: 0.11-0.70)) with ER-negative disease. These results were adjusted for age at first birth. This differs from what is described by Nichols et al. 2019, who reported a reversal in the direction of risk with time since last birth for women with ER-positive breast cancer but not for women with ER-negative breast cancer who had a persistently higher risk over time.[350] However, this association with parity was slightly attenuated by breastfeeding for women with ER-negative breast cancer.[350]

In terms of multiparity, data from pooled prospective studies showed the highest transient breast cancer risk among women with three or more children compared with uniparous, biparous women and nulliparous women and this increased risk persists for at least 20 years since last birth.[350] Thus, if comparisons of multiparous women are made with women with one or two children as the baseline category, odds ratios above one may reflect this higher risk which persists for up to 20 years since last birth.

Population-level trend data from the World Population Prospects 2020 show decreasing fertility rates for almost all sub-Saharan African countries, however, with a faster rate of decline in some nations. These declines in fertility are expected to persist into the next decade. Given the complex interplay between parity, breastfeeding, and age at first birth on breast cancer risk, the effect at an ecological level of declines in parity and breast cancer risk will require careful analyses and interpretation of the changing trends.

Breastfeeding:

Of the included studies that adjusted for confounders, lactation was associated with decreased breast cancer risk among women of all age groups. The largest of the included

studies - Huo et al. 2013 - report a 7% risk reduction for every 12 months of lactation. Results from the CGHFBC suggest that breast cancer risk decreases by 4.3% for every 12 months of lactation (95% CI: 2·9–5·8; p<0·0001).[351]

When stratified by menopausal status, the evidence for the protective effect of breastfeeding from studies in SSA was weaker, particularly among premenopausal women. When stratified by ER status, the strongest protective effect of increased duration of lactation was observed among women ≥50 years with ER-positive disease. However, data from the AMBER consortium showed a protective effect of breastfeeding among parous women with ER-negative breast cancer.[352] Similar findings were reported in the pooled analyses of prospective cohort studies, which suggests that breastfeeding mitigates the increased risk of ER-negative breast cancer with parity.[350]

In SSA, there is a complex interplay between infectious and non-infectious diseases. One of these conditions is infection with HIV. There were approximately 27 million people living with HIV in the WHO African Region in 2018, and it accounts for two-thirds of the global HIV burden.[353] This pandemic disproportionally affects women of childbearing age in SSA. 80% of new infections in the 15-19 age group were among girls in SSA.[354] Although HIV is not directly associated with breast cancer, indirect pathways in high burden areas should be studied; particularly its effect on the distribution of known breast cancer risk factors such as breastfeeding, age at first birth, and parity.[220] Right up to 2009, the WHO advised HIV-positive mothers not to breastfeed if they could obtain safe and sufficient infant formula.[355] Currently, the WHO advises that HIV-positive women in LMIC should breastfeed exclusively for the first 6 months and for at least 12 months, while women who are HIV-negative should breastfeed for at least 24 months.[355] However, in these settings, some women choose not to breastfeed at all, to reduce the risk of infecting their babies. Given the higher prevalence of HIV among women of childbearing years, and the confluence of limited breastfeeding among parous women, this may influence the future burden of breast cancers in these settings.

In spite of this, trends from the DHS still show a relatively high median duration of breastfeeding among all women, in countries for which data are available. However, the median duration of breastfeeding varies with educational status. The need for women in paid employment to return to work after four months of maternity leave, as is the case in many SSA countries,[355] may influence the duration of breastfeeding.

Contraceptive use:

There was significant heterogeneity in the included studies on the association between contraceptives and breast cancer risk in SSA. Currently, in SSA, the most commonly used contraceptives are injectables and implants.[272] The types of contraceptives studied in these African studies are quite varied. This contributes to the heterogeneity observed in the results of these studies, as most studies lacked details on the type of contraceptives used.

The pooled analyses of the odds ratios showed a non-significant increased risk of breast cancer with injectable contraceptive use, while a non-significant protective effect is observed for ever-users of oral contraceptives. The major drawback of most of the included studies was the absence of data on duration of use, and time since last use for ever-users. This did not permit a granular analysis of the association between the duration of contraceptive use, the time since last use, and breast cancer risk; except for the South African studies of Shapiro et al. 2000 and Urban et al. 2012.

Shapiro et al. 2000 reported a 60% increased risk among current users of injectable contraceptives compared with non-users (OR=1.6 (95% CI: 1.1-2.3)), with a non-significant decreased risk observed ≥15years since last use. No differences were observed in risk by duration of use. For combined oral contraceptives (COC), Shapiro et al. 2000 reported an increased risk among women who used COC one to four years previously (OR=1.6 (95% CI:

1.1-2.3)), however, this association was non-significant among current users of COC (OR=1.1 (95% CI: 0.6-2.1)). This increased risk persisted for up to 14 years since the last use of COC.[299]

Urban et al. 2012 reported a 66% increased risk among South African women who had used oral and/or injectable contraceptives <10 years previously (OR=1.66 (95% CI: 1.28-2.16)), but this increased risk was non-significant ≥10 years after cessation (OR=1.11 (95% CI: 0.91-1.36). For women who used only oral contraceptives in this cohort, the risk <10 years after cessation was 1.57 (95% CI: 1.03-2.40) and became non-significant ≥10 years after cessation, while for injectable contraceptives, it was 1.83 (95% CI: 1.31-2.55) <10 years after cessation and 1.08 (95% CI: 0.82-1.43) ≥10 years after.[305] Similar results were reported by the CGHFBC in 1996, who found no excess risk among women who used oral contraceptives more than 10 years previously.[196]

Results from the AMBER consortium present findings by ER status and age from a large cohort of African American (AA) women. They report a higher breast cancer risk with current use of oral contraceptives for ER-positive, ER-negative, and TNBC, and this increased risk persisted for at least 15 years after cessation. Greater risks were observed with increased duration of use and among overweight and obese women.[356]

Population-level data suggest differences in contraceptive prevalence between SSA countries.[335] There has been an increase in uptake of injectable contraceptives in Kenya, Malawi, and Uganda in recent years. In Zimbabwe, high levels of oral contraceptives are being used. On the other hand, a decline in the prevalence of both oral and injectable contraceptives is observed in more affluent countries like South Africa and Mauritius in recent years. These differences in the prevalence of contraceptive use at a population-level in SSA, may influence long-term trends in the breast cancer burden.

5.4.2 Association between anthropometric risk factors and breast cancer risk

Height:

The association between height and breast cancer risk was studied in two Nigerian case-control studies. A 5cm increase in height was associated with an 18% increase in risk (OR=1.18 (95% CI: 1.11-1.27)). Adult height is correlated with energy availability in childhood and adolescence, and with the age at menarche.[357] A later age at menarche allows more time for the long bones to grow before the closure of the epiphyseal plates in girls, and mainly affects leg length.[357] Results from the BWHS show a 2% increase in risk per 1-inch (2.54cm) increase in adult height.[358] In this study, a stronger association with height was observed among women with ER-positive breast cancer, and who were younger at menarche.[358] The European Prospective Investigation into Cancer and Nutrition (EPIC) study also reports this positive association with increasing height. A one standard deviation increase (6.7cm) in adult standing height was associated with a 13% increase in risk (OR=1.13 (95% CI: 1.10-1.17)), and this increased risk was reported for both ER-positive and ER-negative tumours.[359] This increased risk was strongest for ER-positive breast cancers among the tallest women with an earlier age at menarche, similar to findings from the BWHS. This points at a complex interplay between growth promoters (e.g. Insulin-like growth factor (IGF-1)) and hormones in the peri-pubertal period and the subsequent risk of endocrine-sensitive tumour formation.[359] IGF-1 is a growth factor that stimulates mitosis and inhibits programmed cell death (apoptosis). Levels of IGF-1 are correlated with height. IGF-1 has been shown to have a positive association with ER-positive breast cancer, with the strongest associations observed among women with post-menopausal breast cancer.[360]

Height is also influenced by genetic and environmental factors. Data from the DHS suggest that trends in adult female height in SSA are correlated with the per capita income of the country, and thus with nutrient availability in childhood and adolescence. Changes in height have not been uniform in SSA and correlate with economic downturns experienced in certain

nations. Cohorts born between 1965-1990 experienced a decline in adult height, except in South Africa where the trends remained positive.[337] Data from the EPIC study showed that on average, European women grew 0.7cm taller per 5-year birth cohort between 1915 and 1965.[357]

Weight:

Three studies investigated the association between weight and breast cancer risk. There was weak evidence for any association between weight (measured in kg) and breast cancer risk. One study used a body pictogram to study this association, and they report a higher risk in heavier women.[224] Few studies use current body weight on its own, as an independent anthropometric measure in relation to breast cancer risk.

However, absolute weight gain in adulthood has been studied extensively in relation to breast cancer risk.[361–365] Data from the EPIC study suggest that large adult weight gain (>15kg) in women who do not use MHT, is associated with an increased risk of post-menopausal breast cancer.[362] Results from the UK cohort of the Predicting Risk of Cancer at Screening (PROCAS) study show that, a 1 SD (12.2kg) increase in weight from age 20, was associated with a 26.5% increase in risk (OR=1.27 (95% CI: 1.16 – 1.37)) among post-menopausal women. This increased risk with weight gain was not observed for women with pre-menopausal breast cancer. None of the SSA studies included in this review evaluated the effect of changes in adult weight.

Body Mass Index:

There has been consistent evidence of an increased risk of post-menopausal breast cancer with higher BMI from studies including mainly Caucasian women. However, relatively few

studies from SSA have reported on this association by menopausal status. The largest of these studies - Ogundiran et al. (2010) reported a 2% decreased pre-menopausal breast cancer risk per 5-unit increase in current BMI and a non-significant decreased risk per 5-unit increase in current BMI for post-menopausal women. Palmer et al. 2007, using data from the BWHS report similar results; an inverse association between BMI and pre-menopausal breast cancer but no association with post-menopausal breast cancer.[366] The AMBER consortium permitted the study of this association among AA women by menopausal and ER status. They found an increased risk with current BMI for post-menopausal women with ER-positive breast cancer (≥35kg/m^2 vs <25kg/m^2, OR=1.31 (95% CI: 1.02-1.67)), while obesity was protective of TNBC in post-menopausal women (≥35kg/m^2 vs <25kg/m^2, OR=0.60 (95% CI: 0.39-0.93)).[269] There was insufficient evidence to suggest a reduced risk of pre-menopausal breast cancer with a higher current BMI in this cohort of African-American women. It seems likely that some of the disparities in the associations between obesity and post-menopausal breast cancer from studies in AA women as compared with predominantly Caucasian populations may be due to differences in the distribution of ER-positive, ER-negative, and TNBC in these populations. Among pre-menopausal women, adiposity does not significantly influence levels of oestradiol. This is because oestrogen is mainly produced in the ovaries in pre-menopausal women. After menopause, adipose tissue becomes the main site for oestrogen production through the peripheral aromatization of androgens to estrogens.[367] Hence a stronger association is observed between adiposity and oestrogen levels among post-menopausal women, with a corresponding increased risk of ER-positive breast cancers.

One African study (Jordan et al (2013)) reported on the association between young adult BMI and breast cancer risk. Jordan et al. 2013 report a positive association with higher BMI for women with both pre- and post-menopausal breast cancer, however, results were not stratified by ER status.[368] Results from the AMBER consortium suggest a protective effect of

young adult BMI on pre-menopausal ER-positive breast cancer (≥30kg/m^2 vs <25kg/m^2, OR=0.65 (95% CI: 0.42-0.99)).[269]

BMI is a measure of overall adiposity, in contrast to WHR which is a measure of central obesity. However, there are limitations to the use of BMI, with differences in the degree of adiposity by ethnicity for the same unit measure of BMI, such that, different categorisations have been proposed for certain ethnicities.[369] Thus, different ethnicities may have different fat distribution patterns which may not be reflected by a sole focus on BMI.

Furthermore,, breast cancer in SSA is often diagnosed late, with approximately 70% of cases diagnosed in stages III and IV.[13,370] Given that anthropometric measures in these studies are usually measured after diagnosis, the BMI may well have been influenced by the disease process. However, significant weight change is more often observed among patients with lung and gastrointestinal cancers such as gastric, colorectal, and pancreatic tumours.[371] There is also a risk of misclassification by the study subjects, given that many women in these settings do not have access to a scale at home.

Population-level trends in SSA suggest rising mean BMI levels across the continent. This may lead to an increase in the burden of post-menopausal ER-positive breast cancer in countries that have a relatively higher proportion of overweight and obese women.

Waist-to-hip (WHR) ratio:

Two studies from Nigeria reported on the association between WHR and breast cancer. Both studies report a positive association between increasing WHR and both pre- and post-menopausal breast cancer. In contrast to the BMI, which has a protective effect in pre-menopausal women, a higher WHR was associated with an increase in breast cancer risk among women with both pre- and post-menopausal breast cancer. Similar results are reported from studies in other populations.[372] The WHR is a measure of central adiposity

while the BMI is a measure of overall adiposity. Adiposity influences the availability of sex hormone-binding globulins (SHBG) and results in increased activity of sex hormones. It also promotes insulin resistance and results in raised insulin and IGF-1 levels. These in turn stimulate cellular growth and sex-hormone production, and inhibit SHBG production.[367] Central obesity, due to its relationship with visceral adiposity, is associated with these metabolic and hormonal effects and may have a stronger effect on breast cancer risk than observed with peripheral adiposity.[373] The body fat distribution, and hence the WHR is influenced by age, sex, ethnicity, and parity.[369] Data from the AMBER consortium suggests that a higher WHR was associated with an increased risk of post-menopausal breast cancer for all sub-types combined and with an increased risk of pre-menopausal ER-positive breast cancer as well.[269] This complex interplay between adiposity, ER-status, and breast cancer risk needs additional studies from SSA, where there might be variations in levels of visceral adiposity for the same unit of BMI and WHR according to ethnicity.

There are as yet, no data on WHR trends at population-level in SSA.

5.4.3 Association between lifestyle factors and breast cancer risk

Alcohol use:

There are relatively low rates of alcohol use among women in many SSA countries, which makes it a more difficult exposure to assess. There were differences in the strengths of the association reported between alcohol use and breast cancer risk, given the heterogeneity in the type of alcohol, as well as the duration of alcohol use in these studies. The largest of the studies included - Qian et al. 2014 - report a 39% increase in risk per 10g increase in average daily consumption of alcohol. Qian et al. report a similar positive association among both pre- and post-menopausal women.[309] Results from the Nurses' Health Study show a 10% increase in risk per 10g of cumulative alcohol consumption per day.[374] This increased risk

with alcohol consumption was observed irrespective of hormone-receptor status, however stronger associations were observed for hormone-receptor positive disease. Data from AA women in the AMBER Consortium report higher breast cancer risk with alcohol use, irrespective of tumour sub-type. In this study, drinking ≥14 drinks/week was associated with a 33% increase in breast cancer risk (OR=1.33 (1.07-1.64).[375] An earlier study, which pooled results from prospective studies, reports a 9% increase in breast cancer risk per 10g/day of alcohol. The risk of breast cancer was not related to the type of alcohol.[376] Data from the UK Million Women's Study suggest a 12% (95% CI: 9% to 14%) increase in risk per 10g of alcohol (1 drink) consumed per day.[377]

The link between breast cancer and alcohol is not fully understood; however, it is thought that alcohol is associated with an increase in the levels of circulating sex hormones.[374] Alcohol is also known to be a potent carcinogen, which inhibits DNA synthesis and repair, and this carcinogenic effect is observed across different organs.[378]

Alcohol use among women in comparison to men is relatively low in many parts of SSA and varies between countries. Lower levels of alcohol consumption are reported in majority Muslim countries like the Gambia.

Physical activity:

Three studies reported on the association between breast cancer risk and physical activity. These studies relied on participant recall and were not validated against any objective measures. Furthermore, physical activity levels may have been impacted in the time leading to diagnosis by the disease process, especially for women diagnosed at advanced stages. All three showed a protective effect. Huo et al. 2014 the largest of the included studies, reports a 2% decrease in breast cancer risk per unit increase in MET hours/day.[275] Bigman et al. 2020 showed this protective effect of total leisure-time physical activity (walking, jogging,

running, cycling etc) for both hormone-receptor positive and TNBC, reporting a more than 50% risk reduction when comparing women who do ≥11.5 MET hours/week to women who do <3.0 MET hours/week. Among African-American women, similar strong protective effects were observed for total physical activity in women, with a 64% and 17% risk reduction observed in the highest and mid tertile compared with the lowest tertile.[379] Results from the AMBER consortium suggest a protective effect for breast cancer overall (OR 0.88 (95 % CI: 0.81–0.96)) and for ER-positive tumours (OR 0.88 (95 % CI: 0.80–0.98)).[380]

Results from the UK Biobank comparing women in the highest (≥58.28 MET hours/week) to women in the lowest quartile (≤13.78 MET hours/week) show a 25% risk reduction for pre-menopausal breast cancer (OR=0.75 (95% CI: 0.63-0.89)) and a 15% risk reduction for post-menopausal breast cancer (OR=0.85 (95% CI: 0.76-0.96)), after controlling for the effect of anthropometry.[195]

Physical activity is known to reduce the risk of breast cancer by different mechanisms: increasing the circulating SHBG levels and hence decreasing circulating oestrogens, reduction of visceral fat, improvement of insulin sensitivity, and reduction of total circulating IGF-1. It also has anti-inflammatory properties and reduces cellular oxidative stress.[381]

Population-level surveys from SSA, show differences in the proportion of women with insufficient physical activity levels, with higher proportions observed in some countries like the Gambia and Seychelles, and a lower proportion of insufficient physical activity observed in countries like Malawi.

5.4.4 Conclusion

This review highlights the paucity of quality epidemiological studies on breast cancer aetiology from SSA. There are several countries in SSA where epidemiological studies have not been undertaken. Added to this, there were few studies examining these risk factors by hormone receptor status – a factor that can influence the associations studied. As yet, no

cohort studies in SSA set up to investigate the aetiology of the most common cancer on the continent.

There is a complex interplay between genetic, reproductive, anthropometric, lifestyle and environmental factors in the aetiology of breast cancer. In this review, the focus was only on known reproductive, anthropometric, and lifestyle factors. However, the importance of the other aetiologic agents must be emphasized. Among Nigerian women, non-selected for family history, 14.7% of women carried a loss of function mutation in breast cancer genes – 11% of these were from mutations in the *BRCA-1* and *BRCA-2* genes.[226]

There are other lifestyle and environmental factors such as diet, the use of hair relaxers, and DDT for which there have been very few studies carried out.[109] Some of these potential environmental risk factors are more prevalent in SSA - for example, the use of substances like DDT for malaria control and residual indoor spraying. DDT has been shown to be associated with a nearly three-fold increase in breast cancer risk for women exposed before puberty.[211] Other unique factors are the use of hair straighteners and skin lighteners which are more commonly used by African women.[242] Of these putative risk factors, Brinton et al. 2018 investigated the role of skin-lighteners and hair-relaxers among Ghanaian women. They found insufficient evidence of an association between the use of skin lighteners and breast cancer. However, they highlight the need for additional research on the role of hair relaxers on breast cancer risk.[242]

As concerns diet, four recent case-control studies evaluated the association between certain dietary groups and breast cancer risk in SSA - Jordan et al. 2013 in Tanzania, Essiben et al. 2016 in Cameroon,[214] Balekouzou et al. 2017 in Central African Republic,[215] and Jacobs et al. 2019 in South Africa[382].Jacobs et al. 2019, the largest of these studies, was a population-based case-control study with 396 cases and 396 controls. They showed a protective effect of diets rich in fresh fruits and organ meat, and an increased risk with savoury snacks that are usually energy-dense and nutrient-poor.[382] There is as yet insufficient evidence on the role

of dietary groups on breast cancer risk, other than the known associations of alcohol consumption and obesity on breast cancer risk.[383] However, there is some evidence suggesting a reduced risk of ER-negative breast cancer with consumption of vegetables,[384,385]and the protective role of soy isoflavones in Asian populations[386,387]. Ecologic data from SSA suggest a correlation between consumption of diets rich in animal-proteins and breast cancer incidence rates.[217] In SSA, there is an increase in the consumption of ultra-processed foods, particularly in urban cities, which together with decreasing levels of physical inactivity, contribute to the increasing obesity rates.[388] These changes in lifestyle observed in SSA most likely contribute to the rising breast cancer burden.

In summary, more research is needed on the African continent to better understand its risk factor profile and distribution, and their impact on the rising burden of breast cancer. However, disparities in the magnitude of the breast cancer incidence rates are observed across the continent, some of which may be explained by differences at population-level of some of the known risk factors such as changes in reproductive patterns, contraceptive use, alcohol consumption, physical activity, and obesity levels.

Chapter 6. Breast Cancer Survival in sub-Saharan Africa

In addition to their role in monitoring population-level cancer incidence, PBCRs are vital for estimating population-level cancer survival outcomes. Whereas monitoring changes in incidence trends, as seen in chapter 4, will primarily reflect changes in risk factors and to some extent diagnostics; monitoring changes in survival over time will reflect changes in diagnostics, access to care, and therapy improvements.[389] Population-level survival outcomes reflect the overall efficacy of the cancer care system,[390] from early detection, to diagnosis, to treatment, and palliation.

In this chapter, the survival outcomes of women diagnosed with breast cancer in SSA at 1, 3 and 5-years after diagnosis are estimated using PBCR data. This chapter will be presented in two parts. The first part of this chapter will focus on estimating population-level breast cancer survival from 14 population-based African registries, by stage at diagnosis, age at diagnosis, and country-level HDI.

The second part of this chapter will describe the therapy routinely received by women with breast cancer in SSA and their survival outcomes in a subset of sub-Saharan African registries.

6.1 Part I: Population-level breast cancer survival by age, stage, and country-level HDI

The text that follows is expanded from a paper published by the International Journal of Cancer on May 14th, 2019, as:

Joko-Fru, W.Y., Miranda-Filho, A., Soerjomataram, I., et al. Breast Cancer Survival in Sub-Saharan Africa by Age, Stage at Diagnosis and Human Development Index: A Population-

based Registry Study. Int. J. Cancer, 2020, 146 (5), 1208–1218. https://doi.org/10.1002/ijc.32406, published CC-BY 4.0.

In addition to the work presented in the paper, I have added information to the methods, results, and discussion sections. For this paper, I cleaned and analysed the data, prepared the tables and figures, wrote the manuscript drafts, and edited the manuscript based on Comment and feedback from co-authors and the reviewers.

6.1.1 Introduction

Survival statistics have been used as an important tool for monitoring progress made in cancer diagnosis and treatment.[155,391] Due to the paucity of data from SSA, previously published international studies have often not had an adequate representation of the African continent. Most of the information we have on survival are from clinical series, which can often not be generalised to the general population. A recent systematic review on cancer survival in Africa by Ssentongo et al. (2019), included 21 sub-Saharan African studies, all but 1 of these included studies were hospital-based.[14]

However, we cannot effectively estimate progress that has been made in breast cancer diagnosis and treatment in SSA if we do not aim at measuring population-level survival as accurately and as comprehensively as we can, using the actual data generated from the population-based registries, as opposed to modelled estimates.

To fill the gap, IARC launched the SURVCAN studies,[392] whose key role is to focus on cancer survival in LMIC countries, often underrepresented in large international benchmarking studies. SURVCAN-1, published in 1998 contained survival data from five LMIC from Asia and South America.[393] SURVCAN-2 was published in 2011 and contained data from three sub-Saharan African countries, the Gambia, Uganda and Zimbabwe.[154] The IARC team is currently working on SURVCAN-3.[392]

The AFCRN, in collaboration with the IARC and the individual registries, provided a unified framework for cancer registration and monitoring of survival across 14 PBCRs from 12 different African countries. In this chapter, estimates are made of breast cancer survival at 1, 3 and 5 years after diagnosis, the stage distribution is described, and the effect of stage, age, and country-level HDI on breast cancer survival in SSA are explored at population-level.

6.1.2 Methods

6.1.2.1 Study population

Completely anonymised data were obtained from the AFCRN on malignant breast cancers (ICD-10: C50) diagnosed in African females aged 15 and above. Approval for this study was obtained from the Research Committee of the AFCRN and from the individual member registries which contributed data for the analyses. Only black African females were included – cases among women of European, Asian, or mixed-race origin were excluded. The number of cases sampled per registry was determined by the practical feasibility of obtaining follow-up information. Where patient follow-up was passive, a larger number of cases could be included, when active methods were used the sample was smaller. Once the number of cases per registry was agreed upon by the investigators and registry staff, a random number generator was used to randomly select cases by registration number from the PBCR database for the years included. A random sample of incident cases diagnosed in 2005-2015 were selected from each registry. None of the cases had been previously diagnosed with breast cancer. The follow-up time was measured from the date of incidence until the date of last contact, the date of death or until the end of the study by registry, which ever occurred first.

6.1.2.2 Vital status

This was obtained by active methods for all but one registry (Mauritius). In active follow-up, clinical records are traced and the patient's vital status at the closing date recorded. Cases whose vital status could not be confirmed at the end of this procedure were called when a

mobile number was registered in the registry record. When no further information could be obtained, home visits were made by the registry staff. Patients whose vital status (alive/dead) could not be ascertained by the closing date of the study were censored “alive”. In Mauritius, passive follow-up was done to ascertain the vital status of patients; this involves linkage of the list of registered cases with the population death records held in the vital statistics office. Patients not found to have died are assumed to be still alive.

