Extended Cost Effectiveness Analysis of Interventions for Early Detection, Screening and Breast Cancer Control: Case Studies of South Africa and Uganda

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Abstract

The global statistics for the year 2022 indicate that female breast cancer is the second leading cause of global cancer incidence with an estimated 2.3 million cases and among women, it is the most frequently diagnosed cancer and the leading cause of cancer death among women in 157 countries[1]. In the African region, breast cancer incidence and mortality are on an upward trajectory and predicted to double in Sub-Saharan African by 2050. Given the growing burden of breast cancer in low- and middle-income countries (LMICs), these countries now face the challenge of effectively detecting and treating a disease that was previously considered too uncommon to merit the allocation of finite health care resources. As such, in LMICs there is a need to scale up early detection and screening strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor.

We constructed a dynamic state transition model to estimate the cost effectiveness of three breast cancer down-staging interventions in Uganda and South Africa. Our model is premised on a comprehensive mathematical framework that estimates the stage shifts in early versus late stages of breast cancer diagnosis based on proportional performance rates of three early detection and screening interventions (awareness raising, clinical breast examination (CBE) and mammography) spanning 40 years. This study then used the extended cost effectiveness analysis framework to assess the possible distributional impact of utilizing universal public financing as a tool to increase access and coverage of breast cancer early detection interventions in these two countries.

This dissertation found that biennial CBE and awareness raising interventions are not only crucial for down-staging breast cancer diagnosis, but they are also economically attractive and viable for options for both Uganda and South Africa. Biennial CBE coupled with treatment interventions for all stages was cost-effective for South Africa with an ICER of $2,708 per healthy life year gained. Awareness raising interventions were also found to be cost effective with an ICER of 3,201 per health life year gained. Mammography screening combined with treatment for all stages was not found to be a cost-effective intervention for South Africa with an ICER of $9,491 per healthy life year gained.

For Uganda, we found awareness raising interventions to be the most cost-effective interventions for breast cancer control with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $416 per healthy life year gained. Biennial MMG screening combined with treatment for all stages was not cost effective with an ICER of $3,110 per healthy life year gained.

Further, this thesis demonstrated that publicly financing early detection and screening interventions in LMICs for breast cancer can alleviate a considerable proportion of breast cancer burden and catastrophic health expenditures benefiting the poorest wealth quintiles. In South Africa 44% of the deaths averted are in the wealthiest two quintiles while the poorest two quintiles would account for 34% of the total deaths averted. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $7.89 million over the 40-years, this translates to US $197,254 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the poorest wealth quintile accounting for 76% of the averted catastrophic

health expenditure cases, on the other hand, the wealthiest two quintiles account for approximately 1.4% of the catastrophic health expenditure cases averted.

In Uganda, our analysis shows that 55% of the deaths averted are concentrated in the wealthiest two quintiles while the poorest two quintiles would account for 26% of the total deaths averted. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $29.2 million over the 40-years, this translates to US$729,098 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the lowest three wealth quintiles accounting for 63% of the catastrophic cases averted while the richest two quintiles account for 37% of the cases of catastrophic expenditures averted.

The findings from this thesis are notable for breast cancer policy in LMICs as the analysis demonstrated significant down-staging associated with early detection and screening interventions for breast cancer. Implementation of these interventions will require substantial additional financial investments, but our analysis shows that the health benefits will broadly outweigh these requirements for CBE and awareness raising interventions.

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Lastly, I thank God and give Him all the glory for enabling me to start and finish this PhD journey. May my efforts always honor You, as I continue to walk in Your light. *By my God I have run through a troop and by my God I have leaped over a wall (2 Samuel 22:30).* **I dedicate this body of work to God.**

Preface

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy in the School of Public Health, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author.