6.1.2.3 Data-analyses

For each registry, the sampling fraction, the mean age at diagnosis and the proportion of cases with microscopic verification (MV%) were calculated. Cases diagnosed based on a death-certificate-only, with no follow-up information or with incoherent follow-up dates were excluded from the survival analyses. Survival was estimated using the semi-complete approach,[78] which uses the survival probabilities of patients with complete follow-up (diagnosed 5 years before the closing date) and the survival probabilities of patients diagnosed more recently (with less than 5-years complete follow-up) but with a potential minimum follow-up time – which was of 1 year, for this study. The semi-complete approach falls between the cohort approach (which uses data from only patients with potential for complete follow-up i.e., diagnosed 5 years before the closing date) and the complete approach (which uses all the survival information of patients diagnosed at any time before the closing date, with no minimum follow-up duration).[78]

Kaplan-Meier survival curves are plotted and described and the observed and Ederer II relative survival at 1, 3, and 5-years after diagnosis are estimated using the “strs”[81] command in Stata 14. The relative survival is the ratio of the “observed” survival in the study population to the “expected” survival.[83] The expected survival derived from country-specific life tables is the survival experience of the general population of the same age, sex, and period. As such differences in background mortalities of cases are taken into account. The relative survival is especially useful for estimating breast-cancer specific survival in settings where there is

limited availability of quality cause of death data, which is the case for almost all SSA countries.

Although the relative survival adjusts for differences in background mortality by age, it does not adjust for the fact that excess mortality from cancer could differ by age. Thus, in order to make comparisons between populations of different age structures or between different time periods, the relative survival estimates are age-standardised.[81] Age standardisation was done with the "strs" command using the International Cancer Survival Standard (ICSS)–1[87] - for cancers whose incidence increases with age. Age standardisation was done using the ICSS-1 external weights, to facilitate international comparisons.

6.1.2.4 Life tables

Abridged life tables by sex, and country were obtained from the WHO Global Health Observatory data repository.[394] Age-specific death rates were obtained, calculated from the number of deaths among persons in a given age group during a given time period, and the total person-years for the population in the same time period. The number of deaths and person-time by sex, year, and country were used to estimate mortality rates using a Poisson regression with a flexible function to expand the abridged age groups (0-4, 5-9, 10-14 …80+) to single ages (0,1,2,3,4,5...99) based on methods first described by Rachet and colleagues (2015).[395] The abridged mortality probabilities were thus expanded to obtain a complete life table by 1-year age group, sex, and period.

6.1.2.5 Stage at diagnosis

Whenever available, information on stage had been abstracted at time of registration by the registrars. Stage was categorised using the Tumour-Node-Metastasis (TNM) system in all registries. From individual categories of Tumour, Node and Metastasis, stage was classified from stages I to IV using the anatomic stage groupings of the American Joint Cancer Committee TNM8 classification for breast cancer which was described in more detail in

Chapter 3.[396] For registries with no individual T, N and M data, the available summary stage information was used. Stages I and II were grouped as “Early Stage” and Stages III and IV as “Late Stage”. Records with no information on stage were grouped into a separate category referred to as “Missing Stage”.

6.1.2.6 Assessing loss to follow-up (LFU)

The proportion of LFU was assessed at 1, 3 and 5 years after diagnosis. Using a Cox regression model with patients LFU as the outcome, I evaluated whether LFU was random or if it was associated with either age or stage at diagnosis. For sensitivity analyses, the overall all-cause survival was estimated assuming that all patients with stage IV breast cancer who were LFU, and a random sample of 25% of patients with unknown stage at diagnosis who were LFU, had in fact died 6 months after the date of last contact.

6.1.2.7 Human Development Index (HDI) classification

The HDI is a composite measure developed by the United Nations Development Programme that aims at assessing the level of development of countries.[397] It has three main components: life expectancy at birth, the educational attainment of citizens, and the gross national income per capita. The HDI 2015 classification was used to categorise the included SSA countries and for comparisons of survival within SSA by HDI. Countries with a development index of <0.550 are categorised as being of “low”, 0.550-0.699 are of “medium”, 0.700 - 0.799 are of “high” HDI, and ≥0.800 are of “very high” HDI.[398]

6.1.2.8 Modelling excess hazards

The excess hazard of death was modelled in a relative survival framework for patients with breast cancer as a function of age at diagnosis, stage at diagnosis, and country-level HDI using a Poisson regression model.[81] Time was split into monthly intervals and restricted cubic splines were used. Interaction terms were fitted between age at diagnosis and stage at diagnosis, to assess if the effect of age was constant within these categories. The likelihood

ratio test was used to compare the main model with the models that included the interaction parameter. A test for linear trend was performed using a likelihood ratio test by incorporating ordered categorical variables with more than two categories as a linear term in the model. A test for heterogeneity was performed with a likelihood ratio test to assess for differences between groups.

6.1.3 Results

6.1.3.1 Patient and registry characteristics

In total, there were 2,558 randomly selected cases from 12 countries, representing 37.2% of the total female breast cancers diagnosed in 14 individual PBCRs within the study period (Table 6.1). These registries had national coverage in Mauritius, Namibia, and Seychelles; covered an urban area for all the other registries except for the Eastern Cape registry which covers a rural area. Of the countries represented by these PBCRs, seven were of low HDI, three were of medium HDI and two were of high HDI. Cases were included from the period 2005-2015, but the included period of diagnosis differed by registry. Cases without any follow-up information after the date of diagnosis, or with incoherent dates were excluded, and this proportion ranged from 0% in Cotonou (Benin) to 31% in Eldoret (Kenya) (Table 6.1). Finally, 2,311 cases (90.3%) were included in this study. Of the total number of incident breast cancer cases by registry, the proportion included ranged from 7.9% in Bamako (Mali) to 100% in Eastern Cape (South Africa). Mauritius, with passive follow-up of cases, had the highest number of included cases, with 491 cases included for survival analyses from this registry. The proportion of cases morphologically verified (MV%) ranged from 54.7% in Kampala (Uganda) to 100% in Maputo (Mozambique), and Namibia.

Table 6.1: Total number of breast cancer cases, included and excluded cases, and data quality indicator by population-based cancer registry.

Country	HDI 2015*	Registry	Period of diagnosis	End of follow-up	Total number of incident breast cancer cases	No. (%) of DCO during study period excluded	Number of randomly sampled cases for survival study	Sampling fraction (%)	MV (%)	Included for survival analyses No. (%)	No. excluded (%)
Benin	Low	Cotonou	2013 – 2014	30/11/2017	132	0 (0.0)	91	68.9	79.1	91 (100)	0
Cote d'Ivoire	Low	Abidjan	2012 – 2013	25/08/2017	531	23 (4.3%)	242	47.6	81.8	209 (86.4)	33 (13.6)
Ethiopia	Low	Addis	2012	12/01/2017	437	0 (0.0)	418	95.7	94.7	389 (93.1)	29 (6.9)
Kenya	Medium	Eldoret	2009 – 2013	03/07/2017	307	15 (4.9%)	113	38.7	97.4	78 (69.0)	35 (31.0)
Kenya	Medium	Nairobi	2009 – 2013	02/06/2017	1544	80 (5.1%)	148	10.1	91.9	141 (95.3)	7 (4.7)
Mali	Low	Bamako	2012 – 2013	18/01/2017	639	5 (0.8%)	50	7.9	96	48 (96.0)	2 (4.0)
Mauritius	High	Mauritius	2005 – 2009	31/12/2013	1,616	5 (0.3 %)	500	31.0	95.4	491 (98.2)	9 (1.8)
Mozambique	Low	Maputo	2015	16/03/2017	81	14 (17.8%)	43	64.2	100	42 (97.7)	1 (2.3)
Namibia	Medium	Namibia	2012 – 2013	31/12/2017	454	0 (0.0)	75	16.5	100	64 (85.3)	11 (14.7)
Seychelles	High	Seychelles	2008 – 2013	04/12/2017	124	1 (0.8%)	111	90.2	93.7	105 (94.6)	6 (5.4)
South Africa	Medium	Eastern Cape	2008 – 2013	31/12/2016	369	0 (0.0)	369	100	87	313 (84.8)	56 (15.2)
Uganda	Low	Kyadondo (Kampala)	2009 – 2013	31/12/2017	645	19 (2.9%)	150	24	54.7	112 (74.7)	38 (25.3)
Zimbabwe	Low	Bulawayo	2012 – 2013	11/12/2016	167	16 (9.6%)	57	37.8	89.5	54 (94.7)	3 (5.3)
	Low	Harare	2009 – 2013	26/06/2017	725	50 (6.7%)	191	28.3	93.7	174 (91.1)	17 (8.9)
Total cases			**2005 – 2015**		**7,108**	**228 (3.2%)**	**2,558**	**37.2**	**91.3**	**2,311 (90.3)**	**247 (9.7)**

**HDI: Human Development Index (source: United Nations Development Program. Human Development Report 2016); DCO: Death Certificate Only; No. = number; MV (%) = Proportion of morphologically verified cases.*

Of the cases included for survival analyses (Table 6.2), the mean age at diagnosis ranged from 45.8 years (Standard deviation, SD=14.0) in Addis Ababa (Ethiopia) to 59.6 years (SD= 14.2) in Seychelles, with a median duration of follow-up ranging from 8.5 months in Cotonou (Benin) to 5.4 years in Mauritius. Almost half of the patients (47.4%) were diagnosed under the age of 50. The proportion of patients LFU varied by registry, and this ranged from 0% in Harare (Zimbabwe), Mauritius, and Seychelles to 45% in Cotonou (Benin). The observed survival at 1-year ranged from 61.0% in Bulawayo (Zimbabwe) to 95.0% in Namibia. At 3-years after diagnosis, the observed survival ranged from 19.3% in Bulawayo (Zimbabwe) to 79.1% in Namibia (Table 6.2).

Table 6.2 Patients' characteristics: Mean age at diagnosis, median years of follow-up and observed (all-cause) survival.

Country, Registry	Number of cases included	Mean age at diagnosis (SD)	YEAR 1				YEARS 2 AND 3				YEARS 4 AND 5		Median follow-up (years)
			No. of deaths (%)	LFU	% LFU	1-year Observed Survival (in %)	No. of deaths (%)	LFU	%LFU	3-year observed survival (in %)	No. of deaths (%)	5-year observed survival (in %)	
Benin, Cotonou	91	46.8 (12.3)	10 (11)	44	48.	81.8	12 (13)	5	6	53.0	-	-	0.7
Côte d'Ivoire, Abidjan	209	47.3 (12.4)	27 (13)	39	19	85.1	55 (26)	6	3	51.2	-	-	2.3
Ethiopia, Addis	389	45.8 (14.0)	33 (9)	46	12	90.7	91 (23)	7	2	63.6	-	-	3.3
Kenya, Eldoret*	78	47.2 (12.8)	10 (13)	22	28	83.6	17 (22)	7	9	49.5	3 (4)	40.1	1.2
Kenya, Nairobi*	141	48.4 (11.1)	7 (5)	38	27	94.4	17 (12)	17	12	75.8	8 (6)	64.0	2.5
Mali, Bamako	48	46.2 (14.3)	12 (25)	8	17	71.4	10 (21)	3	6	44.1	-	-	1.2
Mauritius*	491	55.9 (13.6)	51 (10)	0	0	89.5	58 (12)	0	0	77.6	20 (4)	73.2	5.4
Mozambique, Maputo	42	50.3 (11.8)	8 (19)	12	28	75.8	-	-	-	-	-	-	1.1
Namibia*	64	53.3 (14.2)	3 (5)	5	8	95.0	9 (14)	3	5	79.1	4 (6)	70.4	4.5
SA, Eastern Cape*	313	55.8 (15.3)	70 (22)	61	20	74.5	66 (21)	29	9	44.9	19 (6)	33.3	1.3
Seychelles*	105	59.6 (14.2)	14 (13)	0	0	86.7	11 (11)	1	1	76.2	13 (12)	61.2	4.2
Uganda, Kyadondo*	112	47.4 (12.1)	25 (22)	30	27	74.1	29 (26)	8	7	31.5	10 (9)	11.1	1.0
Zimbabwe, Bulawayo	54	57.1 (14.8)	17 (32)	17	32	61.0	12 (22)	5	9	19.3	-	-	0.8
Zimbabwe, Harare*	174	52.4 (13.3)	45 (26)	0	0	74.0	39 (22)	1	0.6	51.3	12 (7)	43.5	3.3

*LFU: Lost to follow-up; No.: number; SA= South Africa, SD = Standard deviation *Registries with a potential follow-up time of 5 years (or more).*

Information on stage at diagnosis was obtained for all registries except for Mauritius. Of the 13 registries which submitted data on stage at diagnosis, stage was known for 47.0% of patients (892 women). Patients from Seychelles and Namibia (of high and medium HDI respectively) had the greatest proportions of early-stage diagnosis with 51.4% and 35.9% of patients diagnosed at early stages respectively (Figure 6.1). These registries also had the lowest proportion of patients with unknown stage. When limited to patients with known stage, 64.9% of women with known stage were diagnosed at a late stage (stages III and IV) with 18.4% being metastatic at diagnosis (stage IV).

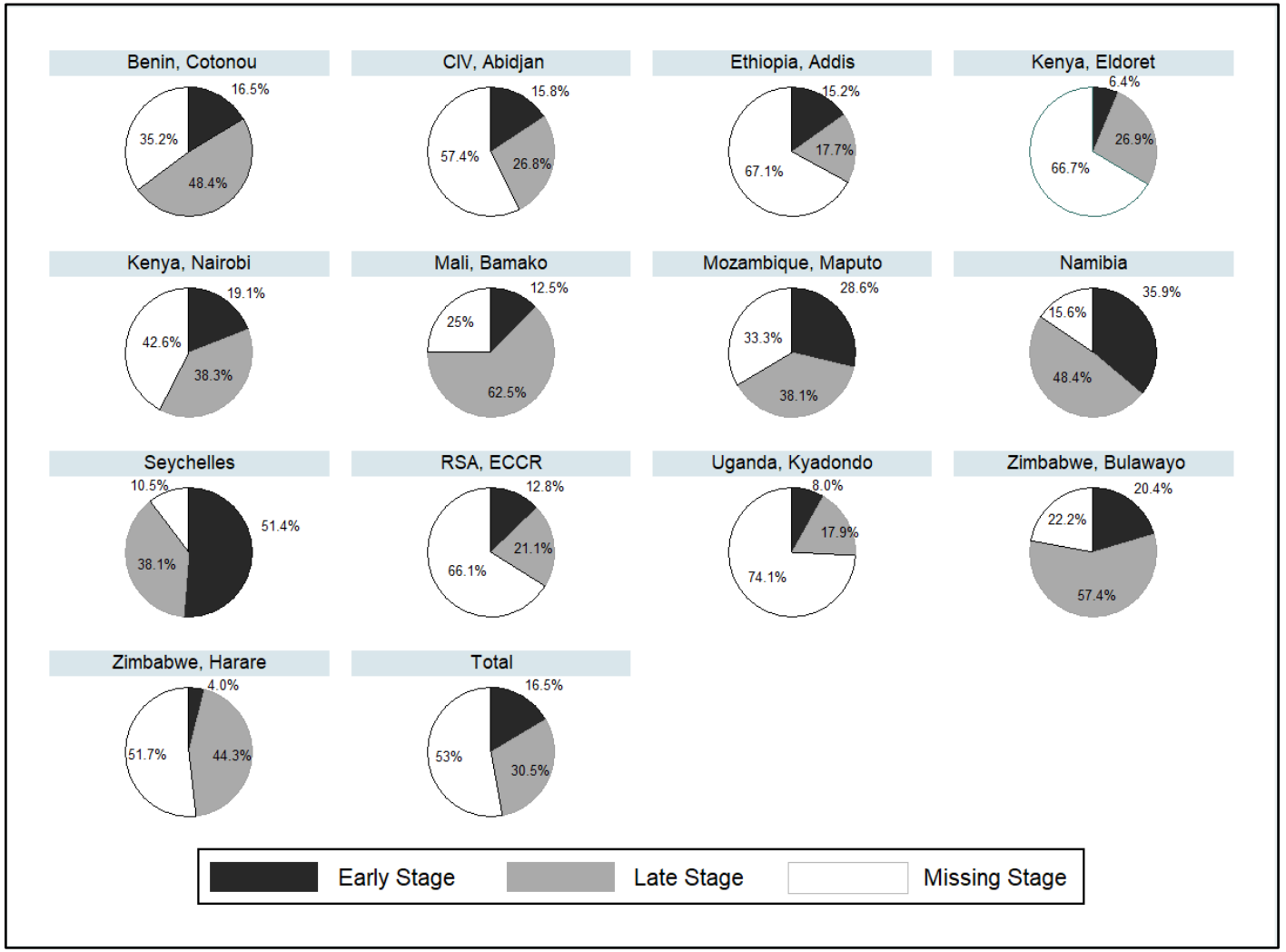


Figure 6.1: Stage distribution by registry.
CIV: Côte d'Ivoire; RSA: Republic of South Africa; ECCR: Eastern Cape Cancer Registry.

6.1.3.2 Assessing loss to follow-up

The proportion of cases LFU was generally highest in the 1st year following diagnosis (Table 6.2). However, among those for whom we had information on stage, LFU at year 1 was not related to stage or age at diagnosis for all registries, when assessed in a Cox model with LFU as outcome and adjusted for the effect of age and stage at diagnosis. When LFU at year 3 was assessed, LFU was non-differential by age and stage in all registries except for Abidjan, where patients diagnosed at a late stage had a greater risk of being LFU, as did patients aged 45-54.

6.1.3.3 Survival for all ages, and by registry

The overall all-cause Kaplan-Meier (KM) survival was 84.1% (95% CI: 82.5-85.6) at year-1, 61.4% (95% CI: 59.1 – 63.5) at year-3 and 52.3% (95% CI: 49.9-54.6) at year-5 (Fig.1) for all included cases. Survival was lowest in the oldest age group (log-rank test: p=0.01), among patients from countries of low HDI (log-rank test: p<0.001), and among patients with advanced stage tumours (log-rank test: p<0.001) (Figure 6.2).

Figure 6.3 shows the KM survival by registry. The 5-year KM survival was lowest in Kampala (Uganda) and highest in Mauritius.

For all registries combined, based on the assumption for the sensitivity analysis that all patients with stage IV breast cancer who were LFU (N=63) and a random sample of 25% of patients with unknown stage at diagnosis who were LFU (N=179), had died six months after the date of last contact, the overall all-cause Kaplan-Meier survival was 79.7% (95% CI: 78.0-81.4) at year-1, 56.5% (95% CI: 54.3 – 58.6) at year-3, and 45.3% (95% CI: 43.0-47.6) at year-5.

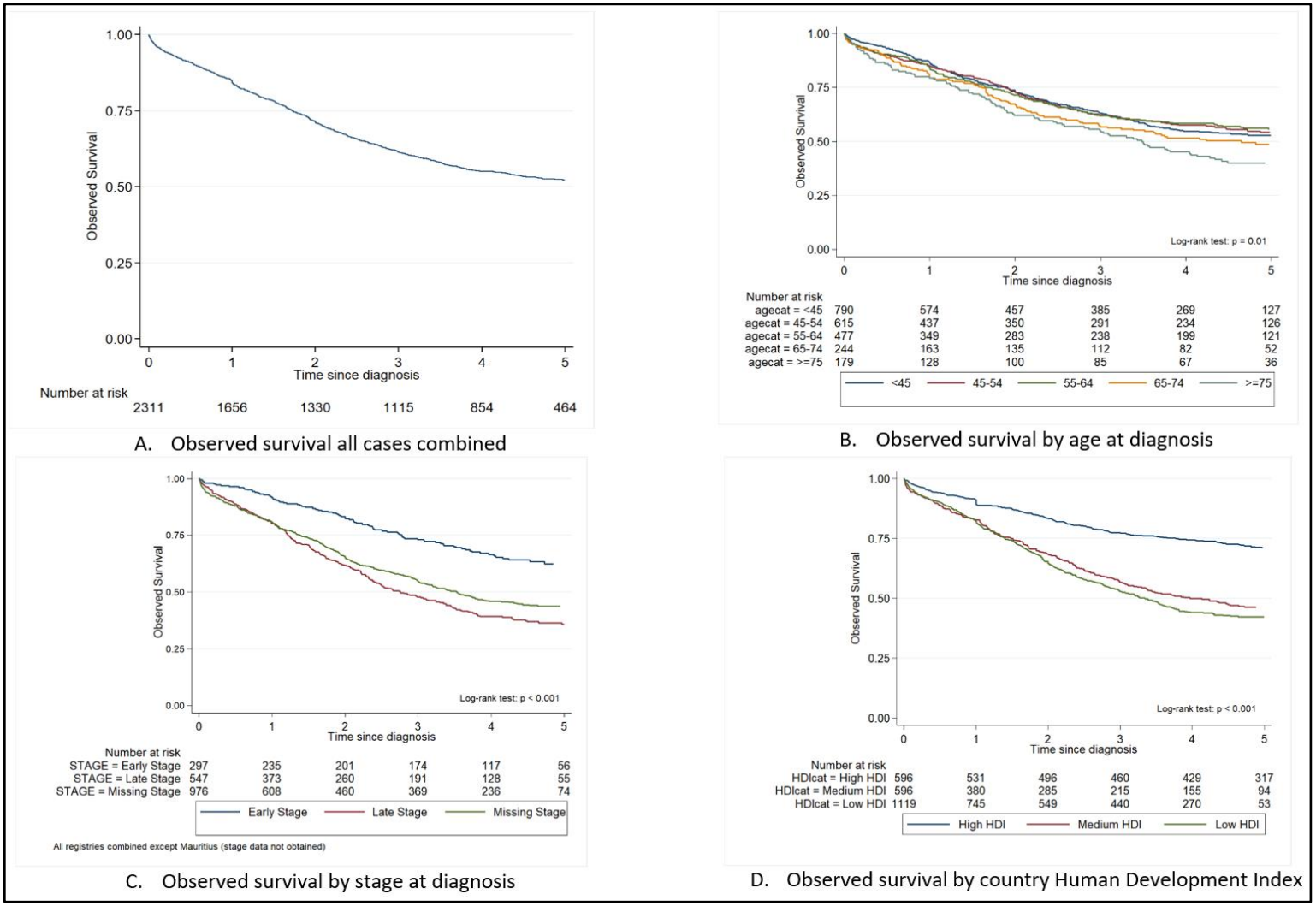


Figure 6.2: Observed survival (all-cause survival) for all registries combined (A), by age (B), stage (C), and country-level Human Development Index (D).

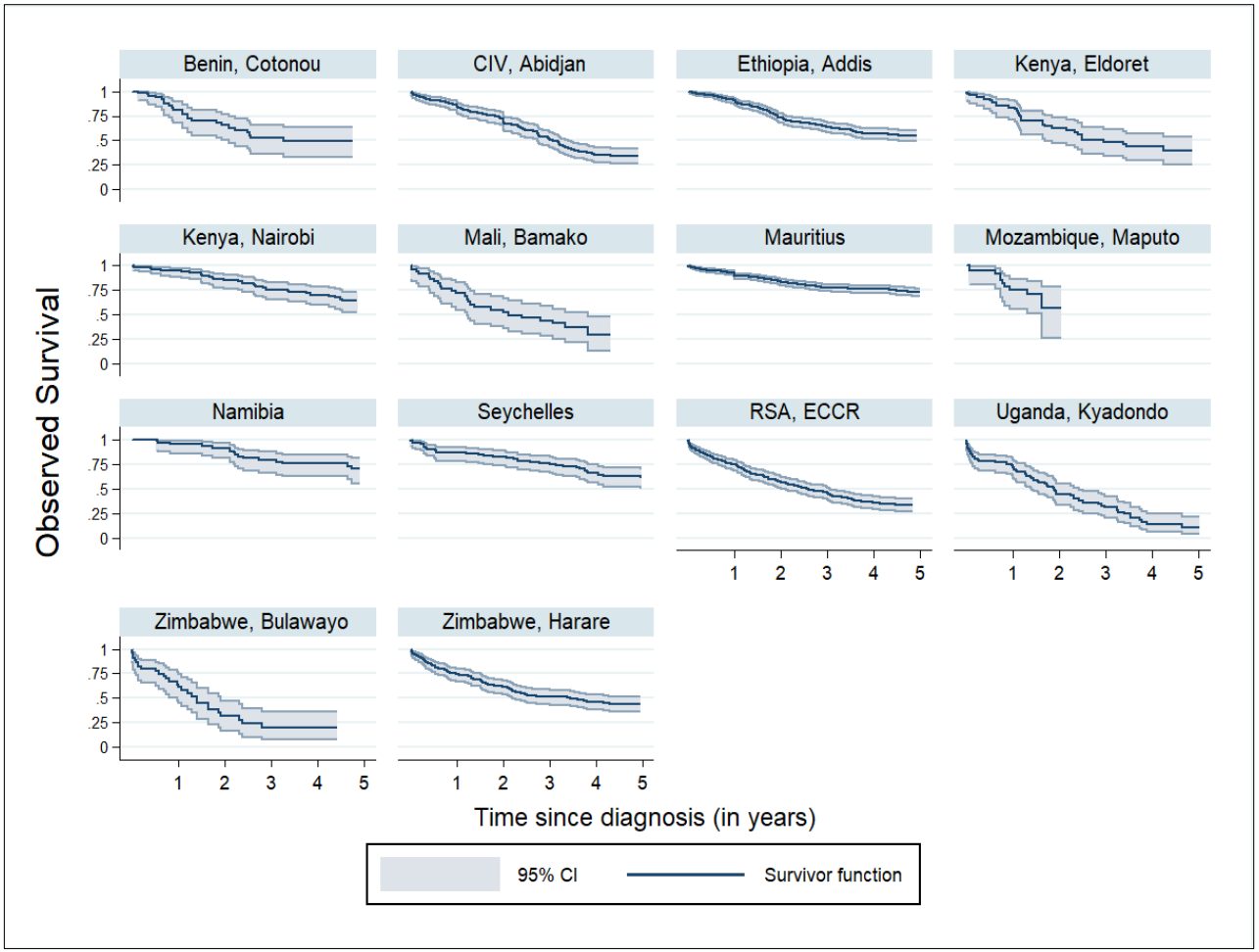


Figure 6.3: Observed (all-cause) survival from breast cancer by registry.
CIV: Côte d'Ivoire; RSA: Republic of South Africa; ECCR: Eastern Cape Cancer Registry.