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Abbreviations

AJCC	The American Joint Committee on Cancer's (AJCC)
BAR	Breast Awareness Raising
BC	Breast Cancer
BRAC 1/2	Breast Cancer 1/2
CBE	Clinical Breast Examination
CEA	Cost Effectiveness Analysis
ECEA	Extended Cost Effectiveness Analysis
Globcan	Global Cancer Observatory
HER2	Human Epidermal Growth Factor Receptor 2
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HREC	Human Research Ethics Committee
IARC	International Agency for Research on Cancer
ICER	Incremental Cost-Effectiveness Ratio
LMICs	Low- and Middle-Income Countries
MAR	Mass Awareness Raising
MMG	Mammography
MOH	Ministry of Health
MR	Magnetic Resonance
NCDs	Non-Communicable Diseases
NDoH	National Department of Health
NHA	National Health Accounts
OOPE	Out of Pocket Expenditure
PER	Public Expenditure Review
PhD	Doctor of Philosophy
SDGs	Sustainable Development Goals
SSA	Sub-Saharan Africa
TASO	The Uganda Aids Support Organization
UHC	Universal Health Coverage
US	Ultrasonography
WB	World Bank
WHO	World Health Organization
WHO-CHOICE	WHO's Choosing Interventions that are Cost Effective Project

CHAPTER

1

"For with God nothing shall be impossible" Luke 1:37

Chapter 1: Introduction and Overview

1.1 Introduction

The global statistics for the year 2022 indicate that female breast cancer is the second leading cause of global cancer incidence with an estimated 2.3 million cases, and it is the fourth leading cause of mortality worldwide with 666,000 deaths[1]. Moreover, the cancer morality burden in the African and Asian regions is disproportionately greater than the corresponding cancer burden in the region [2]. Among women, it is the most frequently diagnosed cancer and is the leading cause of cancer death among women in 157 countries [1]. In the African region, breast cancer incidence and mortality are on an upward trajectory and predicted to double in Sub-Saharan African by 2050[3], [4]. Notably, breast cancer incidence, mortality, and survival rates vary considerably between the global regions up to approximately fourfold [5]but what has been unequivocally consistent across the regions is that the incidence of breast cancer is increasing, and in regions without early detection programs, mortality is also increasing [1]. Late-stage presentation and delayed treatment are major contributors to poor breast cancer survival rates in low- and middle-income countries (LMICs) [2], [5].

In addition to the rising absolute numbers, it is important to recognize that breast cancer is also increasing as a share of overall disease burden in both Uganda and South Africa. While communicable diseases such as HIV/AIDS, malaria, and tuberculosis have historically dominated the health landscape, recent health data indicate a shifting burden toward non-communicable diseases (NCDs), with cancers, particularly breast cancer, contributing significantly to this epidemiological shift. According to the Global Cancer Observatory, in 2022, Uganda reported approximately 3,200 new breast cancer cases among women, accounting for around 22% of all female cancer diagnoses[6]. Similarly, South Africa reported about 11,020 new breast cancer cases in 2022, representing roughly 24% of all female cancer cases[7]. National cancer registry data further highlight breast cancer as the leading cancer among women in both countries. While breast cancer's absolute DALY numbers are lower compared to HIV/AIDS and malaria[8], its proportion relative to the total disease burden is increasing, especially as interventions for communicable diseases become more effective.

Early detection coupled with appropriate treatment is the most effective strategy for breast cancer control as demonstrated largely by evidence from high income countries [9]. However, there is limited empirical evidence in LMICs on the impact of the various early detection and screening modalities on breast cancer control [10]. Furthermore, evidence from Uganda and South Africa highlight disparities in utilization of breast cancer service due to socioeconomic factors that hinder access to health care and screening services especially in the rural and underserved areas[11]. However, there is no study known to the authors that has estimated the distributional consequences of investing in early detection and breast cancer control interventions in Sub-Saharan African countries.

As such, in LMICs there is a need to strengthen and scale up early detection and screening interventions that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor[12], [13], [14], [15], [16]. While several breast cancer early detection methods and tools exist, they are largely unavailable in many LMICs due to resource constraints and disparities persist in the utilization of the available services. It is therefore critical to understand the costs, effectiveness, and distributional consequences of using public financing to scale up early detection, screening and subsequent treatment of breast cancer in LMICs. This study focused on the economics of breast cancer early detection, screening, and treatment in one low-income country (Uganda) and one middle-income country (South Africa). Uganda and South Africa were purposefully selected as the focus countries for this study to provide a comparative analysis between a low-income and a middle-income country context within sub-Saharan Africa. Uganda, classified by the World Bank as a low-income country, has a gross national income (GNI) per capita of approximately USD 850 [17]and faces significant challenges in health financing, infrastructure, and human resources. By contrast, South Africa, an upper-middle-income country with a GNI per capita of around USD 6,530 [17], operates within a dual public-private health system and has more established cancer screening infrastructure. Importantly, both countries are undergoing an epidemiological transition, with non-communicable diseases, including breast cancer, emerging as leading health threats alongside longstanding infectious disease burdens [8], [14], [15], [18]. By selecting these two settings, the study aims to explore how differences in economic status, health system capacity, and policy environments affect the cost-effectiveness and implementation of breast cancer early detection and treatment strategies. Additionally, the availability of reliable national-level data from cancer registries and participation in global surveillance platforms (such as GLOBOCAN[2]) further supported the choice of these two countries for rigorous comparative analysis.

1.2 Aims and Objectives

This overarching aim of this study was to assess the cost effectiveness and distributional impact of publicly financing interventions for early detection, screening, and breast cancer control on the health system in Uganda and South Africa. The specific objectives of the study were:

1. To estimate the downstaging effect of early detection and screening interventions for breast cancer.
2. To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in South Africa.
3. To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in Uganda.
4. To quantify the financial and health distributional impacts of publicly financing early detection, screening, and breast cancer control interventions in South Africa and Uganda.

For early detection and screening interventions, this study considered the following: Awareness Raising, clinical breast examination (CBE) and mammography (MG).

1.3 Brief Overview of Methods

This dissertation firstly conducted a conventional cost effectiveness analysis (CEA) following the WHO standardized guidelines on how to conduct a CEA[19]. We constructed a dynamic state transition model to estimate the cost effectiveness of three breast cancer down-staging interventions in Uganda and South Africa for a time horizon of 40 years. We used a mixture of empirical estimates, and assumptions from low-income countries to populate parameters in the model. Our model is premised on a comprehensive mathematical framework that estimates the stage shifts in early versus late stages of breast cancer diagnosis based on proportional performance rates (Z's) of three early detection and screening interventions (awareness raising, clinical breast examination and mammography) spanning 40 years. This study then used the extended cost effectiveness analysis framework to assess the possible distributional impact of utilizing universal public financing as a tool to increase access and coverage of breast cancer early detection interventions in Uganda and South Africa. This study considered a provider's perspective, and this implies that only the health provider costs were estimated. The provider's perspective was selected primarily because the study focuses on costs borne by the public health system, including costs of screening, diagnostic services, treatment, and follow-up, which are central to informing health policy, budgeting, and resource allocation decisions within Uganda and South Africa.

Costs and benefits were discounted at 3%. Multivariable sensitivity analyses were conducted to assess for uncertainty in some key variables that influence costs and effectiveness parameters. All costs are presented in United States Dollars and in each country's local currency. Table 1 presents a summary of the methods for each specific study objective and the relationship between the objectives.

Sensitivity analysis

For all the key parameters that influence the result Incremental Cost Effectiveness Ratio (ICER), multivariable sensitivity analysis was carried out to assess for robustness of the values used to estimate the ICER.

1.4 Ethical Considerations

Ethical approval was obtained from the Human Research Ethics Committee at University of Cape Town (HREC 257/2018) as well as from a Uganda Human Research Ethics Committee at TASO (TASO REC/010/19-UG-REC-009).