The relative survival 1 year after diagnosis was highest in countries of medium or high HDI ranging from 97.1% in Namibia to 63.0% in Bulawayo (Zimbabwe) (Table 6.3). Similarly, at 5-years after diagnosis, the relative survival was highest in Mauritius at 83.2% and lowest in Kyadondo (Uganda) at 12.1% (Table 6.3). The overall relative survival at year-1 for the entire cohort was 86.1% (95% CI: 84.4-87.6), 65.8% (95% CI: 63.5-68.1) at year-3 and 59.0% (95% CI: 56.3-61.6) at year-5.

The corresponding overall age-standardised relative survival (ASRS) for female breast cancer patients in our cohort was 86.3% (83.4-88.8) in year 1, 70.0% (95% CI: 65.6-74.0) in year 3 and 66.3% (95% CI: 60.4-71.5) in year 5. There are disparities within SSA in the 5-year ASRS by registry, ranging from 5.3% (95% CI: 1.9-11.3) in Kyadondo (Uganda) to 93.7% (95% CI: 75.5-98.5) in Mauritius (Table 6.3). There are also survival differences within the same country, with better 3-year survival for patients in the capital cities of Harare (Zimbabwe) and Nairobi (Kenya) in comparison with other cities such as Bulawayo (Zimbabwe) and Eldoret (Kenya) respectively (Table 6.3).

Table 6.3: Age-specific relative survival and age-standardised relative survival (ASRS) by registry.

Country, Registry	1-year relative survival										1-year ASRS	
	< 45	95% CI	45 - 54	95% CI	55 - 64	95% CI	65-74	95% CI	All ages	95% CI	All ages	95% CI
Benin, Cotonou	87.3	69.1 – 95.3	81.2	56.5 – 93.0	84.8	49.0 – 97.2	104.8	-	83.0	69.6 – 91.1	100	-
Cote d'Ivoire, Abidjan	88.5	79.5 – 94.0	84.4	71.1 – 92.3	90.2	68.5 – 98.6	85.3	59.4 – 97.7	87.0	80.8 -91.6	94.3	83.4 – 98.1
Ethiopia, Addis	90.8	85.6 – 94.2	98.4	91.1 – 100.3	89.3	76.2 – 95.9	89.7	66.4 – 98.9	92.2	88.6 – 94.8	92.5	81.4 – 97.1
Kenya, Eldoret	84.7	66.2 – 93.9	87.2	64.1 – 96.3	89.0	39.3 – 99.8	103.3	-	85.3	72.9 – 92.7	88.3	38.2 – 98.4
Kenya, Nairobi	96.6	84.5 – 99.9	93.7	80.0 – 98.6	94.2	75.1 – 99.7	103.6	-	95.9	89.9 – 98.8	103.8	-
Mali, Bamako	70.4	45.3 – 85.8	81.7	43.3 – 95.8	102.2	-	45.2	10.3 – 77.4	72.5	55.9 – 84.0	72.3	55.7 – 83.6
Mauritius	94.4	87.7 – 97.6	90.8	84.3 – 94.8	90.9	84.1 – 95.1	84.1	71.9 – 91.8	91.6	88.4 – 94.0	91.3	86.0 – 94.7
Mozambique, Maputo	66.2	36.3 – 84.8	89.3	41.6 – 99.5	92.9	51.9 – 100.8	52.7	0.6 – 96.0	77.1	58.2 – 88.6	73.2	38.0 – 90.5
Namibia	94.3	62.8 – 99.9	95.7	68.8 – 100.3	101.5	-	89.3	34.8 – 102.0	97.1	87.2 – 100.5	99.8	-
SA, Eastern Cape	88.2	77.7 – 94.3	80.2	67.1 – 88.8	66.5	54.3 – 76.4	79.2	62.3 – 90.2	77.0	71.2 – 82.0	76.0	68.3 – 82.1
Seychelles	100.2	-	92.7	72.9 – 98.5	97.5	78.7 – 100.5	87.9	55.3 – 98.7	89.4	81.0 – 94.8	85.0	73.0 – 91.9
Uganda, Kyadondo	74.6	57.3 – 85.9	67.1	47.9 – 80.7	85.0	57.9 – 96.2	103.6	-	75.4	65.1 – 83.2	85.5	60.3 – 95.3
Zimbabwe, Bulawayo	63.6	23.4 – 87.6	41.5	16.2 – 65.7	79.3	37.2 – 95.8	75.2	38.3 – 93.3	63.0	46.0 – 76.3	75.2	51.4 – 88.5
Zimbabwe, Harare	75.0	61.1 – 85.0	75.5	60.7 – 85.7	70.1	51.6 – 83.0	72.9	46.9 – 88.7	76.5	69.0 – 82.6	84.8	75.8 – 90.7
					3-year relative survival						3-year ASRS	
Benin, Cotonou	54.2	29.8 – 73.6	58.6	29.6 – 79.8	59.8	20.5 – 86.8	118.5	-	55.9	39.4 – 70.1	58.9	49.3 – 67.3
Cote d'Ivoire, Abidjan	56.2	44.3 – 66.8	57	39.7 – 71.5	50.6	27.4 – 71.2	48.9	23.6 – 73.3	55.0	46.6 – 62.9	64.8	35.5 – 83.4
Ethiopia, Addis	69.1	61.6 – 75.5	67.4	54.9 – 77.4	53.5	37.6 – 67.4	63.8	37.4 – 83.8	66.8	61.2 – 72.0	69.2	54.9 – 79.8
Kenya, Eldoret	47.7	27.0 – 66.1	62.6	35.1 – 81.8	30.8	4.5 – 65.3	109.8	-	52.4	37.3 – 66.0	87.1	3.0 – 99.5
Kenya, Nairobi	77.0	58.5 – 88.7	74.3	54.2 – 87.2	78.8	55.0 – 92.4	111.4	-	79.5	69.1 – 87.2	112.9	-
Mali, Bamako	41.6	19.2 – 63.0	59.6	22.9 – 84.4	77.2	9.7 – 103.1	16.8	0.8 – 54.7	46.4	29.6 – 62.0	46.0	27.5 – 62.8
Mauritius	87.0	78.7 – 92.4	76.7	68.3 – 83.3	86.0	78.0 – 91.8	71.6	57.3 – 82.9	83.4	79.1 – 87.1	86.0	77.8 – 91.3
Namibia	88.7	56.9 – 99.0	75.5	48.6 – 90.7	90.9	59.1 – 101.2	78.4	24.3 – 104.3	84.5	70.6 – 93.5	87.7	26.8 – 98.7
SA, Eastern Cape	58.7	44.0 – 71.1	57.9	41.9 – 71.4	35.1	23.2 – 47.4	64.8	43.7 – 82.0	49.5	42.4 – 56.5	49.3	40.0 – 57.9
Seychelles	80.6	50.4 – 93.8	81.9	60.7 – 92.8	92.4	73.3 – 99.5	85.6	51.5 – 100.8	82.6	72.4 – 90.2	82.0	66.1 – 90.9
Uganda, Kyadondo	43.4	24.3 – 61.4	30.5	13.9 – 49.3	18.3	3.0 – 44.6	56	6.5 – 94.6	33.2	22.2 – 44.8	27.1	12.2 – 44.6
Zimbabwe, Bulawayo	16.6	8.0 – 52.2	10.7	0.7 – 37.5	-	-	46.9	10.9 – 80.4	21.6	8.2 – 39.8	-	-
Zimbabwe, Harare	53.1	38.4 – 66.3	53	37.7 – 66.5	54.8	36.2 – 70.7	45.2	21.8 – 67.8	56.7	48.2 – 64.6	72.1	57.5 – 82.5

Table 6.3 continued,

	5-year relative survival										5-year ASRS	
Country, Registry	**< 45**	**95% CI**	**45 - 54**	**95% CI**	**55 - 64**	**95% CI**	**65-74**	**95% CI**	**All ages**	**95% CI**	**All ages**	**95% CI**
Kenya, Eldoret	36.4	16.7 – 57.1	52.2	22.6 – 76.5	31.7	4.6 – 67.2	-	-	43.7	27.7 – 59.2	-	-
Kenya, Nairobi	74.7	55.5 – 87.6	70	47.6 – 85.3	68	40.8 – 86.9	-	-	69.5	57.0 – 79.7	27.1	23.1 – 35.2
Mauritius	85.5	76.8 – 91.3	71.9	62.9 – 79.2	84.1	75.3 – 90.8	72	56.3 – 85.1	83.2	78.4 – 87.4	93.7	75.5 – 98.5
Namibia	63.3	30.0 – 85.5	77.3	49.7 – 92.8	94.5	61.5 – 105.2	87.4	27.1 – 116.3	78.5	62.4 – 90.2	80.0	22.2 – 96.8
SA, Eastern Cape	46.4	31.1 – 60.7	42.2	25.4 – 58.6	29.8	18.1 – 42.9	67.1	43.3 – 87.4	39.2	31.5 – 46.9	38.2	28.7 – 47.6
Seychelles	81.1	50.7 – 94.4	69.4	46.6 – 84.5	80.4	56.4 – 93.9	72.7	36.4 – 96.3	70.2	58.0 – 80.6	66.3	49.2 – 78.8
Uganda, Kyadondo	20.7	6.4 – 41.1	14.3	3.3 – 33.3	9.5	6.0 – 34.9	-	-	12.1	4.4 – 24.2	5.3	1.9 – 11.3
Zimbabwe, Harare	40.6	26.2 – 55.2	52.5	36.9 – 66.7	57.1	37.7 – 73.7	41.3	17.6 – 66.5	51.2	42.2 – 59.9	60.8	38.4 – 77.3

CI=Confidence Interval; SA=South Africa

6.1.3.4 Survival by age at diagnosis and registry

There were no observed patterns in the relative survival by age at diagnosis. Women younger than 45 at diagnosis had lower survival point estimates at year-3 compared with women in the 55-64 age group in Seychelles, Cotonou (Benin), Bamako (Mali), and Namibia, although with wide and generally overlapping confidence intervals (Table 6.3).

6.1.3.5 Survival by stage at diagnosis

Survival strongly differed by stage at diagnosis, cases diagnosed at an early stage had a 62.5% (95% CI: 55.6-68.6) 5-year observed KM survival probability and those diagnosed at a late stage at 35.8% (95% CI: 30.9-40.7) for all registries combined (except for Mauritius) (log-rank test $p < 0.001$) (Figure 6.2). Table 6.4 shows the relative survival (RS) by stage at diagnosis for each registry, and we observe differences in survival for patients of the same stage by registry. For example, in rural Eastern Cape (South Africa), the 3-year RS for patients with an early-stage disease was 60.3% (95% CI: 39.1-77.6), in comparison with 95.0% (95% CI: 81.5 – 102.1) for Seychelles; while for women with late-stage disease, the 3-year RS was 39.4% (95% CI: 25.7 – 53.3) in Eastern Cape (South Africa), in comparison with 68.7% (95% CI: 50.9 – 82.0) in Seychelles (Table 6.4). For all cases combined, women diagnosed at an early stage had a 69.3% (95% CI: 61.5-76.2) relative survival probability at year-5 in comparison with a RS of 40.3% (95% CI: 34.9-45.7), if diagnosed at stages III and IV.

Table 6.4: Relative survival (RS) by stage at diagnosis and registry

Country, registry	No. of cases included	No. with known stage	No. with late stage (%)	1 YEAR RS (95%CI)			3 YEAR RS (95%CI)			5 YEAR RS (95%CI)		
				Early Stage	Late Stage	Missing stage	Early Stage	Late Stage	Missing stage	Early Stage	Late Stage	Missing stage
Benin, Cotonou	91	59	44 (74.6)	74.1 (29.0 – 93.5)	80.4 (59.7 – 91.8)	90.2 (64.0 – 98.3)	60.4 (19.0 – 86.9)	48.5 (25.7 – 69.2)	64.7 (35.6 – 84.1)	–	–	–
Cote d'Ivoire, Abidjan	209	89	56 (62.9)	95.5 (78.2 – 100.4)	87.4 (74.0 – 94.6)	85.5 (76.7 – 91.4)	85.0 (64.3 – 96.4)	40.7 (25.2 – 55.9)	52.7 (41.4 – 63.2)	–	–	–
Ethiopia, Addis	389	128	69 (53.9)	94.1 (83.3 – 98.4)	90.8 (80.3 – 96.3)	92.5 (88.0 – 95.5)	71.4 (56.8 – 82.2)	57.5 (43.7 – 69.4)	68.6 (61.6 – 74.8)	–	–	–
Kenya, Eldoret	78	26	21 (80.8)	101.5‡ (-)	90.5 (64.8 – 98.4)	83.5 (68.1 – 92.7)	105.3‡ (–)	49.2 (21.9 –72.4)	49.0 (30.3 – 66.0)	73.1‡ (5.9 – 103.6)	39 (13.1 – 65.7)	45.4 (26.4 – 63.6)
Kenya, Nairobi	141	81	54 (66.7)	92.9 (72.0 – 99.1)	101.7 (–)	91.5 (79.0 – 97.2)	81.0 (57.0 – 93.6)	80.3 (62.0 – 91.7)	78.1 (59.9 – 89.7)	72 (46.3 – 88.5)	74.8 (53.4 - 89.7)	63.6 (42.5 – 89.7)
Mali, Bamako	48	36	30 (83.3)	83.4‡ (24.4 – 99.1)	65.4 (44.5 – 80.3)	91.6 (49.7 – 99.9)	86.5‡ (25.3 – 102.8)	25.3 (9.7 – 44.8)	82.1 (38.7 – 98.7)	–	–	–
Mauritius	491	NA	NA	–	–	–	–	–	–	–	–	–
Mozambique, Maputo	42	28	16 (57.1)	81.0 (39.8 – 95.3)	81.8 (52.0 – 94.7)	73.7 (37.6 – 91.5)	–	–	–	–	–	–
Namibia	64	54	31 (57.4)	101.9 (-)	95.8 (77.9 – 100.9)	91.4 (46.4 – 100.6)	89.4 (63.5 -99.8)	81.3 (59.4 – 94.5)	83.9 (40.0 – 100.8)	79.7 (50.3 – 96.2)	74.5 (50.2 – 91.2)	89.1 (42.5 – 107.1)
SA, Eastern Cape	313	106	66 (62.3)	92.4 (76.7 – 99.0)	74.7 (61.4 – 84.4)	75.9 (68.6 – 81.9)	60.3 (39.1 – 77.6)	39.4 (25.7 – 53.3)	51.9 (42.8 – 60.4)	44.2 (23.4 – 64.8)	29.3 (16.4 – 44.1)	42.7 (32.7 – 52.7)
Seychelles	105	94	40 (42.6)	99.0 (88.4 – 101.8)	79.9 (63.1 – 90.3)	78.1 (39.8 – 97.0)	95.0 (81.5-102.1)	68.7 (50.9 – 82.0)	74.1 (34.6 – 98.4)	84.7 (67.4 – 96.9)	53.6 35.1 – 69.8)	61.2 (20.2 – 94.1)
Uganda, Kyadondo	112	29	20 (69.0)	66.0‡ (26.1 – 88.8)	86.3 (60.7 – 96.7)	73.3 (60.8 - 82.5)	41.1‡ (9.9 – 72.8)	37.9 (15.3 – 61.3)	29.9 (17.1 – 44.2)	42.1‡ (10.1 – 74.4)	30.4 (9.7 – 55.6)	3.7 (0.3 – 15.0)
Zimbabwe, Bulawayo	54	42	31 (73.8)	103.2 (–)	57.2 (36.1 – 74.1)	44.7 (11.5 – 75.4)	54.8‡ (6.3 – 92.6)	18.6 (4.7 – 40.7)	–	–	–	–
Zimbabwe, Harare	174	84	77 (91.7)	87.9‡ (34.3 – 100.4)	74.9 (63.2 – 83.7)	76.8 (66.0 – 84.9)	77.2‡ (27.9 – 99.4)	46.6 (34.3 – 58.4)	63.6 (51.5 – 74.1)	81.6‡ (29.5 – 105.1)	37.6 (25.3 – 50.4)	60.2 (47.4 – 71.9)
All cases	**2311**	**844**	**547**	**93.5 (89.4 - 96.3)**	**82.0 (78.1 - 85.3)**	**83.0 (80.1 - 85.6)**	**78.0 (71.6 - 83.3)**	**51.1 (46.0 - 56.0)**	**59.0 (55.1 - 62.8)**	**69.3 (61.5 - 76.2)**	**40.3 (34.9 - 45.7)**	**49.2 (44.8-53.6)**

NA=Not available SA = South Africa

6.1.3.6 Survival by country-level Human Development Index (HDI)

The survival experience of patients diagnosed in countries with a high HDI was better than for patients in countries with low and middle HDI (Figure 6.2). Cases from countries with a high HDI were diagnosed on average at age 56.5 years while cases from a low HDI country at age 48.0. Figure 6.4 shows differences in the relative survival by HDI, even after categorisation by stage. For women with breast cancer diagnosed at stages III and IV, women in countries with a high HDI had a 5-year relative survival estimated at 53.4% (95% CI: 35.0 – 69.5) while patients in countries with low HDI at 31.9% (95% CI: 25.4 – 38.5). If diagnosed early, patients in countries of high HDI have a 5-year relative survival estimated at 84.7% (95% CI: 67.4-96.9) while for patients from low HDI countries it is 67.1% (95% CI: 55.4-77.0).

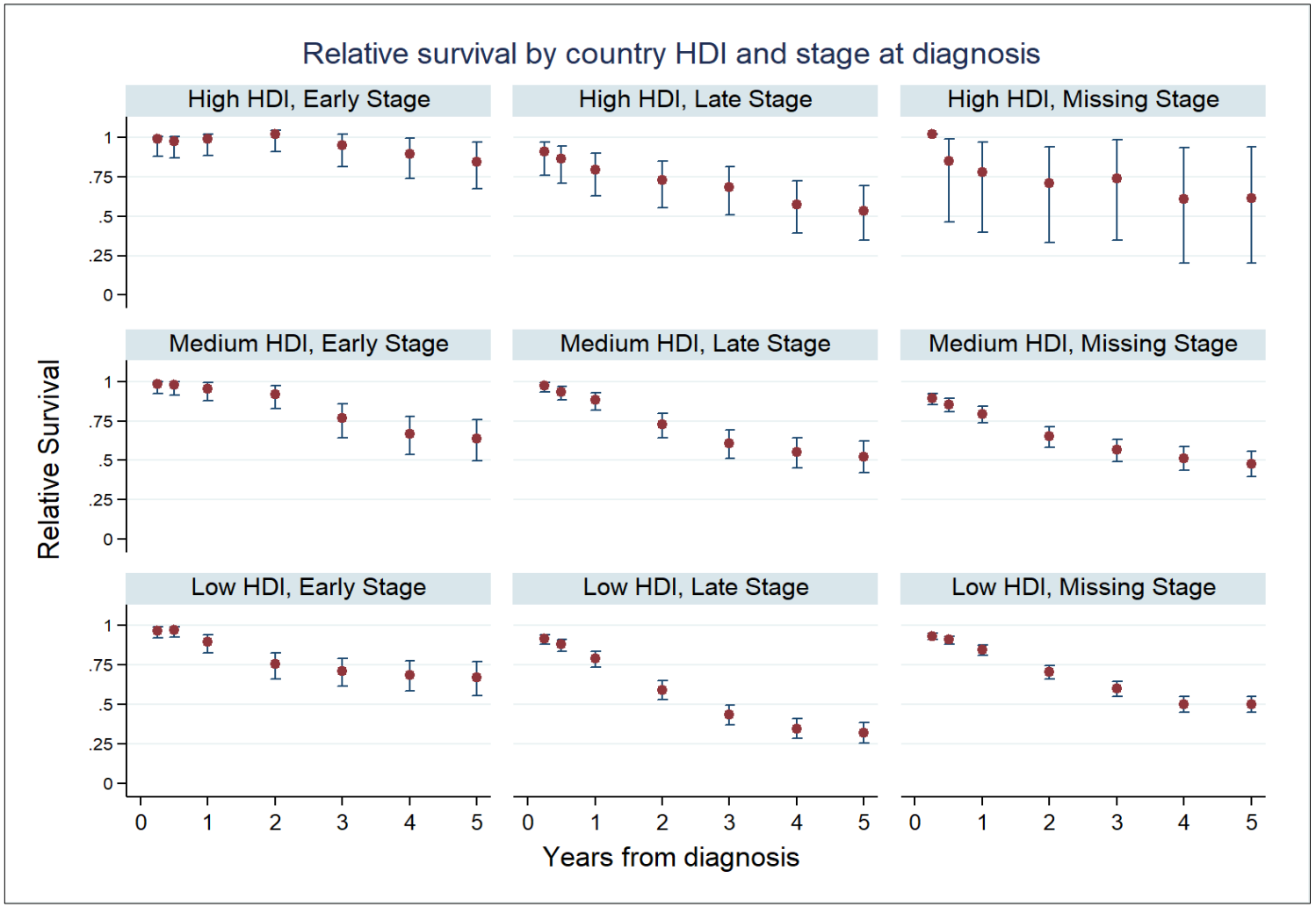


Figure 6.4: Relative survival by country-level Human Development Index (HDI) and stage at diagnosis.

6.1.3.7 Excess mortality - incorporating the effect of age, stage and country HDI

The excess mortality rate ratio was 2.5 (95% CI: 1.8-3.3) times higher for patients diagnosed at a late stage compared with patients diagnosed early, even after controlling for the effect of the country HDI (test for heterogeneity: $p< 0.001$) (Table 6.5). The country-level HDI was equally independently associated with an increased hazard of death, with patients diagnosed in a country with either a medium or low HDI having a hazard of death twice that in a country of high HDI, even after controlling for the stage at diagnosis (test for heterogeneity: $p< 0.001$) (Table 6.5). However, age at diagnosis was not an independent predictor of higher excess hazards after controlling for the effect of stage and country HDI in our model (test for heterogeneity: $p=0.519$). There was no evidence of an interaction between age and stage at diagnosis.

Table 6.5 Breast cancer excess mortality hazard by stage, country HDI and age at diagnosis.

Prognostic factors	Number of cases	Univariable analysis			Multivariable adjusted model*			
		Excess mortality rate ratio	95% CI	*p*-value	Excess mortality rate ratio	95% CI	Test for heterogeneity	Test for linear trend
Age at diagnosis (years)							*p=0.159*	*p=0.246*
<45	790	1 (Ref)			1 (Ref)			
45-54	615	1.0	0.8 - 1.2	0.83	1.0	0.8 - 1.2		
55-64	477	1.1	0.9 - 1.3	0.61	1.2	0.9 - 1.4		
65-74	244	0.9	0.7 - 1.3	0.70	1.1	0.8 - 1.5		
75+	179	0.9	0.6 - 1.4	0.70	0.9	0.6 - 1.5		
Stage at diagnosis							*p<0.001*	-
Early Stage	301	1 (Ref)			1 (Ref)			
Late Stage	555	2.7	2.0 - 3.6	< 0.001	2.5	1.8 - 3.3		
Unknown Stage	962	2.2	1.6 - 2.9	< 0.001	1.9	1.4 - 2.5		
Country-level HDI							*p<0.001*	*p<0.001*
High HDI	596	1 (Ref)			1 (Ref)			
Medium HDI	596	2.3	1.4 - 3.8	0.001	1.9	1.2 – 3.1		
Low HDI	1119	2.8	1.7 - 4.5	< 0.001	2.3	1.4 – 3.7		

**Adjusted for stage at diagnosis, country-level Human Development Index (HDI) and age at diagnosis; CI=Confidence Interval, Ref = reference category*

6.1.4 Discussion

6.1.4.1 Main findings in the context of previous studies

Population-level survival statistics from high-income countries are widely available,[399–401] but these are very sparse from SSA. Results from individual cancer registries have been published previously,[402,403] and limited data have been published in previous international compilations.[15,76] However, this study includes the largest number of sub-Saharan African PBCRs in a single comparative study on survival and is the first to explore survival differences by stage between multiple SSA PBCRs.

There were wide variations in breast cancer survival within SSA, with the lowest survival observed in patients diagnosed at a late stage and in countries with a low HDI. For all cases combined, the 5-year ASRS was 66.3% (60.4-71.5), similar to survival observed 60 years ago in developed countries. For example, in England and Wales, women diagnosed with breast cancer in 1945-1949 had an estimated overall RS of 44%, and it was 55% in Connecticut, USA.[404] In 1950-1954, 5-year RS was 48% in England and Wales, 56% in Connecticut, 52% in Finland and 57% in Norway.[404] In recent years, the 5-year ASRS from breast cancer was 81.8% in Europe (79.2% in UK and Ireland) for cases diagnosed in 1999-2007[399] and 91.1% in the USA (83.1% in black women) for cases diagnosed in 2008-2014.[405]

There were three PBCRs included in this study which were also included in the CONCORD- 3 study - Bamako (Mali), Eastern Cape (South Africa) and Mauritius.[15] In this study, women diagnosed with breast cancer in the period 2012-2013 were included from Mali, while the CONCORD-3 study included women diagnosed in 2010-2012. The CONCORD-3 study reported no survivors at 5-years (ASRS=0.00%) for this period.[15] In this study, the included women from Bamako (Mali) did not have the potential to be followed-up for 5-years, so the age-standardised relative survival (ASRS) at 1-year (72.3%, 95% CI: 55.7-83.6) and at 3-years after diagnosis (46.0%, 95% CI: 27.5-62.8) (Table 6.3) was reported. For Eastern Cape (South Africa), the CONCORD-3 study reported the 5-year Pohar-Perme ASRS for the period 2005-

2009 (32.0%, 95% CI: 23.3-40.7) and the period 2010-2014 (40.1%, 95% CI: 30.7-49.6). In this study, data were included for the period 2008-2013 from Eastern Cape (South Africa) - the Ederer II ASRS was estimated at 38.2% (95% CI:28.7-47.6) in this period, which is similar to results reported in the CONCORD-3 study. For Mauritius, both studies included data from the period 2005-2009. The CONCORD-3 study estimated the 5-year Pohar-Perme ASRS at 83.6% (95% CI: 75.9 – 91.3), while this study estimated the 5-year Ederer II relative survival at 83.2% (95% CI: 78.4-87.4) and the ASRS at 93.7% (95% CI: 75.5-98.5) in Mauritius. The Ederer II and the Pohar-Perme methods are used for the estimation of the expected survival probability. The Pohar-Perme method gives more weight to older patients, who have higher competing risks of death.[82,85] The Ederer II method has been shown to be more precise for longer-term survival, however, at 5-years after diagnosis, there should be negligible differences between these methods. [82,86]In the Ederer II method, a small bias may be introduced for patients 75+,[82] of which there was a higher proportion of older patients in Mauritius.

The SURVCAN-2 study included PBCRs data from Kampala (Uganda), and Harare (Zimbabwe). The 5-year relative survival was estimated at 46.9% among blacks in 1993-1997 in Harare (Zimbabwe),[406] and it is 60.8% (95% CI: 38.4-77.3) in this study. In Kampala (Uganda), there has been a decline in the 5-year ASRS, which was estimated at 36.1% in 1993-1997 from a random sample of 162 women[407] and is estimated at 5.3% (1.9-11.3) in 2009-2013 in this random sample of 112 women. This difference observed in Uganda, may be related to factors such as therapy interruptions from stock-outs and breakdown of the lone cobalt -60 radiotherapy machine,[408,409] which may have negatively impacted access to quality therapy in these more recent years before the set-up of the Uganda Cancer Institute - Hutchinson Centre Research Institute which has more state-of-the-art facilities.

In this study, the stage at diagnosis was an important predictor of survival, even after adjusting for age and country HDI. Of those with known stage, 64.9% were diagnosed at a late stage. An equally high proportion of late-stage disease (77%) was described in a meta-

analysis including 24,213 women from a variety of hospital settings within SSA.[13] A study on breast cancer stage at diagnosis using population-based data in Abidjan, Cote d'Ivoire and Brazzaville, Congo for cases diagnosed from 2008-2009 reported 74% and 81% of breast cancers diagnosed at stages III and IV.[119] It has to be noted that there is a considerable delay between first symptoms and presentation to health care practitioner; a recent systematic review found between three to over six months delay, and there is an additional three to six months interval between first presentation to health care practitioner and confirmation of diagnosis of breast cancer in SSA;[124] while in comparison, the median time from symptom recognition to diagnosis in 2000 -2007 among black women in the USA was on average 53.6 days in comparison with 36 days among Caucasian women.[410] The median overall time from first symptom recognition to diagnosis has been estimated at 7.9 months in Accra, Ghana,[122] 8.5 months in Western Cape, South Africa, at more than 10 months in Abidjan, Cote d'Ivoire[411] and at 15 months in rural Rwanda.[123] In contrast, in 2006, about 30% of all breast cancer cases in England, Scotland and Wales were diagnosed asymptomatically by screening.[412]

Some reasons for late presentation in SSA include low breast cancer awareness,[125] difficult access to healthcare (both physical[256] and economic), fear, distrust of conventional medicine and belief in alternative sources of healing.[124,413] Additionally, pathways within the healthcare system often hinder early diagnosis.[127,132] Unfavourable tumour biology such as triple-negative disease or the luminal-B-like phenotype may also be associated with late-stage presentation,[414] as these tumours generally grow faster leading to late-stage at diagnosis. Furthermore, the possibility of underestimation of stage IV disease due to the paucity of facilities for accurate staging needs to be considered in SSA. This can also explain variations in the proportion of stage IV disease between registries depending on local availability and access to imagery facilities.

In addition to diagnostic delays, there are further delays between confirmation of diagnosis and onset and completion of therapy, as a result of both patient and system-related factors.

However, even for patients with the same stage at diagnosis, those in a high HDI country had a better survival experience. This may be linked to the availability and access to treatment as most people in LMIC have to pay out-of-pocket for healthcare.[176] Hence improving survival among women diagnosed with breast cancers in SSA would require at least two major developments that is downgrading the stage at presentation (through improved breast health awareness and clinical breast examination) and improved access to diagnosis and adequate treatment.[415]

Age was not an important predictor of survival after adjusting for the effect of stage and country HDI in this study. In most developed countries, poorer survival at 5 years is observed among older women[399] particularly in recent years [416] and also among women diagnosed with early-onset breast cancer, before the age of 40.[417] This has been linked to the effect of screening in the middle-age group[416] resulting in a lead-time bias, and less aggressive treatment in older women.[418] However, in Africa, the population is young, and most of the patients are diagnosed before age 55. Young age at diagnosis has been associated with higher proportions of familial breast cancer with *BRCA* mutations but also unfavourable tumour biology factors. Since there may be a lack of the large group of middle-aged breast cancer patients with favourable tumour biology seen elsewhere, this could be one of the reasons why no survival differences were detected.

To facilitate international comparisons, age standardisation was done using the external ICSS weights, which are largely derived from the age distribution of cancer patients in Europe and have been used by the "Survival of cancer patients in Europe" (EUROCARE) and the "Global surveillance of cancer" (CONCORD) studies.[15,87] However, due to differences in the age structures of European and the African populations included this study, the ASRS were often a lot different from the country-specific relative survival estimates. Internal weights can also be used for age standardisation, with weights derived from the age distribution of the study population at the beginning of the study. However, this may make comparisons

between populations with different age distributions and over time challenging. Recently, an updated World Cancer Patient Population was proposed by IARC, which better reflects the age distribution in LMIC, with more weight given to younger patients.[88]

6.1.4.2 Limitations

There are several potential sources of bias in survival studies – particularly from cancer registries in low-income settings, which should be considered in interpreting these results.

Firstly, although all participating registries were population based, the level of completeness of ascertainment of incident breast cancer cases is not known. Although all registries, as members of AFCRN, are evaluated as registering 70% or more of the incident cancers in their population[32], only five were of a quality permitting their publication in Cancer Incidence in Five Continents for the relevant period.[419] Of course, this is only a source of bias if the cases missed by registration are non-random, with respect to their prognosis. Since few of the registries have access to (or use) death certificates from vital registration as a source of information, one might suppose that there was a differential loss of fatal cases, with resultant overestimation of survival probabilities. On the other hand, the inclusion of cases notified to the registry via death registration, which would otherwise have been missed (death certificate initiated cases), is known to bias survival in the opposite direction.[420,421]

Only one registry (Mauritius) relied entirely on passive follow-up (linkage with death certificates) to ascertain the vital status and identify cases that had died. This method potentially biases survival upwards, if there is a failure of record linkage, or cancer cases have migrated out of the registry area before dying. However, the registry actively followed up a 10% random sample of the breast cancer cases who were alive as per passive follow-up – none of them had died.

With active follow up, despite all attempts to trace cancer patients, a varying proportion are lost to follow up before the closing date of the study. Again, this is only a problem if these

cases are more, or less, likely to have died than those that were successfully followed up. In Abidjan, cases with advanced breast cancer were more likely to be LFU by year 3, but for the rest of the registries, among patients with known stage, LFU was non-differential by either stage or age at diagnosis.

However, there was a large proportion of patients with missing information on stage at diagnosis (53%), in spite of active follow-up done by registry staff. The proportion of patients with an unknown stage at diagnoses varied from 10% in Seychelles to 74% in Kyadondo, Kampala. Some of the possible reasons for the absence of stage information are challenges in record-keeping and inadequate resources to adequately stage patients (limited access and availability of financial resources to pay for these investigations as well as a limited plateau technique in some areas, lacking ultrasounds, x-rays, and computerised tomography (CT) scans). In high-income countries it has been shown that older patients are less likely to have exhaustive investigations compared with younger women,[422] however, in our context most of our patients are below age 55.

With respect to generalising the results to the populations studied, the size of the sampling fraction was relatively small for some registries, thus with larger uncertainty intervals for some registries.

In order to estimate the relative survival, national life tables were used to obtain the "expected" rates of death. Relative survival estimates above 100% were observed in some age groups (Table 6.3), indicating higher survival in this cohort of women coming from urban areas compared with that observed in the general population of women of the same age in the same country using country-specific life tables inclusive of both rural and urban areas. Also, the registries were categorized according to the country-level HDI, however, the level of development of an urban capital will be different from that of a rural setting. The countries with medium HDI represented were South Africa, Namibia, and Kenya. However, the majority of the patients in this category were from Eastern Cape, South Africa, which is a rural area,

with a level of development lower than that of South Africa as a whole. This could explain why little difference was observed between countries with medium and low HDI. However, correlations have been shown between national breast cancer Mortality-to-Incidence ratio (MIR) and country HDI with the use of GLOBOCAN 2012.[423,424]

Finally, other important predictors of survival were not adjusted for such as time to onset of therapy, treatment received, and the tumour biology.

6.1.4.3 Implications

Despite its limitations, this work produces estimates of survival by stage, not previously estimated from SSA using population-level data. Due to the absence of mortality data, modelled survival from mortality to incidence ratios from the USA black population scaled by the country-level HDI were used to make estimates for mortality for most SSA countries in GLOBOCAN 2018.[425] This work produces survival estimates from actual data from more registries, which could be used to inform public health authorities on population-level breast cancer survival in SSA and were used to improve models for breast cancer mortality from sub-Sahara Africa in GLOBOCAN 2020, as described in Chapter 2.[426]

6.2 Part II: Population-level breast cancer therapy and outcome in sub-Saharan Africa

The second part of this results chapter is focused on the therapy received by a subset of women from 11 PBCRs in SSA. The therapy received is compared with therapy guidelines and the association of therapy with short-term survival is explored.

The results presented in this section have been submitted to the Journal of the National Comprehensive Cancer Network and was accepted for publication in January 2021 as:

Joko-Fru. WY, Griesel M., Mezger NCS, et al. Breast Cancer Diagnostics, Therapy, and Outcome in sub-Saharan Africa: A Population-Based Registry Study.

At the time of thesis submission, this manuscript was still in press.

The primary data for this chapter was collected by the team of cancer registrars from the member PBCRs, who were supported in collecting more in-depth data on therapy by a team of final year medical students supervised by Dr Eva Kantelhardt, from the Martin-Luther University, Halle-Wittenberg. I spent 3 months at the Martin-Luther University, Halle-Wittenberg as an exchange student working with the team, to clean and homogenize the data before data analyses.

For this chapter, I analysed the data, produced the tables and figures, wrote the drafts of the manuscript, and made edits based on co-authors and reviewers' Comment.

6.2.1 Introduction

Approximately 7 in 10 women diagnosed in SSA present at advanced stages (stages III/IV)[13]; as discussed more comprehensively in Chapter 3. As a result, survival from breast cancer is relatively poor. However, there are survival differences between African countries, and some of these differences in survival are related to differences in stage at diagnosis and access to quality care.[14,15,156]

Breast cancer treatment is resource intensive. For non-metastatic breast cancer, the main pillars of therapy include loco-regional (surgery, radiotherapy) and systemic therapies (chemotherapy, endocrine therapy (if hormone-receptor-positive), and biological therapies/immunotherapies). In SSA, all these recommended treatment modalities are available in only a few state-of-the-art cancer facilities. Typically, accessibility to such institutions is limited to those who are residents of these areas, covered by health insurance schemes or who can afford to pay out-of-pocket. Few African nations have country-specific treatment recommendations, and most often, clinicians offer therapy options based on available local resources. The Breast Health Global Initiative (BHGI) has worked on developing and implementing context-specific guidelines for breast cancer control in LMIC

for nearly the last two decades.[427,428] In line with the work of the BHGI, The National Comprehensive Cancer Network (NCCN) developed resource-stratified therapy recommendations for SSA for the treatment of the most common cancers in order to facilitate therapeutic decision making for clinicians in resource-constrained settings.[17] There is limited information, however, on whether the breast cancer therapy received in SSA is concordant with these resource-stratified therapy recommendations.

Most information on breast cancer therapy and survival from SSA are from hospital-based reports, and these describe the survival of patients treated in cancer referral centres. However, what is not known is the experience of the general population of breast cancer patients in different settings (not only those reaching specialist treatment centres) by way of the therapy received and how this influences survival. To address this knowledge gap, this study was carried out. It included random samples of women from 11 sub-Saharan African PBCRs. The principal goals were to describe the cancer-directed therapy (CDT) received by women at population-level in SSA, compare these to recommended guidelines, and evaluate the impact on survival.

6.2.2 Methods

6.2.2.1 Study population and data source

The sampling frame was the database of the AFCRN.[16] After excluding cases registered based on a death certificate only, random samples of at least 40 patients with breast cancer (ICD-10: C50) per registry were drawn, of patients diagnosed in 2009-15, from 11 PBCR: Abidjan (Côte d'Ivoire), Bamako (Mali), Brazzaville (Congo), Bulawayo (Zimbabwe), Cotonou (Benin), Eldoret (Kenya), Kampala (Uganda), Maputo (Mozambique), Namibia, and Nairobi (Kenya). In Addis Ababa (Ethiopia), all cases diagnosed from January to March 2012 were included (Appendix 8). All included patients were African females who were residents of the registry area. The number of randomly selected cases per registry was determined by the practical feasibility of retrospectively tracing health records across multiple centres. All these

PBCRs cover a city, except for the Namibian cancer registry which covers the national territory. All the registries use the CanReg5 software developed by IARC for data entry and for verification checks.[33] Records were traced from the registry to the source of registration, and information on the date of diagnosis and stage were verified or updated, and any duplicates excluded. The registry records were updated with information on diagnostic procedures, treatment received, and patients' vital status from clinical records. However, if this information could not be found in clinical records, as a last resort, the patients or relatives were contacted by registry staff when a contact number was available. Patients whose data were updated from medical records or from active follow-up with additional data on diagnostics, therapy and/or outcome are subsequently referred to as "traced" patients.

Data entry and management was done using SPSS version 25 and data analyses were done with Stata version 14.2.

6.2.2.2 Explanatory and outcome measures

The main explanatory variable was the therapy received. The outcome measure was the patients' vital status at the closing date of the study. This was ascertained by active follow-up methods as described above. The observational time was the time from diagnosis to death, date of last contact, or until the close of the study, which ever occurred first. Patients not found to have died following active methods were censored.

6.2.2.3 Ethical considerations

The dataset received from the AFCRN was anonymized and encrypted. The study protocol was approved by the Research Committee of the AFCRN, by the individual registries, and by Martin-Luther-University Halle-Wittenberg Review Board. The study complied with the declaration of Helsinki.

6.2.2.4 Assessing Therapy

The NCCN Harmonized Guidelines for SSA for breast cancer version 2.2017[174] was used as a guide for therapy evaluation. In order to use the same classification categories as the NCCN guidelines, tumours were categorised into three stage groups for therapy evaluation: early stage breast cancer (Stages I, II and T3N1M0), locally advanced breast cancer (Stage IIIA (except T3N1M0), IIIB, IIIC) and metastatic disease (Stage IV, M1).[116] This classification system is based on the TNM classification system described in Chapter 3, however, patients with T3N1M0 tumours which is a stage IIIA tumour, are categorised as "early stage" in this section, to permit therapy evaluation using the NCCN therapy guidelines for SSA. Patients with early and locally advanced disease are subsequently referred to as with "curable" or non-metastatic disease. In addition to information on stage at diagnosis, in order to follow these therapy guidelines adequately, the HRS, and the tumour histology should be known.

It was verified if there was documented evidence that the patient initiated any cancer-directed treatment – surgery, chemotherapy, radiotherapy, hormonal therapy, or immunotherapy. To evaluate breast cancer surgery use, patients were categorised as having received surgery (either a mastectomy or a lumpectomy) or not. The proportion of patients who received any CDT was calculated (either of surgery, chemotherapy, radiotherapy, endocrine therapy, or targeted therapy). To assess the completeness of treatment with chemotherapy, chemotherapy was categorised as ">85% complete" if the patient received all but one prescribed chemotherapy session, as "≤85% complete" if the patient had 2 or more missed chemotherapy sessions,[429,430] as "none recorded" if the patient was traced but there was no record of chemotherapy found in medical records. The "unknown" category was used if the patient was not traced.

The completeness of radiotherapy could not be evaluated as the total dose received during radiotherapy was not recorded for most patients. The completeness of endocrine therapy

could not be evaluated as accurate data could not be obtained on endocrine therapy adherence and completion for a duration of five or more years.

A simplified classification schema based on the NCCN harmonized guidelines for SSA was used to evaluate the therapy received. Among traced patients with non-metastatic disease, the following categorisation system was used for therapy evaluation (Table 6.6):

Table 6.6: Therapy assessment guidelines used for patients with non-metastatic breast cancer in this study.

Category	**Classification criteria used in this study**	**Considerations**
Initiated adequate Therapy	Evidence of receiving: **Local therapy** – surgery with or without radiotherapy. A mastectomy with or without radiotherapy was considered as adequate local therapy, however for the few cases where a breast conserving surgery was done, a lumpectomy without radiotherapy was considered inadequate AND **Systemic therapy** – chemotherapy and/or hormonal therapy, depending on tumour hormone receptor status.	NB: If tumour size > 1cm (which is the case for all tumours in this study in the absence of systematic screening), or with node positive disease, systemic therapy after local therapy is a category 1 recommendation (based upon high level evidence)
Inadequate therapy (with no curative potential)	- No surgical therapy - Receiving a single therapy modality e.g., only surgery - No systemic therapy, where indicated	-
No therapy	No documented evidence of receiving any form of cancer-directed therapy.	

NB: This categorisation was adapted from the NCCN Harmonized Guidelines for Sub-Saharan Africa Version 2.2017 for Invasive breast cancer. In this version of the guidelines, radiotherapy was in grey which means – this was considered highly advanced/optimal care that may be costly or technically challenging in SSA.

For patients with metastatic disease, the therapy they received was described but without categorisation according to therapy guidelines.

6.2.2.5 Assessing Loss-to-follow up (LFU)

The proportion of patients lost-to-follow-up by registry at years 1, 3, and 5 was assessed using a Cox-regression model with LFU as the outcome, and age and stage at diagnosis as exposure variables; to determine if LFU was at random or associated with either age or stage at diagnosis.

6.2.2.6 Survival analyses

For estimation of survival, cases for whom the date of last contact was the same as the date of diagnosis, thus with no additional follow-up information were excluded, as well as cases diagnosed based on a death-certificate only. The observed all-cause Kaplan-Meier survival for all patients and by therapy received was estimated at years 1, 3, and 5 after diagnosis. The 3-year Ederer II relative survival by age, stage at diagnosis, therapy modality, and by country-level HDI were also estimated, using methods described more fully in part I of this chapter.

6.2.2.7 Modelling excess mortality

The excess breast cancer mortality rate was modelled in a relative-survival framework with a generalised linear model using a piece-wise Poisson regression model with smoothing splines. Time was split into monthly time bands. The relative excess risk of death from curable breast cancer, after taking into account the background mortality was thus evaluated. The background mortality was obtained from 5-year-age abridged WHO Global Health Observatory life tables, which was expanded from 5-year-ages (0-4, 5-9, 10-14, etc) to single-year ages (0,1,2,3, etc) using a Poisson regression model with a flexible function as in part I of this chapter. The estimates were adjusted for *a priori* confounders – age at diagnosis, stage at diagnosis, HRS, tumour grade, therapy, and country-level HDI. The cancer registries were grouped by their country-level HDI for parsimony and to improve the power of the multivariable model. All patients with at least 30 days follow-up and with non-metastatic disease were included in the multivariable models. Sensitivity analyses were carried out by

limiting the analyses to traced cases only and to registries with less than 50% LFU in the first year.

6.2.3 Results

6.2.3.1 Patient and tumour characteristics

809 patients from 11 PBCRs were included (“population-based cohort”); these patients represented a fifth of all incident breast cancer patients during the study period (Table 6.7). The median age at diagnosis was 48 years for all women. About 16% of our cohort were under age 35 at diagnosis, with 53% of patients under age 50 (Table 6.8). Additional information on stage, therapy, or vital status was obtained for 63.9% (517 records) of patients following active case finding (“traced cases”), and this proportion varied by registry (Table 6.7).

Table 6.7: Description of the population-based registries and patient population.

Registry	Country HDI 2015	Period of diagnosis	Number of BC cases	DCO during study period excluded (n, %)	No. of cases included (n)	Sampling fraction (%)	Traced cohort* (n, %)	Included for survival analyses (n, %)
Abidjan, Cote d'Ivoire	Low	2012 – 2013	531	23 (4.3)	66	12.4	50 (75.8)	53 (80.3)
Addis Ababa, Ethiopia	Low	2012	437	0 (0.0)	114	26.1	51 (44.7)	93 (81.6)
Bamako, Mali	Low	2012 – 2013	639	5 (0.8)	90	14.1	48 (53.3)	47 (52.2)
Brazzaville, Congo	Low	2012 – 2013	212	0 (0.0)	75	35.4	19 (25.3)	75 (100)
Bulawayo, Zimbabwe	Low	2012 – 2013	167	16 (9.6)	56	33.5	35 (62.5)	53 (94.6)
Cotonou, Benin	Low	2013 – 2014	132	0 (0.0)	92	69.7	85 (92.4)	92 (100)
Eldoret, Kenya	Medium	2009 – 2014	379	17 (4.5)	81	21.4	62 (76.5)	69 (85.2)
Kampala, Uganda	Low	2012 – 2013	283	8 (2.8)	58	20.5	35 (60.3)	41 (70.7)
Maputo, Mozambique	Low	2014 – 2015	81	14 (17.8)	43	53.1	34 (79.1)	41 (95.4)
Nairobi, Kenya	Medium	2012 – 2013	722	38 (5.3)	57	7.9	37 (64.9)	55 (96.5)
Namibia	Medium	2012 – 2013	454	0 (0.0)	77	17.0	61 (79.2)	64 (83.1)
Total		**2009 – 2015**	**4037**	**121 (3.0)**	**809**	**20.0**	**517 (63.9)**	**684 (84.6)**

*BC = Breast cancer, DCO = Death certificate only cases, HDI= Human Development Index, * Traced cohort = additional data on diagnostics, therapy and/or outcome found following active record finding*

Half of the registry records were traced to public hospitals, 14.7% to private hospitals and 35.2% could not be traced to a treatment facility (Table 6.8). The tumour grade was unknown for 53.4% of traced cases. The HRS was recorded for 17.5% of all women, and for 27.5% of the traced cohort. The HER2 status was unknown for approximately 75% of traced women (Table 6.8).

In the entire cohort of the 809 patients, the stage at diagnosis was known for 53.5% (433 women) (Table 6.8). Of those with known stage, 20.8% were metastatic at the time of diagnosis and 46.4% were diagnosed at Stage III. Less than 2% of cases were diagnosed with stage I disease. When limited to the traced cases stage at diagnosis was known for 405 patients, and 320 (79.0%) of these patients with known stage had non-metastatic disease at diagnosis (Table 6.8). Thus, approximately 1 in 5 patients with known stage at diagnosis, had metastatic breast cancer at time of diagnosis.

As concerns imaging for staging, imagery type was recorded in all registries apart from Addis Ababa. Less than 7% of patients had a record of using more advanced imagery tools such as a CT scan, a magnetic resonance imaging scan, or bone scintigraphy for tumour staging. Abdominal ultrasounds, chest, and bone x-rays were the most commonly used means of screening for metastases.

Table 6.8: Patient, tumour, and treatment characteristics in the population-based and traced cohort.