Table 1: Summary of proposed methods for each study objective

Specific Objective	Analytical Method	Main Outcome
1.To estimate the downstaging effect of early detection and screening interventions for breast cancer	Construct a dynamic state transition model to predict and quantify the downstaging effect of early detection and screening interventions.	-Downstaging effect of early detection and screening interventions
2.To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in South Africa.	*Health services costs*: Per person screening, diagnosis, treatment, and program costs were primarily obtained from published costing studies and Ministry of Health reports or plans for South Africa and Uganda. Where data on costs of a particular step in the patient pathway was unavailable from published sources, we drew on existing micro-costing frameworks developed by WHO to estimate the resources involved in a given procedure. *Effectiveness data*: Obtained from published literature. *Cost effectiveness analysis*: Used a dynamic state transition model state-transition cohort simulation model to link the costs to effectiveness data.	-Cost analysis of early detection and treatment of breast cancer. -Total and unit costs for early detection and treatment of breast cancer. -Cost effectiveness analysis for early detection and treatment of breast cancer. -Incremental Cost Effectiveness Ratio (ICER) per Healthy Life Year gained and deaths averted
3. To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in Uganda.	*Health services costs*: Per person screening, diagnosis, treatment, and program costs were primarily obtained from published costing studies and Ministry of Health reports or plans for South Africa and Uganda. Where data on costs of a particular step in the patient pathway was unavailable from published sources, we drew on existing micro-costing frameworks developed by WHO to estimate the resources involved in a given procedure. *Effectiveness data*: Obtained from published literature. *Cost effectiveness analysis*: Used a dynamic state transition model state-transition cohort simulation model to link the costs to effectiveness data.	-Cost analysis of early detection and treatment of breast cancer. -Total and unit costs for early detection and treatment of breast cancer. -Cost effectiveness analysis for early detection and treatment of breast cancer. -Incremental Cost Effectiveness Ratio (ICER) per Healthy Life Year gained and deaths averted
4. To quantify the financial and health distributional impacts of publicly financing early detection, screening, and breast cancer control interventions in South Africa and Uganda	*Extended cost effectiveness analysis*: to assess the distributional impact of utilizing universal public financing as a tool to increase access and coverage of breast cancer early detection interventions	-Distribution of the health gains (deaths averted) across wealth quintiles. - Distribution of the health gains (healthy life years gained) across wealth quintiles. -Distribution of cases of catastrophic health expenditures averted.

1.5 Thesis Outline

The overarching goal of this thesis is to provide evidence-based information for low- and middle-income countries on the economics of breast cancer control interventions. The thesis is presented in nine chapters with the current chapter providing an introduction and overview of the body of work. This chapter also contains a brief background, aims and objectives of the thesis, and an outline of this thesis.

Chapter two presents a comprehensive literature review on clinical manifestation of breast cancer, breast cancer and resource allocation, breast cancer screening priorities and challenges, and an in-depth overview of previous economic analyses of breast cancer in low- and middle-income countries. The chapter ends with a discussion on what economic evidence on breast cancer exists for low- and middle-income countries and its implication for future economic analyses.

Chapter three presents an overview of the methodological approach used for this thesis including the description of the development of a dynamic state transition model to predict the stage shift distribution associated with various breast cancer early detection, screening, and treatment alternatives in one low-income country and one middle income country. Further details of each analysis are contained in the results chapters (4 to 8).

Chapters four to eight present results on downstaging, cost effectiveness, and extended cost-effectiveness of early detection and screening interventions for breast cancer control in Uganda and South Africa.

Chapter nine presents a synthesis and discussion of the thesis findings; the chapter also discusses generalizability concerns of the thesis findings, study limitations, the novel contributions of this thesis, the policy implications, and proposals for future research.

CHAPTER

2

"So then it is not of him who wills, nor of him who runs, but of God who shows mercy" Romans 9:16

Chapter 2: Literature Review

2.1 Introduction

The aim of this chapter is to provide an in-depth exploration of breast cancer management in low- and middle-income countries (LMICs), and also an exploration of economic and equity evidence to support resource allocation decisions for breast cancer management specifically focusing on early detection, screening, and treatment strategies for breast cancer in low- and middle-income countries (LMICs). Considering that this study has a special focus on early detection of breast cancer – sections 2.2 and 2.3 discuss clinical manifestation, staging, and early detection of breast cancer and screening tools. Section 2.4 discusses breast cancer and issues pertaining to resource allocation and in section 2.5 the review turns to breast cancer screening priorities and challenges for LMICs. Section 2.6 presents a summary of an overview of empirical evidence from costing and cost effectiveness analyses for breast cancer in LMICs. Section 2.7 discusses equity and financial protection considerations in economic analyses for breast cancer. Finally, in section 2.8 the chapter presents a summary of the key findings of the literature review highlighting the pertinent outstanding context-specific research questions for the Sub-Saharan African region that need to be answered.