Patient characteristics	Categories	Number of cases in the population-based cohort (n = 809)	Percentage	Number of cases in the traced cohort (n = 517)	Percentage
Age at diagnosis	20-34	129	15.9	78	15.1
	35-49	300	37.1	196	37.9
	50-64	273	33.8	175	33.9
	65+	107	13.2	68	13.1
Additional information found	Yes (traced cohort)	517	63.8		
	No additional information except registry data	292	36.2		
Hospital type	Public hospital	405	50.1	385	74.5
	Private hospital	119	14.7	94	18.2
	Unknown	285	35.2	38	7.3
ECOG Performance Status	ECOG 0/1	144	17.8	144	27.8
	ECOG 2	31	3.8	31	6.0
	ECOG 3	19	2.4	19	3.7
	ECOG 4	4	0.5	4	0.8
	Unknown	611	75.5	319	61.7
Tumour size	≤ 5cm (T1 – T2)	120	14.8	110	21.3
	> 5cm (T3 -T4)	257	31.8	252	48.7
	Unknown	432	53.4	155	30.0
Nodal involvement	Present	89	11.0	85	16.4
	Absent	256	31.6	248	48.0
	Unknown	464	57.4	184	35.6
TNM stage	Stage I	12	1.5	10	1.9
	Stage II	130	16.1	119	23.0
	Stage III	201	24.8	191	36.9
	Stage IV	90	11.1	85	16.4
	Stage Unknown	376	46.5	112	21.7
Tumour grade	Grade I	32	4.0	32	6.2
	Grade II	124	15.3	124	24.0
	Grade III	85	10.5	85	16.4
	Unknown	568	70.2	276	53.4
Hormone receptor status	ER & PR negative	45	5.5	45	8.7
	ER/PR positive	97	12.0	97	18.8
	Unknown	667	82.5	375	72.5
HER2[H] status	Positive	43	5.3	43	8.3
	Negative	87	10.8	87	16.8
	Unknown	679	83.9	387	74.9
Therapy received	Surgery	332	41.0	332	64.2
	Chemotherapy	289	35.7	289	55.9
	Radiotherapy	135	16.7	135	26.1
	Endocrine therapy	148	18.3	148	28.6
	None recorded	102	12.6	102	19.7
	Unknown	292	36.1		

[I]*ECOG = Eastern Cooperative Oncology Group; ER=Oestrogen-receptor; HER2 = Human epidermal growth factor receptor 2 PR=Progesterone receptor*

6.2.3.2 Therapy characteristics

6.2.3.2.1 Therapy received and guideline adherence

In the population-based cohort, there was no record of any CDT for 48.7% of patients (12.6% of these were traced but without any therapy, and 36.1% records were not traced) (Table 6.9). More than 40% of patients from registries such as Eldoret (Kenya), Maputo (Mozambique) and Namibia initiated adequate therapy. However, in other registry populations such as in Cotonou (Benin), Brazzaville (Congo), Abidjan (Cote d'Ivoire), and in Kampala (Uganda), less than 20% of patients were recorded to have initiated adequate therapy (Figure 6.5).

There was no statistical association between age at diagnosis and therapy receipt, although there were lower proportions of women who initiated adequate therapy among patients aged 65+ (Figure 6.6).

When the analyses were limited to the traced cohort (N=517), there was no record of any form of CDT for 19.7% of patients (Table 6.8). Of these traced patients, 104 (20.1%) had recorded diagnostic information (stage at diagnosis and HRS) necessary for assessing therapy according to the NCCN recommendations, the main characteristic unknown was the HRS. The HRS was unknown for 72.5% of traced cases (Table 6.8). 40.5% of traced patients with early breast cancer and 58.2% of traced women with locally advanced disease received inadequate therapy with no curative potential or had no record of therapy (Table 6.9). In total, of all traced patients diagnosed with stage I-III breast cancer, 50.9% initiated inadequate therapy or received no CDT.

Table 6.9: Therapy characteristics for patients with breast cancer by stage at diagnosis, with stage classified following the categories used in the Harmonized NCCN Breast Cancer therapy guidelines for sub-Saharan Africa.

		Total cohort (n = 809)	**Traced breast cancer cohort (n = 517)**				
Therapy	**Characteristics of therapy**	**Number of patients (n, %)**	**Number of patients (n, %)**	**% With early stage[ǂ] (n = 163)**	**% With locally advanced cancer [♯] (n = 153)**	**% With metastatic cancer (n = 85)**	**%, Unknown stage (n = 112)**
Chemotherapy	Anthracycline based regimen (without a taxane)	149 (18.4)	149 (28.8)	36.8	26.8	27.1	21.4
	Anthracyclines & Taxanes	94 (11.6)	94 (18.2)	18.4	25.5	18.8	8.0
	Others	41 (5.1)	41 (7.9)	6.1	4.6	10.6	12.5
	CMF	5 (0.6)	5 (1.0)	1.8	0.6	0.0	0.9
	None recorded	228 (28.2)	228 (44.1)	36.8	42.5	43.5	57.1
	Not traced	292 (36.1)					
Surgery	Mastectomy	277 (34.2)	277 (53.6)	66.3	57.5	37.6	42.0
	Lumpectomy	43 (5.3)	43 (8.3)	10.4	3.3	5.9	14.3
	None recorded	197 (24.4)	197 (38.1)	23.3	39.2	56.5	43.7
	Not traced	292 (36.1)					
Radiation therapy	Yes	135 (16.7)	135 (26.1)	28.8	30.1	23.5	19.6
	None recorded	382 (47.2)	382 (73.9)	71.2	69.9	76.5	80.4
	Not traced	292 (36.1)					
Surgery and radiotherapy	Mastectomy and radiotherapy	102 (12.6)	102 (19.7)	25.2	22.9	9.4	16.1
	Lumpectomy and radiotherapy	6 (0.7)	6 (1.2)	2.4	0.7	28.2	0.9
	Mastectomy only	175 (21.6)	175 (33.8)	41.1	34.6	5.9	25.9
	Lumpectomy only	37 (4.6)	37 (7.2)	8.0	2.6	0.0	13.4
	No surgery	197 (24.4)	197 (38.1)	23.3	39.2	56.5	43.7
	Not traced	292 (36.1)					
Hormone therapy	Yes and HRS+	74 (9.3)	74 (14.3)	22.7	13.7	7.1	8.9
	Yes and HRS unknown	70 (8.6)	70 (13.5)	15.3	13.1	14.1	11.6
	Yes and HRS-	4 (0.5)	4 (0.8)	0.6	0.0	1.2	1.8
	No and HRS+	23 (2.7)	23 (4.4)	4.9	4.6	2.3	4.5
	No and HRS-	41 (5.1)	41 (7.9)	8.6	8.5	12.9	2.7
	No and HRS unknown	305 (37.7)	305 (59.0)	47.9	60.1	62.4	70.5
	Not traced	292 (36.1)					
Targeted therapy	Yes and HER2+	8 (1)	8 (1.5)	2.4	0.7	2.3	0.9
	No and HER2+	35 (4.3)	35 (6.8)	11.7	3.9	9.4	1.8
	No and HER2-	87 (10.7)	87 (16.8)	20.9	19.6	7.1	14.3
	No and HER2 unknown	387 (47.8)	387 (74.9)	65.0	75.8	81.2	83.0
	Not traced	292 (36.1)					
All CDT received	Surgery + Systemic therapy +/- radiotherapy	234 (28.9)	234(45.3)	59.5	41.8	36.5	36.6
	Surgery without systemic therapy /monotherapies / therapy combination without surgery	181 (22.4)	181 (35.0)	27.0	39.2	42.3	34.8
	No therapy	102 (12.6)	102(19.7)	13.5	19.0	21.2	28.6
	Not traced	292 (36.1)					

[ǂ] *Early Stage= Stages I, II, T3N1M0;* [♯] *Late Stage = Stages IIIA apart from T3N1M0, IIIB, IIIC; CMF: Cyclophosphamide Methotrexate 5-Fluorouracil. CDT: cancer-directed therapy HRS: Hormone receptor status; HER2= Human epidermal growth factor receptor 2; NCCN=National Comprehensive Cancer Network. For 4 patients the stage at diagnosis was recorded as stage III, without additional details thus could not be dichotomised for this table and thus not included.*

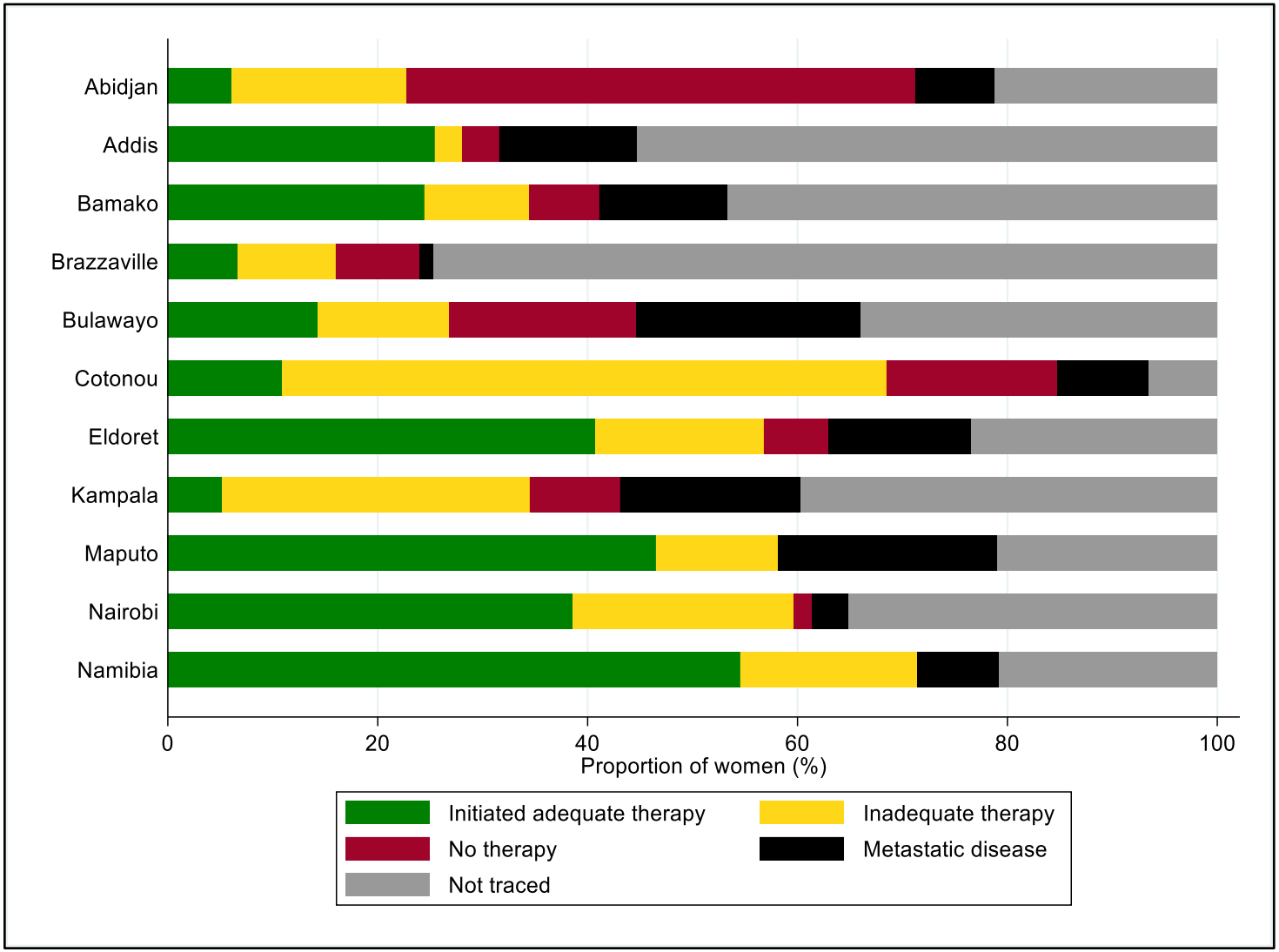


Figure 6.5: Therapy received by women of all stages with breast cancer by registry area (N=809).

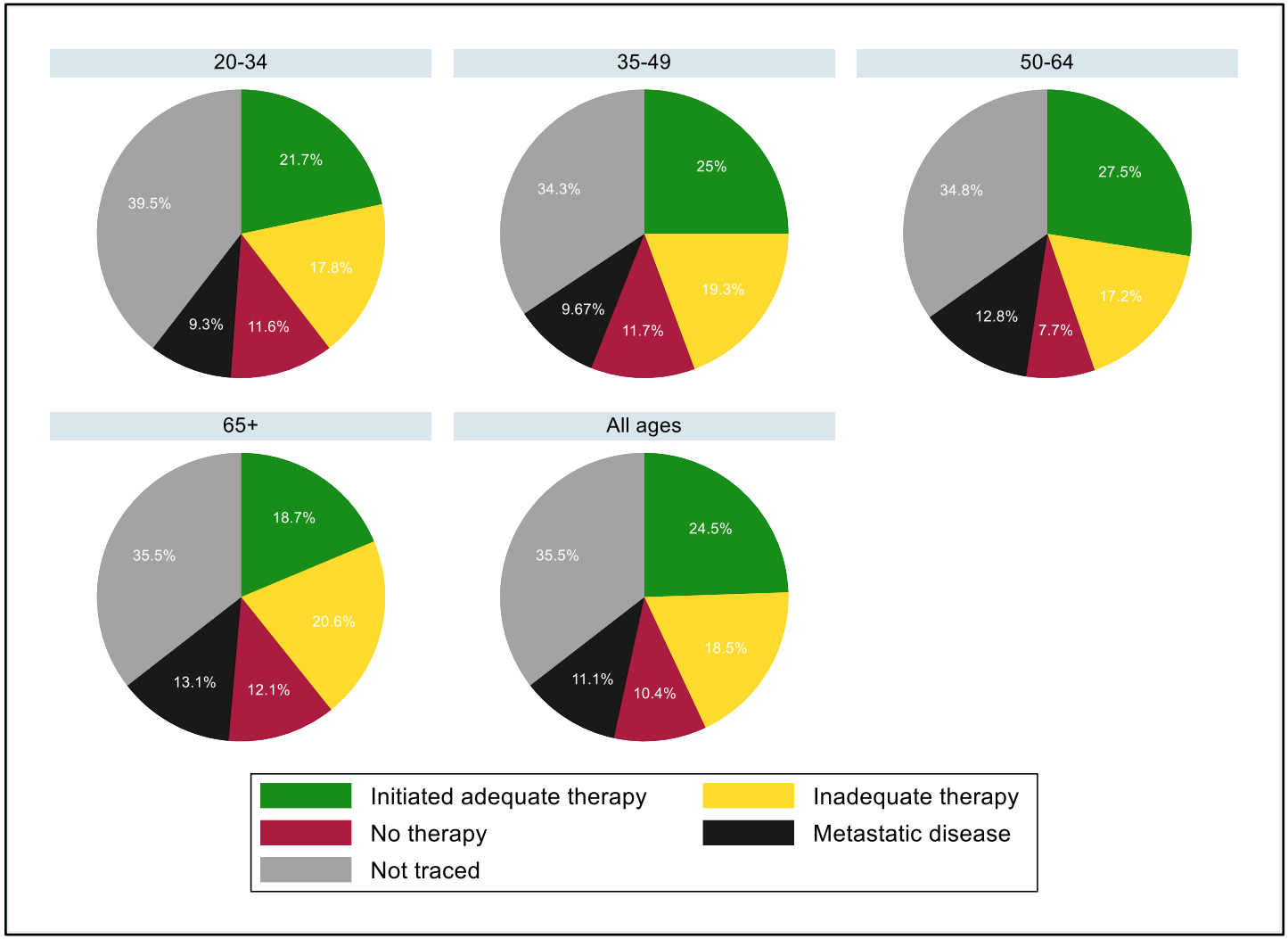


Figure 6.6: Therapy receipt by age at diagnosis among women of all stages with breast cancer (N=809).

Surgery

Surgery was the most available form of therapy, with a surgical intervention documented for 41.0% of all women, and for 64.2% of the traced cohort (Table 6.8). Of the 517 traced patients, 53.6% had a mastectomy, 8.3% had a lumpectomy and 38.1% had no surgery recorded (Table 6.9). Of those who had surgery recorded, 86.6% had a mastectomy. However, the type of mastectomy (simple, modified radical, or radical) was not always specified, and neither were details on surgical axillary node staging and dissection.

Systemic therapy

55.9% of the traced cohort (289 women) had a record of chemotherapy, (Table 6.8). Of those who had chemotherapy recorded, 51.6% had an anthracycline-based regimen, 32.5% had an anthracycline with a taxane while the other patients received different combinations of drugs.

28.6% of the traced cohort received endocrine therapy (Table 6.8). 13.5% of patients with receptor status unknown, received endocrine therapy. However, 4.4% of patients who had receptor-positive disease had no record of receiving endocrine therapy. More patients diagnosed at early stages had a record of receiving endocrine therapy (Table 6.9).

Radiotherapy

Approximately one in four traced patients received radiotherapy as part of their treatment regimen (Table 6.9). Approximately one in five traced patients had radiotherapy after mastectomy. Of the 43 patients who had a lumpectomy, only six of these received radiotherapy following lumpectomy (Table 6.9). The proportion of patients who received radiotherapy varied by registry area.

Immunotherapy

In the traced cohort, 35 patients (6.8%) who were HER2 positive, received no therapy with monoclonal antibodies such as trastuzumab (Table 6.9). The use of trastuzumab was recorded for eight patients in the entire cohort, five of them were from Namibia.

6.2.3.3 Loss to follow-up (LFU)

LFU was highest in the first year after diagnosis (Table 6.10), and the proportion varied by registry area. Namibia had the lowest fraction of patients LFU following diagnosis. The median follow-up time ranged from less than one year in Brazzaville, Bulawayo, and Cotonou to almost five years in Namibia. LFU was not differential by age or stage at diagnosis among patients with known stage. However, for patients with unknown stage, there was a more than 2-fold increased risk of being LFU compared with patients diagnosed at an early stage.

Table 6.10: Median age at diagnosis, proportion of deaths and loss-to-follow-up in the first three years after diagnosis by registry index.

Registry	Cases included for survival analyses	Median age at diagnosis	Year 1		Year 2		Year 3		Median follow-up time (years)
			Deaths (%)	LFU (%)	Deaths	LFU	Deaths	LFU	
Abidjan	53	48	3 (5.7)	24 (45.2)	2 (3.8)	5 (9.4)	1 (1.9)	0 (0)	1.0
Addis	93	44	3 (3.2)	29 (31.2)	7 (7.5)	4 (4.3)	7 (7.5)	4 (4.3)	2.7
Bamako	47	45	13 (27.7)	7 (14.9)	5 (10.6)	3 (6.4)	4 (8.5)	1 (2.1)	1.2
Brazzaville	75	52	8 (10.7)	51 (68.0)	2 (2.7)	2 (2.7)	2 (2.7)	1 (1.3)	0.5
Bulawayo	53	57	19 (35.8)	15 (28.3)	9 (17.0)	2 (3.8)	2 (3.8)	3 (5.7)	0.7
Cotonou	92	47	12 (13.0)	42 (45.7)	8 (8.7)	3 (3.3)	5 (5.4)	2 (2.2)	0.7
Eldoret	69	47	10 (14.5)	13 (18.8)	11 (15.9)	5 (7.2)	2 (2.9)	3 (4.3)	1.5
Kampala	42	46	9 (21.4)	11 (26.2)	6 (14.3)	2 (4.8)	5 (11.9)	0 (0.0)	1.0
Maputo	41	49	5 (12.2)	11 (26.8)					1.3
Nairobi	55	51	1 (1.8)	19 (34.5)	4 (7.3)	6 (10.9)	4 (7.3)	1 (1.8)	1.8
Namibia	64	52	3 (4.7)	5 (7.8)	2 (3.1)	2 (3.1)	6 (9.4)	1 (1.6)	4.7
Total	**684**	**48**	**86 (12.6)**	**227(33.2)**	**56 (8.7)**	**34 (5.3)**	**38 (5.9)**	**16 (2.5)**	**1.2**

N: Number of patients; LCI: Lower Confidence Interval; UCI: Upper Confidence interval LFU: Lost-to-follow-up.

6.2.3.4 Survival

The overall observed survival in this cohort was 84.0% (80.5-86.9) at year-1, 58.9% (54.0-63.5) at year-3 and 47.2% (41.1-53.1) at year-5 (Figure 6.7). Patients with non-metastatic breast cancer who received adequate therapy had better overall survival compared with patients who received inadequate or no therapy (log-rank test: $p<0.001$) (Figure 6.7). Figure 6.7 also shows the overall survival for patients with metastatic disease, showing the poorest survival rates irrespective of therapy received.

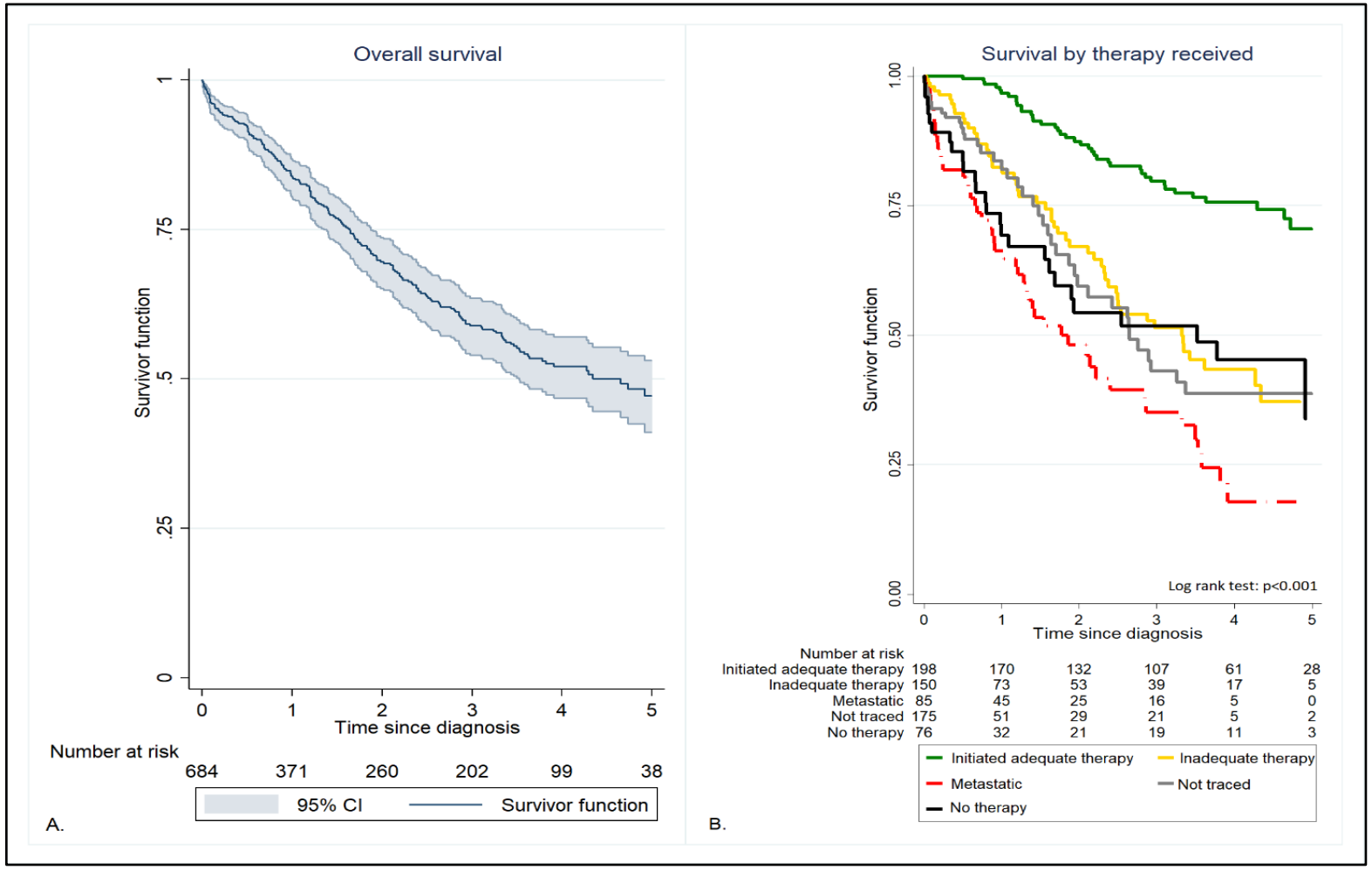


Figure 6.7: Overall (all-cause) survival in (A) the population-based cohort and (B) by therapy received.

6.2.3.5 Excess mortality from non-metastatic breast cancer

The excess mortality rate ratio among women with non-metastatic disease and with at least 30 days of follow-up was estimated. The age at diagnosis was not an independent prognostic factor after adjusting for the effects of stage, tumour grade, therapy, and registry country-level HDI (p=0.389) (Figure 6.8). Being diagnosed at stage III compared with stages I&II was associated with a more than 3-fold excess mortality risk (RR=3.33, 95% CI: 1.81-6.11). Patients who received inadequate or no therapy had more than double the mortality rates compared with patients who initiated adequate therapy. Mortality risk did not differ by registry HDI (low vs medium), after controlling for therapy received, age, and stage at diagnosis (p=0.358) (Figure 6.8).

Concerning specific therapy modalities (Figure 6.9) not receiving surgery was associated with an increased risk of death compared with patients who had surgery (RR=1.67, 95% CI: 1.06-2.65, p=0.027). Having sub-optimal chemotherapy was associated with a more than 2-fold increased risk of death (RR=2.38, 95% CI:1.24-4.57) compared with patients who received more than 85% of the prescribed chemotherapy regimen. Receipt of radiotherapy was not associated with a difference in mortality risk (RR=1.12, 95% CI: 0.63-2.00, p=0.704). Non-receipt of endocrine therapy was associated with a 3-fold increased mortality risk (RR= 2.93, 95% CI: 1.42-6.03, p=0.0008). Limiting the analyses just to the traced cohort and excluding Brazzaville (with more than 50% loss-to-follow-up at year 1), these observed associations remained unchanged.

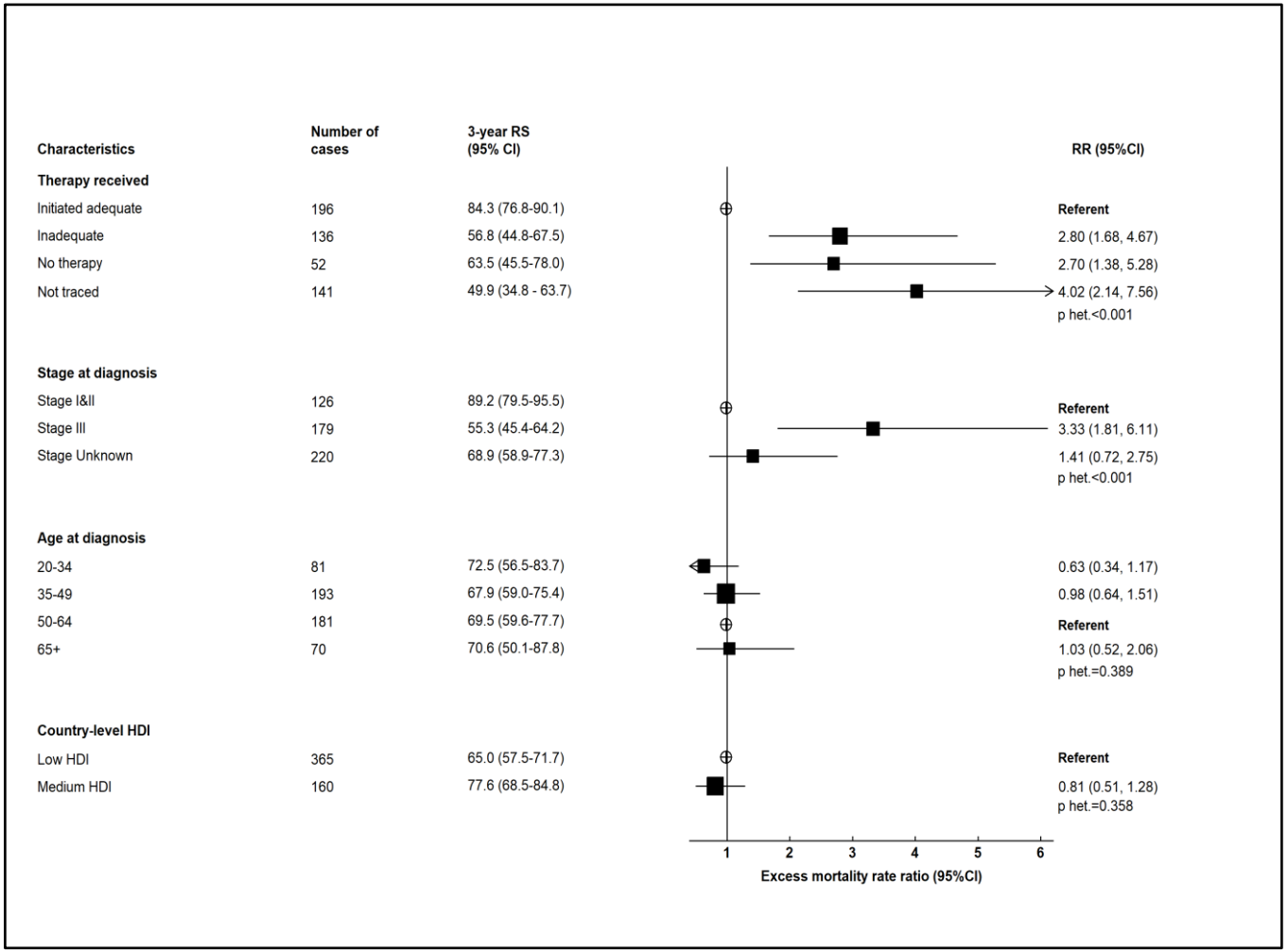


Figure 6.8: 3-year relative survival and excess risk of death from breast cancer among women in the population-based cohort without known metastases and with at least 30 days of follow-up (N=525) adjusted for therapy, stage, age, and country-level HDI.

p. het = p for heterogeneity

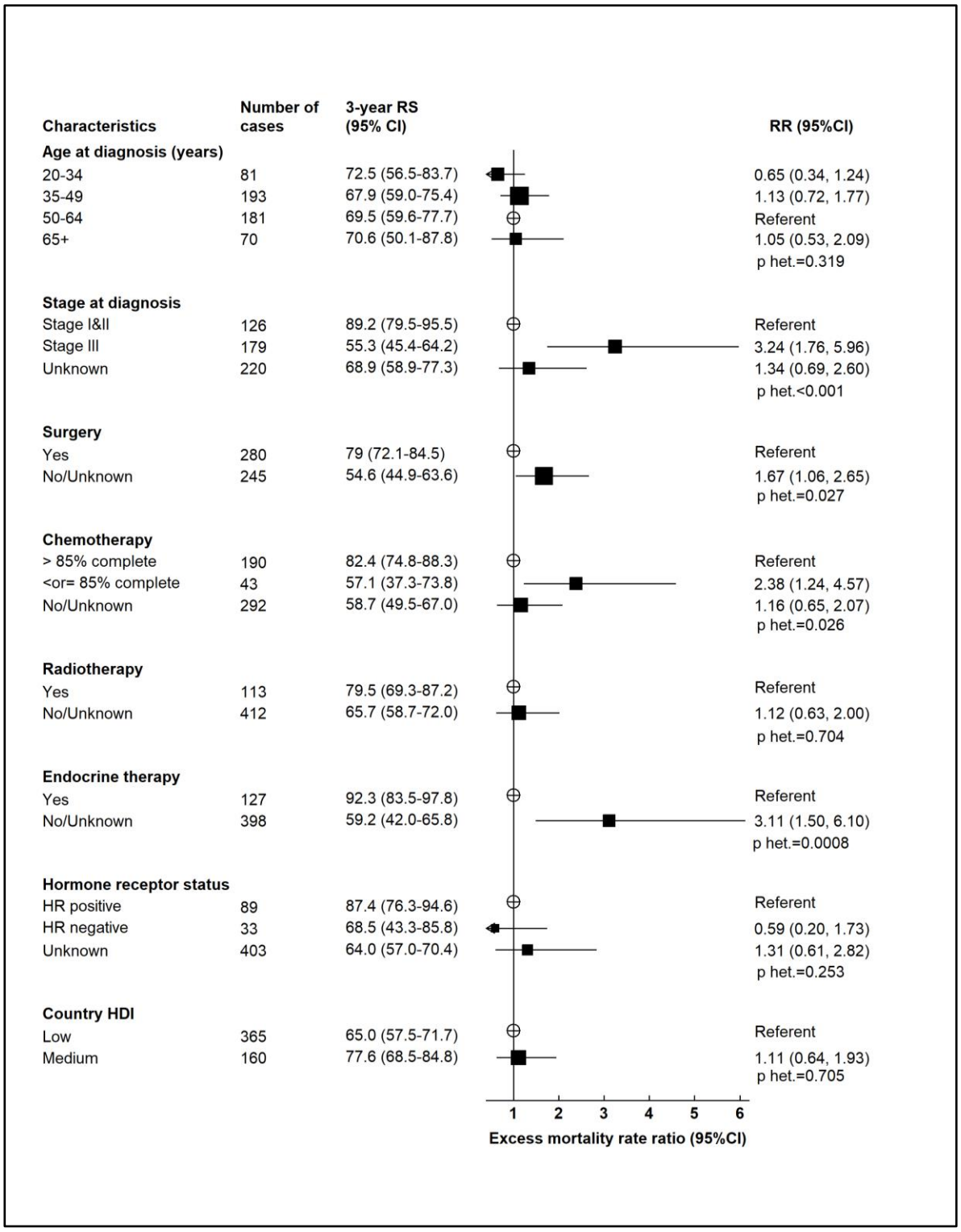


Figure 6.9: 3-year relative survival (RS) and excess risk of death from breast cancer among women in the population-based cohort without known metastases and with at least 30 days of follow-up (N=525) by specific treatment modalities. Adjusted for age, stage, registry area and country-level HDI.

RR= rate ratio p. het = p value for the test for heterogeneity

6.2.4 Discussion

6.2.4.1 Main findings in the context of previous studies

This study shows the tenuous situation of women with breast cancer in SSA as the majority of patients are diagnosed at advanced-stages and only a small proportion received guideline-concordant therapy. Of 809 women from 11 PBCRs in 10 countries, 517 patient records (63.9%) were traced and updated with details of diagnostics, therapy, and vital status. Of traced patients with non-metastatic disease, 50.9% received inadequate or no CDT. Of all traced patients, the HRS was known for 27.5% of patients, making the use of current therapy guidelines challenging.

Adequate breast cancer therapy requires a multi-disciplinary or multimodal approach and is resource intensive. It requires both loco-regional (surgery and radiation therapy) and systemic therapies (chemotherapy, hormone therapy, and immunotherapies). Many of the women in this cohort received only fragmented care or none at all. Limited access to these main forms of therapy have been described in SSA,[431] linked to both geographical and financial inaccessibility, with a majority of women having to pay out-of-pocket for healthcare.[176,432] In this study, surgery was the most available therapy option, with 64.2% of women in the traced cohort having a record of surgery. Still, many women never received surgery – due to either inoperable or stage IV disease, fear of disfigurement, lack of access to surgery, or options to use neoadjuvant chemotherapy.[433] Surgery is the cornerstone of treatment for resectable breast cancer control, and plays an important role in the treatment of more advanced stages of breast cancer in combination with other therapy modalities. In low-resource settings, surgery may be the only available therapy option in the absence of facilities for other therapy modalities.[165] Access to timely, and quality breast cancer surgery is pivotal for breast cancer treatment, especially for resectable disease. Initiatives to task-share surgical care to lower-level health facilities have been proposed to increase the accessibility of this essential intervention.[169] The main type of surgery received was a

mastectomy, in line with recommendations for areas with limited access to radiotherapy. However, in terms of emotional and social coping, mastectomy is often difficult for patients,[434] particularly for young patients in the absence of counselling and with limited access to reconstructive surgery.

Concerning radiotherapy, in 2010, it was estimated that in Africa, there was less than 1 radiotherapy machine per million people, compared with almost 15 radiotherapy machines per million people in Northern America.[170] Even within Africa, there are significant disparities of access: 60% of radiotherapy facilities are found in Southern and Northern Africa, with 23 countries without any radiotherapy facilities.[170] The NCCN guidelines for SSA (version 2.2017) acknowledge in their therapy recommendations this deficit and present therapy guidelines that could be followed in the absence of radiotherapy facilities. A majority of the patients in our cohort are candidates for radiotherapy, however, only 1 in 4 traced patients received radiotherapy. Of the 10 countries included, radiotherapy was available in only five of these countries at the time of the study: Ethiopia, Kenya, Namibia, Uganda, and Zimbabwe. A few patients from registries without in-country radiotherapy had travelled abroad to receive the treatment. Radiotherapy is not only necessary for curative purposes but also for palliation, as approximately 70% present at advanced stages with limited access to opioid analgesics in the region.[172,435] Radiotherapy further decreases the risk of loco-regional recurrence and mortality for women with node-positive breast cancer after mastectomy and axillary clearance.[436] Results from the EBCTCG showed that, among women with early breast cancer and 1-3 positive lymph nodes, radiotherapy reduced locoregional recurrence by 32% (RR:0.68, 95% CI: 0.57-0.82) and reduced mortality by 20% (RR=0.80, 95% CI: 0.67 – 0.95) 10 years after diagnosis. Among women with 4 or more lymph nodes, radiotherapy reduced locoregional recurrence by 21% (RR= 0.79, 95% CI: 0.69 – 0.90) and mortality rates by 13% (RR = 0.87, 95% CI: 0.77-0.99).[436]

Systemic treatment for breast cancer is most often coordinated by specialists. In a review of the oncological workforce worldwide, it was estimated that in 25 of the 32 African countries represented, there was approximately one clinical oncologist per 1000 incident cancer diagnoses.[167] Of the countries included in this study, this number ranged from one clinical oncologist per 325 incident cases in Namibia to one per 10,167 incident cases in Ethiopia. In the United States, there is approximately one clinical oncologist per 137 incident cases. Chemotherapy is not readily available: of the traced cohort, 42.5% of patients with locally advanced cancer received no chemotherapy. A majority of patients received an anthracycline-based chemotherapy, however, survival differences by these chemotherapy regimens were not compared, given the absence of detailed information on dosage and dosing intervals for adequate categorisation into 1st, 2nd or 3rd generation polychemotherapy. Receiving suboptimal or no chemotherapy was associated with a poorer prognosis compared with patients who completed their treatment regimen. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of randomised controlled trials (RCTs) showed that 6-months of anthracycline-based chemotherapy reduced mortality by approximately 38% among women <50 years, and by approximately 20% among women 50-69, independently of the effect of tamoxifen, or the ER status. However, women included in the EBCTCG trials had early-stage disease- stages I, II, and IIIA, which comprised 40.6% of this patient population.[437] As concerns endocrine treatment, it is effective for HRS-positive tumours, has relatively fewer side effects in comparison with chemotherapy, and could be available at comparatively low costs. However, the HRS was unknown for 72.5% of the traced cases. In some of the registry areas included in this study, there was only one (Addis Ababa, Cotonou) or no (Bamako) laboratories with immunohistochemistry facilities for HRS testing.[175] The NCCN therapy guidelines, version 2.2017 for breast cancer treatment in SSA present the standard-of-care situation with availability of HRS and do not make treatment recommendations when the HRS is unknown.[174] Previous recommendations have suggested giving endocrine therapy to

women with locally advanced disease even with unknown HRS.[438] Patients with non-metastatic breast cancer who did not initiate endocrine therapy had a more than 3-fold increased mortality rates compared with patients who did, after accounting for the effect of stage and other therapy modalities. The meta-analysis of clinical trial results from the EBCTCG showed that, among women with early-stage breast cancer, allocation to 5-years of adjuvant tamoxifen reduced annual mortality by 31%, irrespective of chemotherapy or age or tumour characteristics. It also significantly reduced the risk of recurrence.

In general, oncological surgery can be performed in most general hospitals, and systemic therapy is generally available in many tertiary services. Radiotherapy on the other hand, requires specialised facilities and staff, and this makes access challenging in many parts of SSA. Access to these different treatment modalities varied by registry, as seen in Figure 6.5. Of the registries included in our study, the Namibian national health care system provides free therapy for cancer patients,[439] including transport service to and from remote areas. This seems to be reflected in actually seeing the highest proportion of patients who initiated adequate therapy (Figure 6.5). Such government policies may serve as an example for best-practice in access to "oncology health service for all" who most likely otherwise fall out of the system. Less comprehensive or non-existent health coverage at public hospitals for all the other registries at the time of this study probably contributed to high disparities in access to adequate healthcare within countries. Even where government subsidies exist, medication shortages, indirect medical costs, and breakdown of radiotherapy machines make completing therapy challenging,[440] as well as the indirect costs of transport, accommodation, and supportive therapy.

In a recent hospital-based study – the African Breast Cancer – Disparities in Outcome study- which included 2,228 prospectively included breast cancer patients, the survival effects of different risk factors were presented including the impact of late-stage, lack of treatment,

tumour biology, positive HIV status, and age. Notably, little education, poor awareness, rural residence, and low socio-economic status were associated with poorer survival outcomes. From this study, they showed that survival improvement (up to 22%) is achievable through down-staging and availability of basic treatment. Namibians showed much better outcomes compared with patients from South Africa, Uganda, Zambia, and Nigeria.[156] This better 3-year survival for Namibian patients is similar to findings from the population-based registries included in this current study.

6.2.4.2 Limitations

A key limitation of our study is its retrospective nature, which is prone to biases. All potential and known confounders were not measured and controlled for – for example - time until onset of therapy (delay), as this was not consistently recorded for many cases. Other factors that could influence survival, such as adherence to endocrine and radiotherapy, comorbidities, molecular tumour type, nutritional status, as well as psychosocial factors influencing acceptance of diagnosis and therapy were not measured and adjusted for. There is also the risk of reverse causation in the associations observed - some patients may not have completed therapy due to side effects from the prescribed therapy, with inherent increased mortality in the absence of state-of-the-art supportive treatment for side effects such as severe neutropenia or sepsis. Also, relatively large proportions of patients were lost to follow-up in the first year after diagnosis, despite the active methods used to ascertain their vital status, which could result in an overestimation of survival. This high proportion of LFU is linked to a lack of schemes for patient navigation and retention and equally poor record keeping in some of these health systems. Furthermore, the sample size although random, was relatively small, with less power to fully explore some of the associations observed.

There is also the risk of immortal time bias in some of the associations seen,[441] e.g. only women who survived long enough post-surgery could be prescribed systemic therapy. To minimize this bias, patients who died or were LFU within the first 30 days of diagnosis were

excluded from the regression models. A correlation between the severity of disease and choice of therapy or “confounding by indication” is a challenge in observational studies.[442] The relative contribution of different therapy modalities to survival would ideally be disentangled with the use of RCTs. However, RCTs to measure the outcomes in relation to the basic therapy options we investigate are not ethically feasible – thus observation and sensible deduction is the only course available, with very careful interpretation of any observed associations between prognostic factors and outcome. Records of 36.1% of cases registered in the population-based registries could not be traced to a treatment facility -some of these patients never actually initiated therapy. However, inadequate paper-based record systems and the absence of technological frameworks to facilitate record linkage could be a reason for the lack of tracing.

6.2.4.3 Implications

Despite its limitations, this study provides a clearer picture of the actual therapy received by a random sample of women with breast cancer in SSA at a population-level, not simply among patients attending reference treatment centres. Women were included from both public and private institutions from 10 SSA countries, as well as patients with no record of therapy, reflecting different pathways to care. And thus, providing more information on the therapy routinely received by women in SSA and how this influences their survival.

In SSA, a majority of women are diagnosed before age 50, with a less than 50% chance of surviving 5 years after diagnosis. Improving access to adequate cancer therapy to prolong life, prevent recurrence, reduce stigma, and alleviate pain is necessary. Adequate therapy requires awareness of therapy options, the willingness to receive conventional medical therapy, the availability of these resources locally, and the means to finance health care. The study sites included are almost all large urban centres; access to care would even be poorer in rural settings, with more limited awareness, fewer health facilities, longer travel time to access care, and even lower ability to pay for health care.

It would be imperative to improve record-keeping and data management facilities to support patient monitoring and retention; as well as to facilitate cancer surveillance and observational research in these resource-poor settings. Downstaging breast cancer and facilitating access to quality care are necessary to improve cancer survival outcomes in SSA. An inherent challenge remains of financing health care in some of these low resource settings.

Thus, although therapy guidelines are useful tools to help ensure good quality cancer care in LMIC, patients in these resource-poor settings still face challenges such as differences in access to quality cancer care and the limited access to IHC services locally [175] which makes following therapy guidelines challenging and is associated with poorer survival outcomes.

6.3 Conclusion

This chapter reports population-level survival estimates from a greater number, and variety, of populations in SSA than have hitherto been available. It highlights survival differences at population-level across SSA and explores some reasons for the differences observed. Late presentation and differences in access to cancer care are important drivers of these cancer survival differences. It also illustrates challenges of guideline adherence, and the disparities in access to quality cancer care in a random sample of women from the general population of urban SSA.

Chapter 7. Summary, implications for future research, and conclusion

7.1 Introduction

As stated in Chapter 1, the main aim of this thesis was to describe the burden and trends in cancers of the breast in SSA. Specifically, I set out to:

- Measure changes in the breast cancer incidence rates across different regions of SSA.
- To explore possible drivers of the changes in the breast cancer incidence rates observed across SSA.
- To estimate the population-level survival outcomes of women diagnosed with breast cancer across different regions of the sub-Saharan African continent at 1, 3, and 5 years after diagnosis and to determine reasons for survival differences at population-level observed across SSA.

This final chapter presents an overview of the key findings from this thesis, discusses the limitations of this thesis, and proposes recommendations for further research.

7.2 Summary of research findings

In this thesis, I used primary data from population-based registries to do a more in-depth study of the population-level burden and trends in breast cancer in SSA than had been published previously.

Chapters 1, 2, and 3 comprised the background and the literature review chapters. Chapter 1 presented the overall aim and objectives of this thesis. In chapter 2, I described the available sources of data for the measurement of the cancer burden in SSA and discussed the limitations of the available data sources. It also described methods for evaluating the quality of PBCRs. In chapter 3, a descriptive summary of the breast cancer epidemiology in SSA was

presented. I described the current evidence from SSA on breast cancer incidence, stage at diagnosis, biology, survival, therapy, risk factors, and control measures.

The results presented in chapter 4, describe data on breast cancer temporal trends from 11 PBCRs. Temporal data from seven of these registries had not been published before, and for the other four PBCRs for which trend data had been published - Kampala (Uganda), Harare (Zimbabwe), Gambia and from Eastern Cape (South Africa) - updated time trend analyses were done. The temporal trends were studied stratified by pre- and post-menopausal status at diagnosis, using age-50 as a proxy; similar analyses using PBCR data from SSA had not been published before. This chapter shows disparities in the burden of breast cancer across different African cities and communities. The AAPC reveals rising breast cancer incidence trends, although the rate of increase differs across registries. There are higher age-standardised incidence rates for women aged 50 and above, in all registries. However, due to the age structure and distribution of the African population, there is a higher proportion of women diagnosed before age 50. There are also generational effects in the observed incidence rates with progressively higher incidence rates observed in women of the same age, born in successive generations among women 45 and above in Kampala (Uganda) and Harare (Zimbabwe). Chapter 4 also presents historical data from Bulawayo (Zimbabwe) from the 1960s as well as the breast cancer incidence data in more recent years, highlighting a nearly 3-fold increase in the breast cancer burden over the last six decades in this African city. Similar to results from GLOBOCAN, this chapter shows differences in the magnitude of breast cancer incidence rates across SSA, however, where GLOBOCAN uses estimates of national incidence, this thesis presents the actual population-level data from mostly urban PBCRs.

These differences in the incidence burden observed in Chapter 4, led me to investigate what may be the drivers of the breast cancer incidence trends in SSA, and what studies have been carried out on the sub-Saharan African continent to investigate breast cancer risk factors.

The systematic review reported in chapter 5, showed that, at present, there have been no cohort studies designed to investigate the aetiology of breast cancer on the continent. Only 38 case-control studies which reported on anthropometric, reproductive, or lifestyle risk factors from 10 SSA countries met the inclusion criteria. Studies were included from 1975 to July 2020. Of these studies, two studies reported their findings by the tumour HRS. As concerns reproductive factors, similar to studies from Western and African American populations, the largest of the included SSA studies report an increased breast cancer risk with a decrease in age at menarche; an increased risk with later age at first birth, a decreased breast cancer risk with parity, a decreased risk with increased duration of breastfeeding, and an increased risk with the use of injectable and oral contraceptives. There were only six studies which explored the relationship between age at menopause and breast cancer risk, however half of these were of high risk of bias, as they did not adjust for covariates. Contrary to literature from Western populations, the largest of the included studies which reported on the association between parity and breast cancer risk (Sighoko et al. 2015) found no transient increase in breast cancer risk after first birth.[312] This may be because of the relatively younger age at first birth observed in SSA, given that in the pooled analyses of Western cohort studies reported by Nichols et al. 2019, this transient increase in risk was observed if age at first birth occurred after age 25. However, the study by Sighoko et al. 2015 reported this protective effect after first birth irrespective of age at first birth.[312]

As concerns anthropometric factors, the association between height and breast cancer risk was reported in two Nigerian study populations, and similar to Western studies, the pooled analyses show an increased risk with height. The association between weight and breast cancer was reported in three studies, but only one study stratified their results by menopausal status (Ogundiran et al. 2010). Ogundiran et al 2010 found that weight at diagnosis was not significantly associated with breast cancer when stratified by menopausal status.[210] When the association between BMI and breast cancer was studied, the largest included study report

similar findings to Western populations with a protective effect with increasing BMI among women with pre-menopausal breast cancer, however, contrary to studies from Western populations, an increasing BMI was associated with a non-significant protective effect among women with post-menopausal breast cancer. None of these studies reported these associations by hormone-receptors status. Only one study reported on the association between young adult BMI and breast cancer risk. Two studies reported on the association between the WHR and breast cancer among Nigerian women. They found an increase in risk with increasing WHR among women with pre- and post-menopausal breast cancer. Given the relatively advanced stage at diagnosis of breast cancer in SSA, it is probable that anthropometric factors such as weight, BMI, and WHR at diagnosis may have been influenced by the disease process.