Approach to the Comprehensive Review

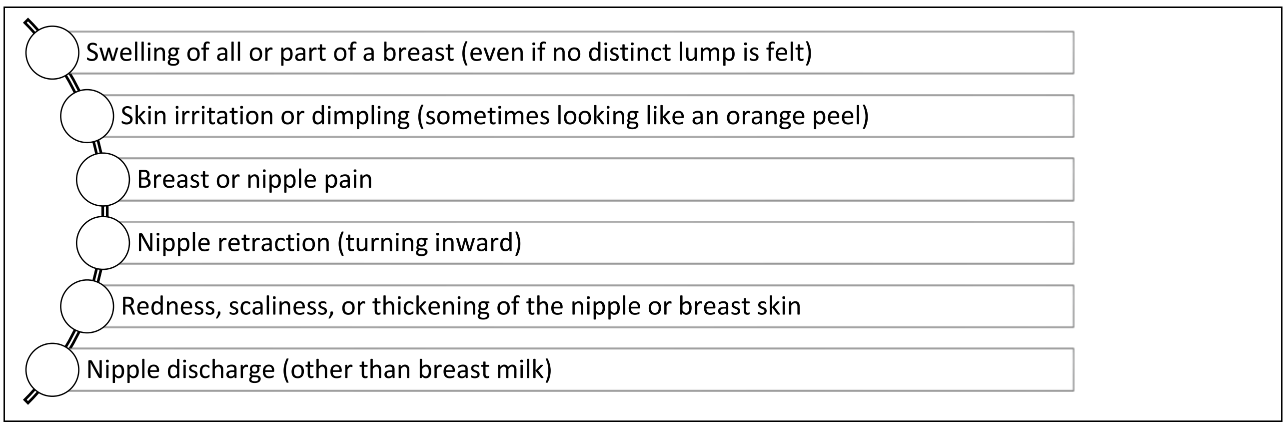
A comprehensive literature review was conducted to inform this study. While not designed or executed as a formal systematic review (except for aspects of sub-section 2.6), the review followed a structured and rigorous approach in line with doctoral level research requirements. This involved extensive searching and critical appraisal of peer-reviewed journal articles, relevant grey literature, national health policies, WHO reports, and Global Burden of Disease datasets, ensuring coverage of both global and country-specific evidence relevant to the research objectives. The broader literature review presented in this section focused on early detection, screening, cost-effectiveness, and financial protection and equity in the remit of breast cancer. Searches were conducted using electronic databases including PubMed, Google Scholar, Scopus, and WHO IRIS, covering literature published from 2000 to 2024. Search terms included combinations of the following keywords and Medical Subject Headings (MeSH): *"breast cancer"*, *"early detection"*, *"screening"*, *"clinical breast examination"*, *"mammography"*, *"awareness"*, *"treatment"*, *"cost-effectiveness"*, *"economic evaluation"*, *"equity"*, *"financial protection"*, *"LMICs"*, *"Sub-Saharan Africa"*, *"Uganda"*, and *"South Africa"*. Boolean operators (AND, OR) were used to refine searches. Inclusion criteria were: (1) studies focused on LMICs; (2) studies that addressed early detection, screening, treatment, economic evaluations, or equity in breast cancer care; (3) English-language publications; and (4) articles published between 2000 and 2024. The focus of this review was to synthesize the empirical evidence and contextual factors necessary to frame the study aims, design, and interpretation of this thesis and the selection of studies was guided by relevance to the thematic scope of the thesis, the credibility of the source, and contextual applicability to Uganda and South Africa.

For the review of empirical evidence on cost effectiveness analyses (sub-section 2.6), we aimed to provide a comprehensive economic overview of breast cancer control in LMICs, and, for this subsection, we borrowed some of the methods for a systematic review approach. It important to note that the decision not to conduct a systematic review for the broader literature was deliberate, as the research questions required integrating insights from multiple sources rather than addressing a narrowly framed clinical or policy effectiveness question.