As concerns lifestyle factors, the largest of the included studies (Qian et al. 2014) report an increased risk with alcohol use among women with pre- and post-menopausal breast cancer.[443] The association between physical activity and breast cancer was reported in three study populations, and they report a decrease in risk with increased physical activity.

Thus, these findings from SSA studies, are largely similar to studies from Western populations. However, relatively few African countries were represented in this review, with large studies from Ghana, Nigeria, and South Africa, but with no studies from approximately three-quarters of SSA countries.

In the second part of chapter 5, an overview of the population-level prevalence of these studied breast cancer risk factors is described. There are differences in the prevalence and distribution of these risk factors across SSA, which may be partly responsible for the differences in the magnitude of the breast cancer incidence burden observed. However, it must be emphasized that the reported population-level surveys are at an ecological level, thus do not tell us specifically about the patients from these mostly urban population-based registries. The real estimates from the urban areas may be different or higher for some of

these risk factors associated with Westernization. There are, however, increases at population-level of the prevalence of some risk factors in these SSA countries for example, increases in the prevalence of obesity, decreasing age at menarche, decreased fertility rates, and an increase in the uptake of contraceptives in some countries. This changing risk factor prevalence would influence the breast cancer burden in future years. This review focused on anthropometric, reproductive and lifestyle factors, however, other risk factors were not studied such as the influence of diet, genetics, and environmental factors.

With the rising incidence rates, it was necessary to investigate the survival of women with breast cancer from these registries. In chapter 6, I explored determinants of breast cancer survival at population-level from 12 countries for which we had follow-up information from the population-based registries. In the absence of cause-specific mortality rates, the relative survival was used to estimate the excess mortality from breast cancer for sub-Saharan African women. This revealed disparities in survival within SSA. Women from countries of high HDI had better survival rates compared with women from countries of low and medium HDI even after adjusting for the effect of age and stage at diagnosis. Age at diagnosis was not shown to be significantly associated with survival outcomes, contrary to what is observed in Western countries. The stage at diagnosis was not known for 53% of included women, and there was a large proportion of loss-to-follow-up particularly in the first year after diagnosis. The overall relative survival for this cohort of women was 86.1% (95% CI: 84.4-87.6) at year-1, 65.8% (95% CI:63.5-68.1) at year-3, and 59.0% (56.3-61.6) at year-5, but with large differences between countries, ranging from a 3-year relative survival of 21.6% (95% CI: 8.2-39.8) in Bulawayo (Zimbabwe) to 84.5% (95% CI: 70.6-93.5) in Namibia. The results reported in chapter 6 are similar to results from the only multinational prospective cohort study on survival - the ABC-DO study which report better survival outcomes for women in Namibia, a SSA country of medium HDI compared with women from Nigeria, Uganda, and Zambia,

however, this study was hospital based.[156] The work presented in this chapter is the largest study using PBCR data from SSA.

In the second part of this chapter, I delved down into the data from registries for which we could obtain more granular data, to try to better understand reasons for the survival differences observed. The survival differences by HDI in the first part suggested that these differences may be correlated with differences in access to care. Survival outcomes were best among patients who initiated adequate therapy. Approximately 1 in 5 traced patients did not receive any CDT, however, the proportion of patients who received adequate CDT differed by registry area. Among traced patients with non-metastatic disease, 50.9% received sub-optimal therapy with no curative potential or no CDT. The HRS was known for less than 30% of patients, making guideline adherence challenging. After adjusting for therapy received, stage at diagnosis, and age at diagnosis, no survival differences by country-level HDI were observed.

There were inherent challenges for women diagnosed with breast cancer in these registries, with limited access to radiotherapy in many of these countries, as well as limited facilities for HRS testing. However, these results reflect data collected on the outcome of women diagnosed about a decade ago for some registries, some of these conditions may have improved over time. Though in comparison with population-level studies done in the late 1990s in Kampala (Uganda) and Harare (Zimbabwe) as reported in SURVCAN-2,[76] there have not been much improvements in cancer survival outcomes for women in SSA, despite remarkable improvements in therapy and survival from more developed countries. In order to effectively translate evidence on therapy into practice, and effectively use resource-stratified therapy guidelines such as the NCCN guidelines, it will be imperative to have coordinated cancer management systems in SSA. However, there are still major challenges of access to care for a majority of women in SSA who have to pay for almost all of their care out of pocket in the absence of universal health care. For the few countries where care is subsidised like

Namibia, we see remarkable differences in survival from countries where women have to pay out of pocket for care.[156] In addition, not all African countries have a functioning radiotherapy machine; even where these facilities do exist, some of these are old and with frequent breakdowns. Radiotherapy is not only useful for therapy but also for palliation, especially as 1 in 5 women present with metastatic disease at diagnosis in SSA.

7.3 Limitations and challenges

It must be acknowledged that these registries are not 100% complete, and of the 11 registries included for the study of time trends, only 5 have been included in recent iterations of cancer incidence in five continents. There are often financial and socio-economic constraints to the effective functioning of PBCRs in the long term. Most of these registries are underfunded with few permanent staff; an example is the Kampala Cancer Registry which has one permanent staff member for a metropolitan city with a current population of more than three million inhabitants. Tangka et al. 2016 evaluated the cost of operating PBCRs in SSA, and they showed variability in registry cost by country-level income, with lower costs in low-income countries and higher costs in high-income countries. They estimate that a registry required approximately 9$ per case in Kampala (Uganda) in 2015, 10$ per case in Harare (Zimbabwe), 33$ per case in Nairobi (Kenya) and 96$ per case in Seychelles.[444] However, most of these registries especially those in low-income countries function with much lower resources. Furthermore, almost all these registries rely on paper-based records and active finding, which increases the time required to find and accurately register new cases. Political and social instabilities are also commonplace in many African nations, and this impacts the functioning of registration activities. Other registries in SSA had long term data on time trends such as Mali (Bamako), Guinea (Conakry), and Eldoret (Kenya), but the instability of the rates precluded their use for the study of long-time trends in this thesis. Some of the differences observed in the magnitude of the breast cancer incidence trends reflect differences in completeness of case ascertainment in different PBCRs, but some of these reflect actual

differences in the burden of breast cancer in these different countries. To minimise the influence of differences in case ascertainment, only registries with relatively stable incidence rates were included for the study of time trends. However, in instances like in Kampala (Uganda) where declining incidence rates were observed in the later years of registration, active efforts were put in to improve case finding and completeness of cancer registration, as reported in Appendix 3. Where it was not possible to update missing cases, due to political and economic instabilities during a given period, as was the case in 2007-2009 in Harare (Zimbabwe), modelling was used to improve the reliability of the data, using patterns from the years before the drop in incidence and the years after this period, to obtain more robust estimates for the period during which there was a decline in the registration activities.

Despite the limitations of population-based cancer registration in SSA, PBCRs provide an invaluable source of information for the understanding of the breast cancer burden in communities in SSA. However, most of the areas covered by a PBCR are urban cities in SSA, with very few areas covering rural areas. Furthermore, less than 10% of SSA is covered by a PBCR, thus very little is known about the actual cancer burden in approximately 90% of the African population. This highlights the need for strengthening health and data monitoring systems in SSA.

The systematic review on reproductive, anthropometric, and lifestyle risk factors in SSA revealed the paucity of quality epidemiological studies from more than 75% of African countries. There were no cohort studies investigating breast cancer aetiology in SSA. Thus, all included studies were case-control studies. Case-control studies, although being the most time and cost-effective method of studying rare diseases, have inherent risks of recall bias, which may be differential between cases and controls for some of the exposures studied. Another limitation was the relatively small size of some of the studies included. The included studies used different cut-offs and different exposure categories, making meta-analyses of effect sizes challenging for most of the studied risk factors. The quality of this review would

have been improved if primary data could be obtained from authors of the included studies, such that more robust estimates of the effect sizes could be obtained. These studies from SSA in general have similar conclusions to studies done among African American and Caucasians. However, there are other risk factors, which are pertinent to the SSA context, for which there has been only one SSA case-control study investigating this such as the use of hair relaxers and skin lighteners.[242] Dietary exposures were investigated in four case-control SSA studies, however, the exposure categories were so different such that, harmonizing these results was challenging. Furthermore, most of the outcomes reported relied on participant recall, with no objective means of ascertaining some of the exposure categories explored.

The final results chapter presented results of population-level cancer survival in SSA. This chapter reported on retrospectively collected PBCR data, with the drawback of large proportions of LFU especially in the first year after diagnosis. Patient record systems are poorly maintained in many parts of SSA, making such retrospective research challenging, and resulting in large proportions of missing data. The associations reported with therapy from this observational study do not represent treatment effects, as the associations of these therapies with outcome are subject to different selection biases. Unfortunately, the data used for the study of therapy outcomes had limitations, it was retrospectively collected, and important confounders such as time to treatment, adherence, tumour biology, comorbidities, and the socio-economic status of the women included in the study were not available. Despite these obvious limitations, this study provided insights into the reasons for the disparities observed in survival outcomes at population-level in SSA.

7.4 Implications for cancer control in SSA

Governments in SSA are plagued by old and emerging communicable diseases, however, with the rising burden of NCDs increased attention needs to be paid to these conditions. This thesis highlights changes in the risk factor profile of African populations, with increases in

the prevalence of overweight and obesity and inadequate physical activity levels, which not only influence the burden of breast cancer but could also influence the burden of other NCDs such as diabetes, and cardiovascular diseases. Thus, interventions targeting such risk factors would not only be beneficial for cancer control, but also for the control of other NCDs. The changes in the risk factor distribution at population-level, would influence the future breast cancer burden. This thesis highlights the need for greater focus on the rising burden of breast cancer in SSA. There is a need to raise awareness on breast cancer control measures that span the entire cancer consortium from primary prevention, early detection, patient navigation pathways, and access to quality cancer care.

It will also be imperative to improve facilities for data capture, and prompt and accurate cancer surveillance systems, to facilitate patient care, resource management, and epidemiological research. Without accurate knowledge of the cancer burden in a community, an effective national cancer control plan cannot be implemented and monitored. Hence it will be essential to support the creation and maintenance of robust cancer registration systems in SSA.

However, it also highlights the need for more representation of different African populations in cancer research in SSA. Cancer aetiology has both genetic and environmental components. A breast cancer risk prediction model was developed using data from the Nigerian Breast Cancer Study to promote more targeted screening of women who may be at higher risk of breast cancer in the absence of systematic population-level BC screening in this setting. This risk prediction model was more discriminatory than the Gail risk prediction model for detecting Nigerian women with a higher breast cancer risk.[445] The Gail risk prediction model was developed using data from American Caucasian women, and later adapted for African-American, Hispanic and Native American populations. Its predictive value in non-US populations require further studies. There is thus a need for more context-specific

aetiological research involving more diverse African populations, given the huge genetic diversity in Africa.

The work in this thesis highlights the comparatively poorer survival outcomes for women diagnosed with breast cancer in SSA. A key determinant is the late stage at diagnosis and the limited access to quality cancer care. It further highlights the need for interventions to downstage breast cancer in LMIC. Guidelines must be context-relevant, with caveats for what may be recommended in the absence of complete patient diagnostics. However, these guidelines must consider local context-specific research on the tumour biology profiles of the populations. This does not cancel out the necessity to increase infrastructure and availability of HRS testing in SSA, to give women the possibility of receiving adequate care which is guided by their tumour profile. The National Comprehensive Cancer Network (NCCN) acknowledge the absence of radiotherapy facilities in many SSA settings in its resource-stratified treatment guidelines. However, radiotherapy should not be an unavailable choice for women in SSA, as it is important for treatment and palliation, not only for breast cancer but also for cervical cancer, which are the two most common cancers in SSA. Although approximately 20% of women are diagnosed with metastatic disease in SSA, there is insufficient access to opiates and palliative care services in Africa.[446] This year, there has been the setup of a major international collaborative effort to help address disparities in breast cancer care worldwide with the launch of the Global Breast Cancer Initiative. The Global Breast Cancer Initiative is a collaborative effort between the WHO, the International Atomic Energy Agency and the IARC. It has 3 main pillars of action – health promotion and early detection of breast cancer, timely diagnostics, and comprehensive cancer management. It aims to use multinational and stakeholder collaboration to help coordinate breast cancer control efforts in LMIC.[447] However, data from PBCRs will be essential to monitor the outcome of these planned interventions.

Financing cancer care is still a challenge for many women and families in SSA. The financial toxicity of cancer care is severe for many in the absence of subsidies. The last years have seen the resurgence of the call for universal health coverage and access to health care for all.[448] However, different countries will attain this laudable goal at different speeds. In the meantime, local and context-specific efforts will be needed to support patients who may not be able to access care.

7.5 Recommendations for future research

Of the PBCRs used for the data analyses reported in this study, there have been few studies that have independently and objectively evaluated the completeness of their registration activities in recent years. It would be important to have external audits of the completeness of these registration activities, especially with the impact of the COVID-19 epidemic on cancer diagnostics and access to care in LMIC in the last year. The impact of the pandemic would most likely result in delays to care, with decreased registration activities in some settings. The completeness of registration activities before and after the onset of the pandemic would have to be studied in order to assess the completeness of registration activities prior to the epidemic and the impact of the epidemic on the cancer registration practices. This would be necessary to accurately measure the current and future cancer burden in these communities.

This work also highlights the need for more research from SSA, given that fewer than a third of SSA countries are included in this thesis. Some risk factors such as the role of the waist-to-hip ratio on breast cancer risk were studied in only a single African country as of July 2020. More aetiologic research is needed in more diverse African populations. Going forward, more aetiologic research should be carried out by molecular sub-types in SSA, given that these subtypes have different aetiological pathways. Other less investigated risk factors need further research, such as the role of skin-lighteners, diet, inflammatory states, DDT, and other environmental factors on breast cancer risk in SSA.[109] Although cohort studies are more resource-intensive than case-control studies, they help us better understand temporal

relationships and are less prone to recall bias than case-control studies. Thus, it would be important to set up cohort studies in SSA such as exist in other continents, to better characterise and understand the breast cancer risk factor profile of African populations. In addition, the collection of biologic samples in either case-control or cohort design studies in SSA, will enable a more in-depth study of the aetiologic pathways, and will be important for assessing genetic predictors and gene-environmental interactions in these settings.

The changing demographics and risk factor profiles in SSA will undoubtedly affect the future cancer burdens. Available data on cancer projections published in GLOBOCAN make projections based on current incidence rates and projected population changes but do not take into account changes in risk factor profiles.[449] Further research and simulation will be needed to investigate different scenarios assessing the impact of different lifestyle interventions on the future breast cancer burden in SSA.

Furthermore, more robust population-based prospective studies on cancer survival in SSA are needed to measure cancer survival outcomes more accurately in more countries than was possible in this thesis. Additional research is also needed on patient-reported outcome measures in SSA such that, we could better understand not only the duration of time lived after a cancer diagnosis, but also the quality of patients' lives in SSA after a cancer diagnosis.

Finally, there is limited information on patient costs associated with cancer care in SSA. Although there are government subsidies for cancer care in some SSA nations, reports have highlighted a high frequency of shortages of key cancer medications.[408] Thus, a large component of care is still from personal patient resources. This differential financial burden of cancer care in SSA will affect their ability to access care, their survival outcomes, and also the quality of life for patients and their families after a cancer diagnosis. There is a need for more health-economic evaluation of the impact of cancer care on patients and families in different parts of SSA.

7.6 Conclusion

Breast cancer is the most common cancer among women in SSA. Using population-level data, this thesis highlights the rising incidence rates observed in some countries, the need for more context-specific aetiological research in SSA, and the relatively poor survival outcomes in some urban African cities. It also highlights the challenges of guideline adherence for breast cancer therapy in urban SSA cities.

It shows the need for more robust cancer surveillance systems in SSA and for representation of more African populations in understanding the magnitude of the breast cancer burden in SSA.

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Appendices

Appendix 1: Peer-reviewed articles published in relation to this research

From the work presented in this thesis, the following peer-reviewed publications have been made:

From Chapter 3:

An earlier version of this chapter was published as a book chapter:

- Cancer of the Breast. in *Cancer in sub-Saharan Africa*; Parkin DM., Jemal A., Bray F, Korir A, Kamate B., Singh E, **Joko WY**, Sengayi-Muchengeti M., Liu B, Ferlay J, Eds.; Union Internationale Contre le Cancer, 2019; Vol. III. https://www.uicc.org/resources/cancer-sub-Saharan-africa

From Chapter 4:

- **Joko-Fru WY**, Jedy-Agba E, Korir A, Ogunbiyi O; Dzamalala C.P, Chokunonga E, et al. The Evolving Epidemic of Breast Cancer in sub-Saharan Africa: Results from the African Cancer Registry Network. Int. J. Cancer, 2020, 147 (8), 2131–2141. https://doi.org/10.1002/ijc.33014.

From Chapter 6:

- **Joko-Fru WY**, Miranda-Filho A, Soerjomataram I, Egue M, Akele-Akpo M, N'Da G, et al. Breast Cancer Survival in Sub-Saharan Africa by Age, Stage at Diagnosis and Human Development Index: A Population-based Registry Study. Int. J. Cancer, 2020, 146 (5), 1208–1218.

- *In press*: **Joko-Fru WY**, Griesel M., Mezger NCS, Hämmerl L, Seraphin PT, Wabinga H, et al. Breast Cancer Diagnostics, Therapy, and Outcome in sub-Saharan Africa: A

Population Based Registry Study. Journal of the National Comprehensive Cancer Network, accepted for publication in January 2021.

Other publications during the course of the DPhil using similar methods:

- **Joko-Fru WY**, Parkin DM, Borok M, Chokunonga E, Korir A, Nambooze S. et al. Survival from childhood cancers in Eastern Africa: A population-based registry study. Int J Cancer 2018; 143, 2409–15.

- Jedy-Agba E, **Joko WY,** Liu B, Buziba NG, Borok M, Korir A,et al. Trends in cervical cancer incidence in sub-Saharan Africa. Br J Cancer 2020; 123,148-154.

- Sengayi-Muchengeti M, **Joko-Fru WY**, Miranda-Filho A, Egue M, Akele-Akpo M, N'Da G, et al. Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index (HDI): A population-based registry study. Int J Cancer 2020; 147 (11), 3037-3048.

- Seraphin TP, **Joko-Fru WY**, Kamaté B, Chokunonga E, Wabinga E, Somdyala N, et al. Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network. Cancer Epidemiol Biomarkers Prev 2021; 30(1), 158-165.

- Bukirwa P, Wabinga H, Nambooze S, Amulen, P. M.; **Joko, W. Y**.; Liu, B.; Parkin, D. M. Trends in the incidence of cancer in Kampala, Uganda, 1991 to 2015. Int. J. Cancer. 2021; 148, 2129–2138.

- Griesel M, Seraphin TP, Mezger NCS, Hämmerl L, Feuchtner J, **Joko-Fru WY**, et al. Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. The Oncologist 2021;26(5), e807-e816.

- Gullickson C, Goodman M., **Joko-Fru WY**, Gnagnon HR, N'Da G, Woldegeorgis MA, et al. Colorectal cancer survival in sub-Saharan Africa by age, stage at diagnosis, and Human Development Index: A population-based registry study. Int. J. Cancer. 2021; published online June 24th, 2021. https://doi.org/10.1002/ijc.33715

- Seraphin TP, **Joko-Fru WY**, Manraj SS, Chokunonga E, Somdyala NI, Korir A, et al. Prostate cancer survival in sub-Saharan Africa by age, stage at diagnosis, and human development index: a population-based registry study. Cancer Causes & Control 2021; published online July 10th 2021. https://doi.org/10.1007/s10552-021-01453-x.

Appendix 2: Declaration and acknowledgement of co-authors

I carried out the literature reviews, and all the data cleaning, data analysis, and wrote the results presented in this thesis. However, this thesis would not have been possible without the co-authors from the PBCRs and the wider network of researchers who collaborate with the AFCRN, who were responsible for the primary data collection and who offered invaluable insight for the interpretation of results, as well as the senior researchers who never hesitated to offer advice and guidance.

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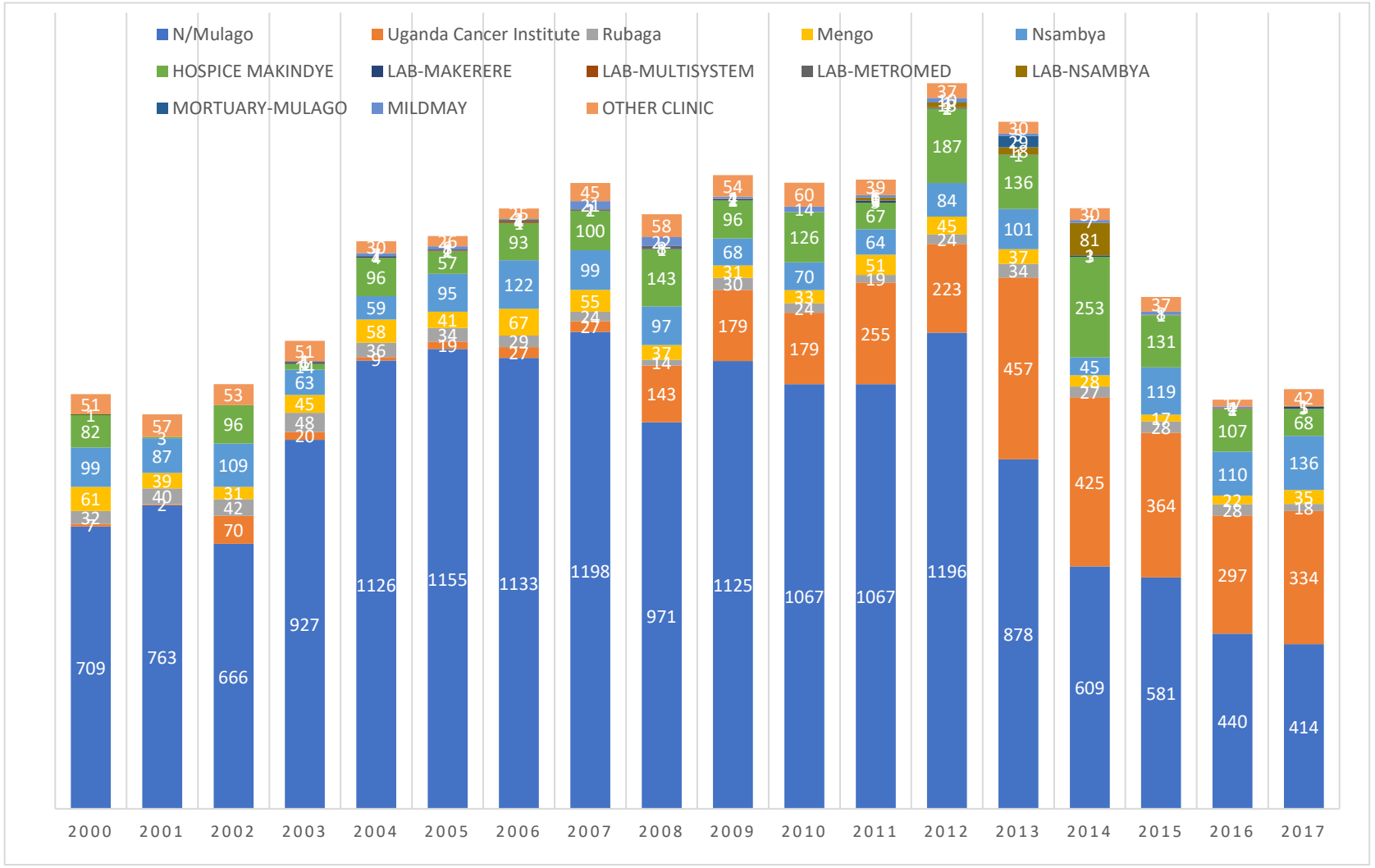
Appendix 3: Report on a working visit to the Kampala Cancer Registry

Purpose of visit: I visited the Kampala Cancer Registry (KCR) in January 2020, to support the cancer registrars in completing case registrations for the years 2014 and 2015 in Kampala (Uganda), given that having quality primary data is preferable to interpolations where possible.

Situational Analyses: There was a decline in the number of registered cases at the KCR from 2014 onwards. The KCR is one of the oldest registries in SSA, one of the few which can be used for study of the long-time trends. Thus, it was necessary to see how to practically improve the completeness of recorded cases for this registry. The number of recorded cases by key sources were on the decline from 2013 onwards as shown on the graphic below.



Appendix Figure 1: Number of cases registered by source and year of diagnosis, Kampala Cancer Registry.

Points to highlight were the declining number of cases from the New Mulago Hospital, the Uganda Cancer Institute (UCI), the Hospice Makindye in 2015, the Nsambya Hospital in 2014 and the Mortuary.

The overarching aim of the visit was to understand and identify reasons for the reduced number of recorded cases and then create a plan for finding unregistered cases and updating the CanReg5 database with a focus on the years 2014 and 2015. The focus on these 2 years (2014 and 2015), is in order to enable the registry to have 25 years of complete good quality cancer incidence data.

I visited all the major data collection sites for which there was a decline in the number of cases.

Friday 24th January 2020: Introduction to the pathology unit and the data management office of the Kampala PBCR, located within the Mulago National Specialised Hospital.

Appendix Figure 2: Entrance to the Mulago National Specialised Hospital.

Saturday 25th January 2020: Visit to the Multisystem Pathology Lab. Studied the system for record collection, went through the records to ensure no folders had been missed for data capture.

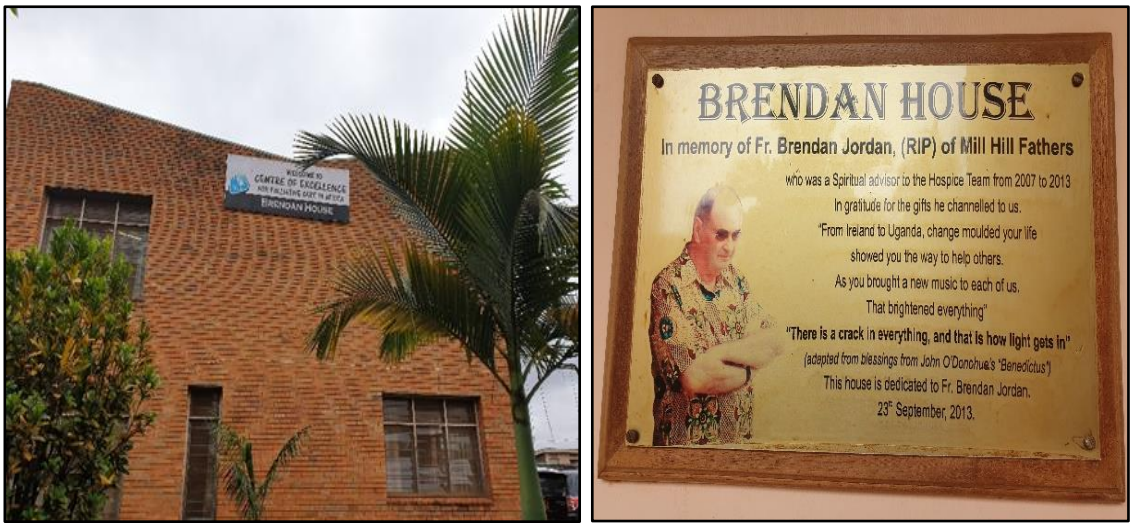
Appendix Figure 3: Folders for paper-based record keeping Multisystem laboratory.

Monday 27th January 2020: Working visit to the Kampala City Mortuary Mulago. We went through all the mortuary records for 2014 and 2015, to identify the cases with a cancer cited as cause of death. From this exercise, we identified 21 new cases and 5 cases were updated as dead. The registrars will subsequently find additional diagnostic information on these 21 new death-certificate initiated cases from other hospital departments.

Appendix Figure 4: Images form the City Mortuary Mulago.

Appendix Figure 5: Records folder, City Mortuary Mulago.

Tuesday 28th January 2020: Working visit to the Hospice Makindye. The cancer registrars and I reviewed the case records for 2015 and filled out forms for 71 cases seen at the hospice, not marked as having been recorded by the KCR. Of these cases, after record checks in CanReg5, 48 were new patient records, and the rest were updated.



Appendix Figure 6: Images from the Hospice Makindye, Kampala, Uganda.

On return from the Hospice, following discussions with registry staff and the registry director, the Kampala cancer registry were able to obtain a backup of records from the Uganda Cancer Institute for the period 2010-2019. For the years 2014 and 2015, there were approximately 815 cases from Kampala and approximately 800 from Wakiso district, not-otherwise specified registered by the hospital-based registry of the Uganda Cancer Institute.

Wednesday 29th January 2020: Record linkage between the 815 cases from the Uganda Cancer Institute and the Kampala Cancer Registry records for 2014 and 2015, initially in excel, using conditional formatting and reverification of differences in spelling. Then we obtained the RECLINK software developed by Andy Clarke at IARC from Prof. Max Parkin later in the afternoon and I used this for the record linkage and reverification of cases from Kampala district.

Thursday 30th January 2020: Worked at the Kampala Cancer Registry with the registry staff. Installed RECLINK on their desktop and showed them how to prepare the tab files to use the program. We practiced using RECLINK together. With the aim, that they could subsequently use the program to update their records using cases from the UCI. It could make the process of case identification faster from UCI.

Challenges identified:

• Due to the renovation work ongoing at the New Mulago Hospital, some units of the hospital and medical records have been displaced to different parts of the city and hospital. As a result, this has made case identification more challenging for the registrar staff, as they have to identify all constituent sources that made up the New Mulago Hospital.

• Furthermore, the records from these different sections are sometimes displaced or due to lack of space, tied up into bags. This makes case finding difficult for cases diagnosed in the past. And this more time consuming identifying these cases for the limited registrar staff available.

Appendix Figure 7: Paper-based records storage system.

• There is still just 1 full time staff of the Kampala Cancer Registry, with the second staff working on a voluntary basis. However, in order to sustain the functioning and quality of this registry, funding needs to be dedicated for staff and stationery.

• Internal challenges and polemics with concomitant projects and sometimes different vested interests.

Opportunities:

There is an on-going hospital-based cancer registry operating at the Uganda Cancer Institute (UCI). There are approximately 20 staff working to input data on all patients seen at UCI into CanReg. Given that most of the patients with cancers seen at New Mulago are subsequently referred to UCI, and the larger number of staff working on this hospital registry. Their records may be more timely, however, the accuracy of the codes need to be reverified. Using the RECLINK software, the KCR could use records from UCI to identify cases faster, which they could subsequently verify and update.

Proposed plan:

1. Update missed cases for 2014 and 2015 following record linkage and verification from the UCI hospital-based registry

2. Visit the other sites that made up New Mulago: Kiruduu (Medical), Kawempe, Radiotherapy and Surgical departments. This in order to verify any missed cases

3. Visit the Nsambya Hospital to update cases diagnosed in 2014. (We were not able to obtain an appointment while I was there due to an on-going training for the Nsambya staff)

4. Visit Mengo and Rubaga to ensure no cases were missed

5. Complete and register in CanReg5 the new death certificate-initiated cases

Outcome:

The registrars kept working to update and complete the cancer registration for 2014 and 2015. With the team of the Kampala Cancer Registry, the updated temporal trends for the major cancers in Kampala, Uganda were studied and published for the period 1991-2015 as: Bukirwa P, Wabinga H, Nambooze S, Amulen, P. M.; Joko, W. Y.; Liu, B.; Parkin, D. M. Trends in the incidence of cancer in Kampala, Uganda, 1991 to 2015. Int. J. Cancer. 2021;148:2129–2138. https:// doi.org/10.1002/ijc.33373.

As concerns breast cancer, the updated breast cancer data from the PBCR had 771 breast cancer patients for the period 2010-2014, whereas using data based on interpolation I arrived at 739 cases for this period.

The AAPC for the period 1991-2015 was estimated at 2.3% (95% CI: 1.3 – 3.4). For the period 1990-2014, I estimated the AAPC at 2.1% (95% CI: 0.9-3.3) (Figure 4.3).

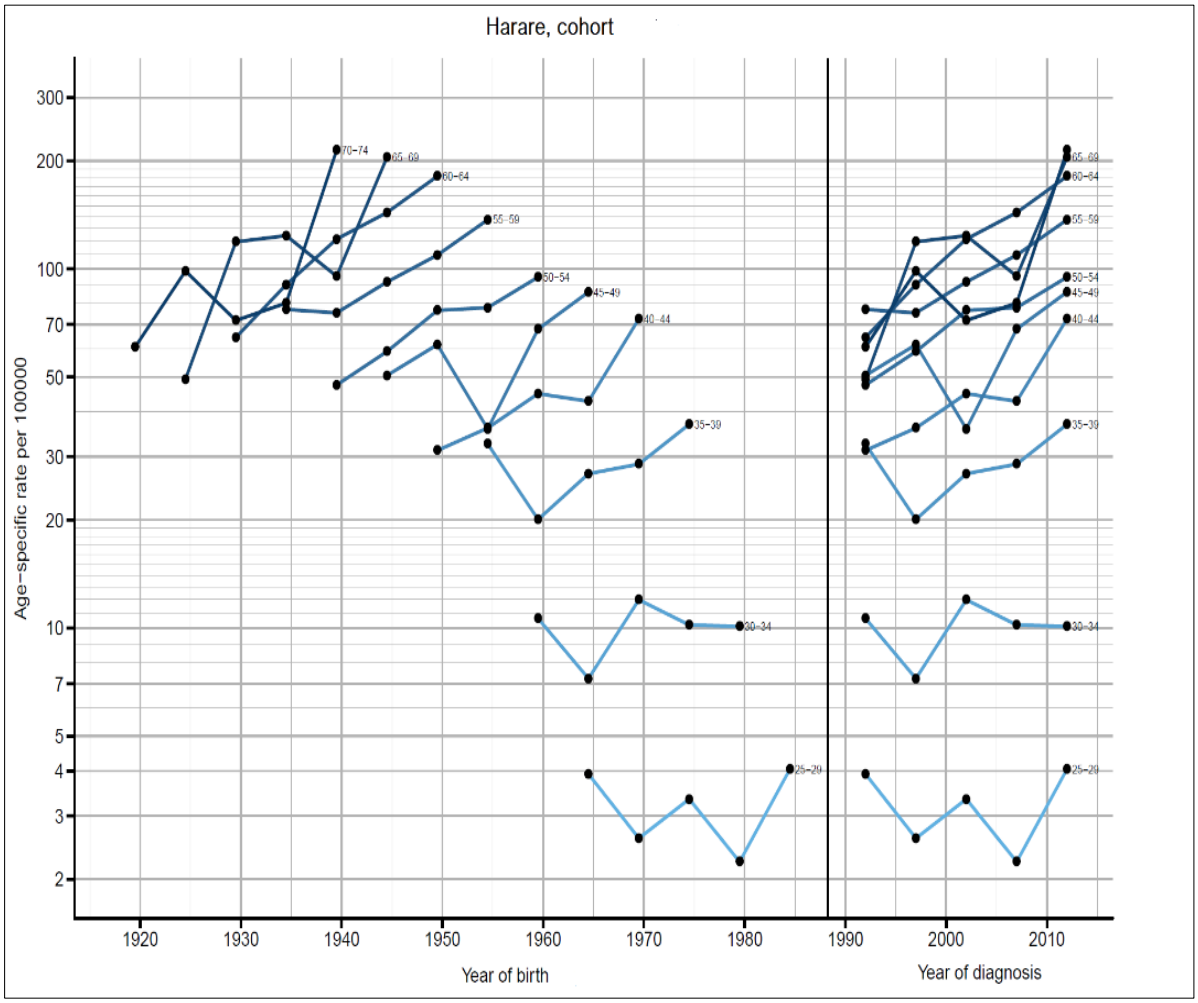
Appendix 4: Ratio of the age-standardised incidence rates and cumulative risk by region, GLOBOCAN 2020

Appendix Table 1: Ratio of age-standardised incidence rates (ASIR) and cumulative risk among women 15-49 and 50-74 across different regions of the world in 2020.

	15-49		50-74		Rate 50-74/Rate 15-49	
Population	ASIR	Cum. risk	ASIR	Cum. risk	Ratio of ASIR	Ratio of cum risk
Eastern Africa	25.9	1.02	102.3	2.57	3.95	2.52
Middle Africa	30.6	1.20	90.3	2.22	2.95	1.85
North Africa	41.5	1.64	143.2	3.53	3.45	2.10
Southern Africa	31.3	1.25	160.3	4.17	5.12	3.14
Western Africa	28.7	1.14	132.7	3.38	4.62	2.96
North America	55.5	2.21	302.4	7.67	5.45	3.47
Northern Europe	52.8	2.12	295.3	7.39	5.59	3.49
Western Europe	61.6	2.45	297.9	7.42	4.83	3.03

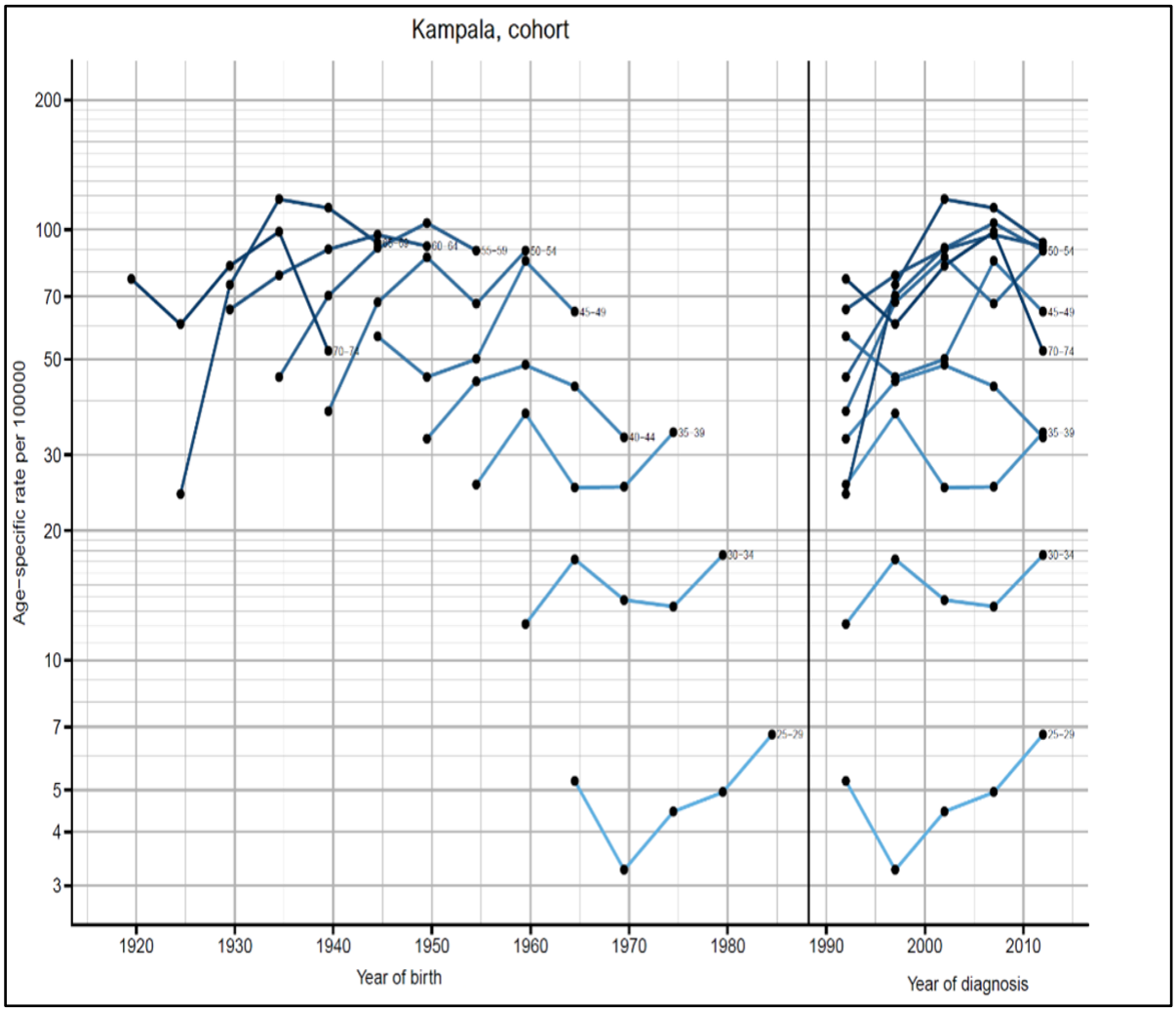
Data source: GLOBOCAN 2020 Cum. Risk = cumulative risk ASIR= Age-Standardised Incidence Rate

Appendix 5: Period and cohort effects, Harare (Zimbabwe)



Appendix Figure 8: This graphic shows the age specific incidence trends by birth period and birth cohort, using the registry data from Harare, Zimbabwe before any interpolations. By year of diagnosis, sharp declines in incidence rates for oldest age groups are observed in the period 2007-2009, seen as a sudden period effect due to challenges in cancer registration activities in these years. Another sudden dent in incidence rates is observed among women aged 45-49 around 2002. This graphic was produced in R using the Rcan package.

Appendix 6: Period and cohort effects, Kampala (Uganda)



Appendix Figure 9: This figure shows the age-specific incidence rates for Kampala, Uganda in the period 1991-2013 using registry data prior to data interpolation. It shows period effects, with declines in the age-specific incidence rates in later years for women aged 40 and above most likely due to incomplete registration. This graphic was produced in R using the Rcan package.

Appendix 7: Primary data re-analysis of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives

The WHO collaborative study of Neoplasia and Steroid Contraceptives was a large multi-national, hospital-based case-control study, which was carried out between 1979 and 1986, and included data from 12 countries. Cases were women born after 1925 or 1929 depending on the study centre, who were residents of the study area during the preceding year. Controls were women admitted at the same hospitals from which the cases were recruited, except from the obstetrical and gynaecological wards.

The papers which reported on lactation and breast cancer risk from this multinational study were published as a pooled analysis of all centres. Results were not published by individual study centre. Data had been collected from two African countries: Kenya and Nigeria. Country-specific results were available only for the data re-analyses by Skegg et al. 1995, which focused on the risk of injectable contraceptives.

I contacted Prof. Thomas by email to ask if it was possible to obtain these results stratified by study centre. I obtained cleaned, anonymised data from his team, and I used this data, to obtain country-specific data for Kenya and Nigeria for inclusion in the systematic review described in Chapter 5. The results are described below:

A. Lactation and Breast Cancer

The final report on the association between lactation and breast cancer from the WHO Collaborative Study of Neoplasia and Steroid Contraceptives was published as:

Thomas DB, Noonan EA. Breast cancer and prolonged lactation. *Int J Epidemiol* 1993; **22**: 619–26.

The reported data included data from Kenya, however it presented combined results for all study centres. The primary aim of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives study was to investigate the association between depot-

medroxyprogesterone acetate (DMPA) and breast cancer risk. However, there were very few cases who used DMPA in Nigeria, thus this centre was not included for subsequent analyses. However, data was available from Nigeria on lactation and breast cancer risk, which I used in this re-analysis of the primary data. I used similar categories and adjusted for the same confounders as the published paper. The analyses were limited to women with at least 1 live birth, as done in the original publication. Data management and analyses were done in Stata 16. A logistic regression model was used to study the association between lactation and breast cancer in these two centres.

Appendix Table 2 describes the characteristics of cases and controls in Kenya and Nigeria. There were 62 cases from both centres; so due to the relatively small sample size, a pooled analysis was done, adjusted for recruitment site.

Appendix Table 3 presents results from the logistic regression model which are reported in Chapter 5. When the total duration of breastfeeding (in years) was fitted as a continuous variable, a 12-months increased total breastfeeding duration was associated with a non-significant 2% reduction in risk (OR=0.98, 95% CI: 0.88-1.10).

Appendix Table 2: Description of participants from Kenya and Nigeria who were included in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives.

	Kenya		**Nigeria**	
	Cases	*Controls*	*Cases*	*Controls*
Number included	43	617	19	147
Mean age	42.1	35.8	41.2	37.9
Median duration of lactation (months)	72	48	72	55
Median number of live births	6	4	6	5
Median age at first birth (years)	19	19	20	21

Appendix Table 3: Association between total duration of lactation and breast cancer risk; adjusted for study centre, age at first birth, age at diagnosis and total number of live births.

Variable	Odds Ratio	LCI	UCI	*p* heterogeneity
Total duration of breastfeeding				*0.634*
< 24 months	1			
>24-72 months	0.67	0.29	1.54	
>72months	0.64	0.23	1.79	
Study centre				*0.045*
Nigeria	1			
Kenya	0.53	0.29	0.97	
Age at first birth				*0.966*
<20	1			
20-24	0.95	0.53	1.70	
25+	1.07	0.40	2.92	
Age at diagnosis	1.09	1.04	1.13	-
Total number of live births	1.03	0.89	1.18	-

LCI=Lower confidence interval UCI=Upper confidence interval

B. **Oral contraceptives and breast cancer risk**

For these analyses, data were included only from Kenya, as there were only two cases from Nigeria who used oral contraceptives. There were no current users of oral contraceptives in Kenya, all cases were former users. Appendix Table 4 shows the numbers of cases and controls from Kenya.

Appendix Table 4: Number of cases and controls from Kenya for the study of the association between oral contraceptives and breast cancer risk in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives.

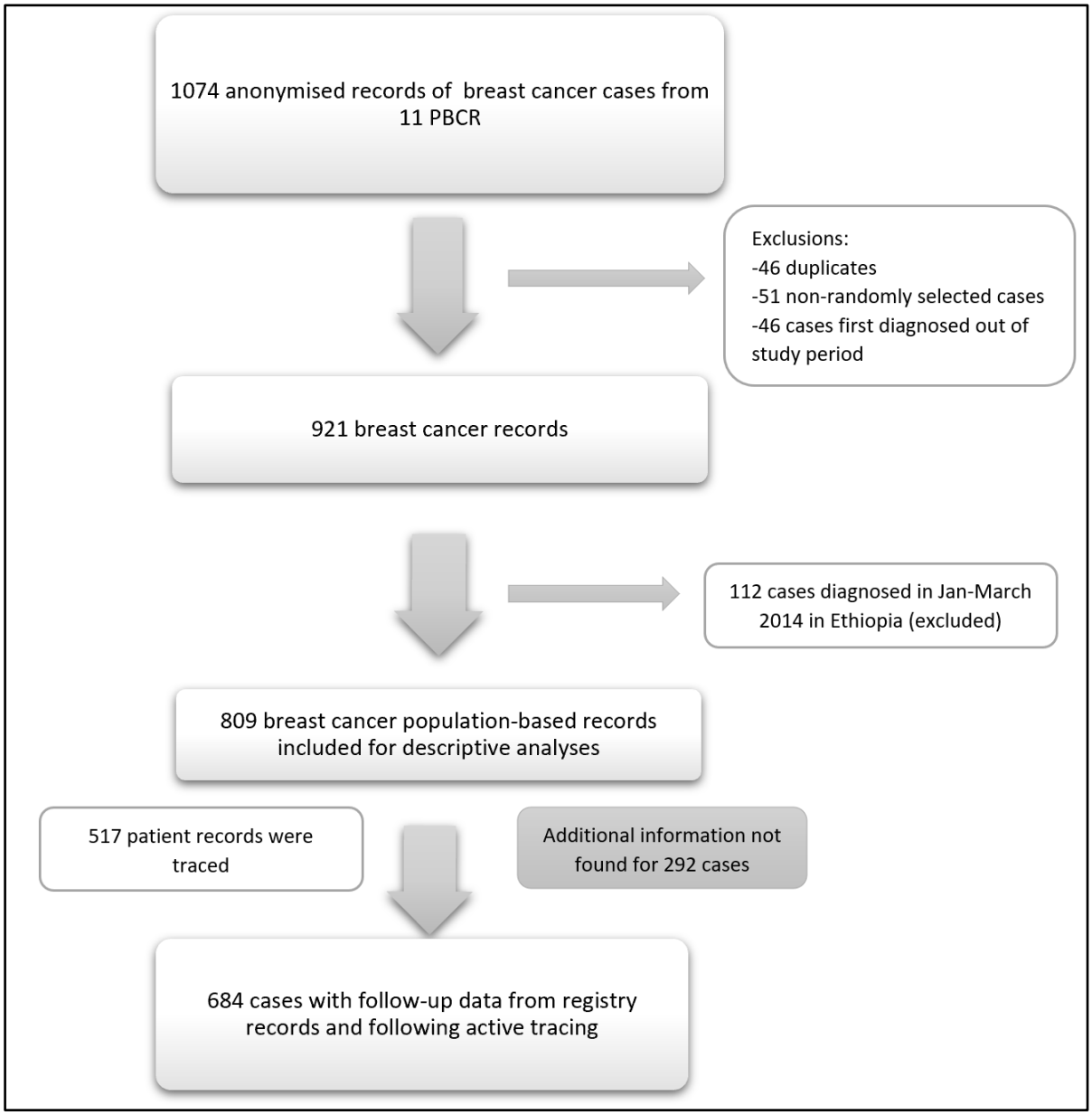
	Cases	Controls
Yes, ever used contraceptives	14	210
Never used	35	541

For the multivariable analyses, following the published paper from the WHO Collaborative Study, I adjusted for age at diagnosis, number of pregnancies, use of an intra-uterine device, educational level, and menopausal status. The results from the logistic regression analyses for Kenya are presented in Appendix Table 5.

Appendix Table 5: Association between oral contraceptives and breast cancer; adjusted for age at diagnosis, number of pregnancies, educational level, ever use of an intrauterine device (IUD), and menopausal status.

Variable	Odds Ratio	LCI	UCI	p heterogeneity
Ever use of oral contraceptives				*0.599*
No	1.00			
Yes	1.22	0.58	2.56	
Age at diagnosis	1.11	1.06	1.16	-
Number of pregnancies	0.96	0.88	1.06	-
Educational level				*0.214*
No education	1.00			
Primary	0.95	0.48	1.90	
Secondary	0.98	0.37	2.61	
Higher education	0.94	0.10	8.62	
Ever used an IUD				*0.844*
No	1.00			
Yes	0.92	0.40	2.11	
Menopausal				*0.068*
Yes	1.00			
No	1.75	0.82	3.74	

Appendix 8: Patient inclusion for study of breast cancer therapy and survival outcomes



Appendix Figure 10: Patient inclusion flowchart for the study of therapy received and survival outcomes.