2.2 Clinical manifestation and staging of Breast Cancer

Breast cancer is one of the most prevalent and potentially life-threatening forms of cancer affecting individuals, particularly women, worldwide[1], [5]. It arises from the uncontrolled growth of abnormal cells in the breast tissue, forming a malignant tumor. Despite significant advancements in diagnosis and treatment, breast cancer remains a significant public health concern, emphasizing the importance of early detection and intervention[20]. The most common symptom of breast cancer is a new lump or mass. A lump that is most likely cancerous is a painless, hard mass, and has irregular edges, however, it's important to note that breast cancers can also be round, tender, or soft, and even painful [21]. That is why it is important to have any new breast mass or lump examined by a healthcare provider. According to the American Cancer Society, any of the unusual changes in the breast presented in *Figure **1*** can be a symptom of breast cancer[21].

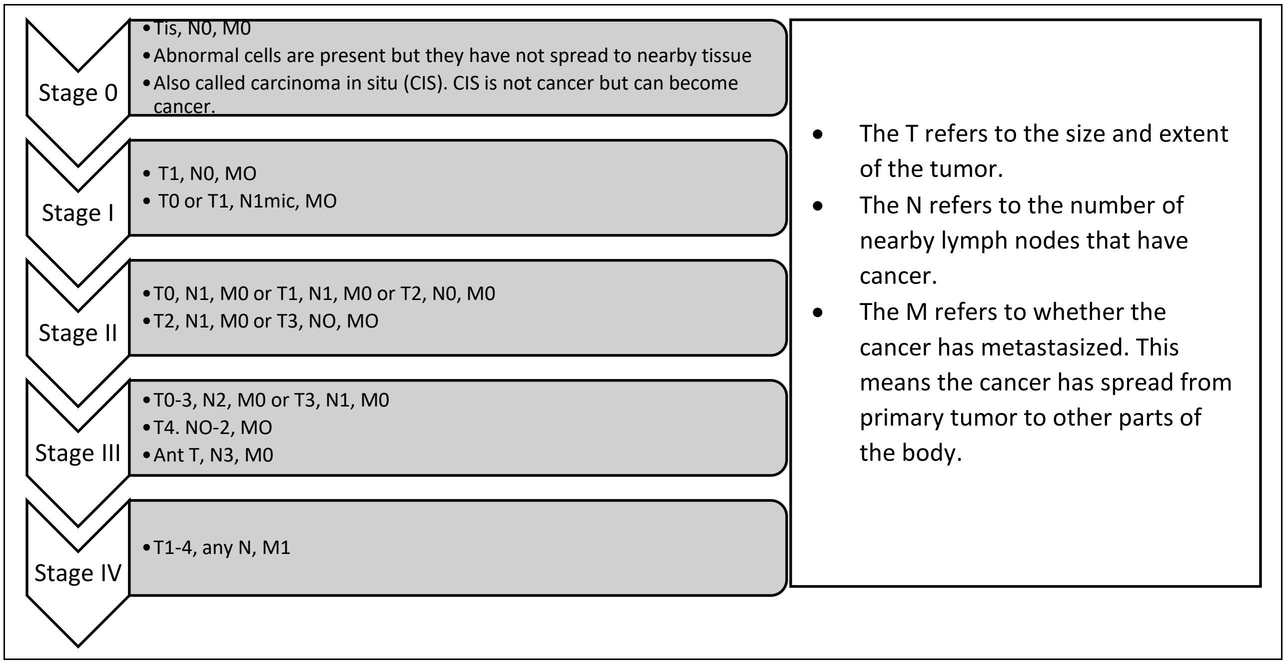
Figure 1: Possible Symptoms of breast cancer



Source: American Cancer Society

However, sometimes these changes are not symptoms of breast cancer but instead ensue from other less serious conditions such as cysts or infections. Physicians diagnose approximately 1 in 20 women with invasive breast cancer [22], [23] although this statistic is highly dependent on the level of awareness of breast cancer signs and symptoms in a population. In cases where breast cancer is confirmed (through screening and diagnostic tests), the extent of the cancer can be described by stage. Staging of breast cancer is the process of determining how widespread the cancer is and this depends on several factors such as: the size of the tumor, if the cancer is invasive or non-invasive, the number of lymph nodes involved, and whether the cancer has spread to other parts of the body (metastasis) [24]. The American Joint Committee on Cancer's (AJCC) TNM system is the most commonly used system to describe staging of breast cancer [24]. This system classifies breast cancers into four stages (I to IV), see *Figure **2***.

Figure 2: The American Joint Committee on Cancer's (AJCC) TNM staging system

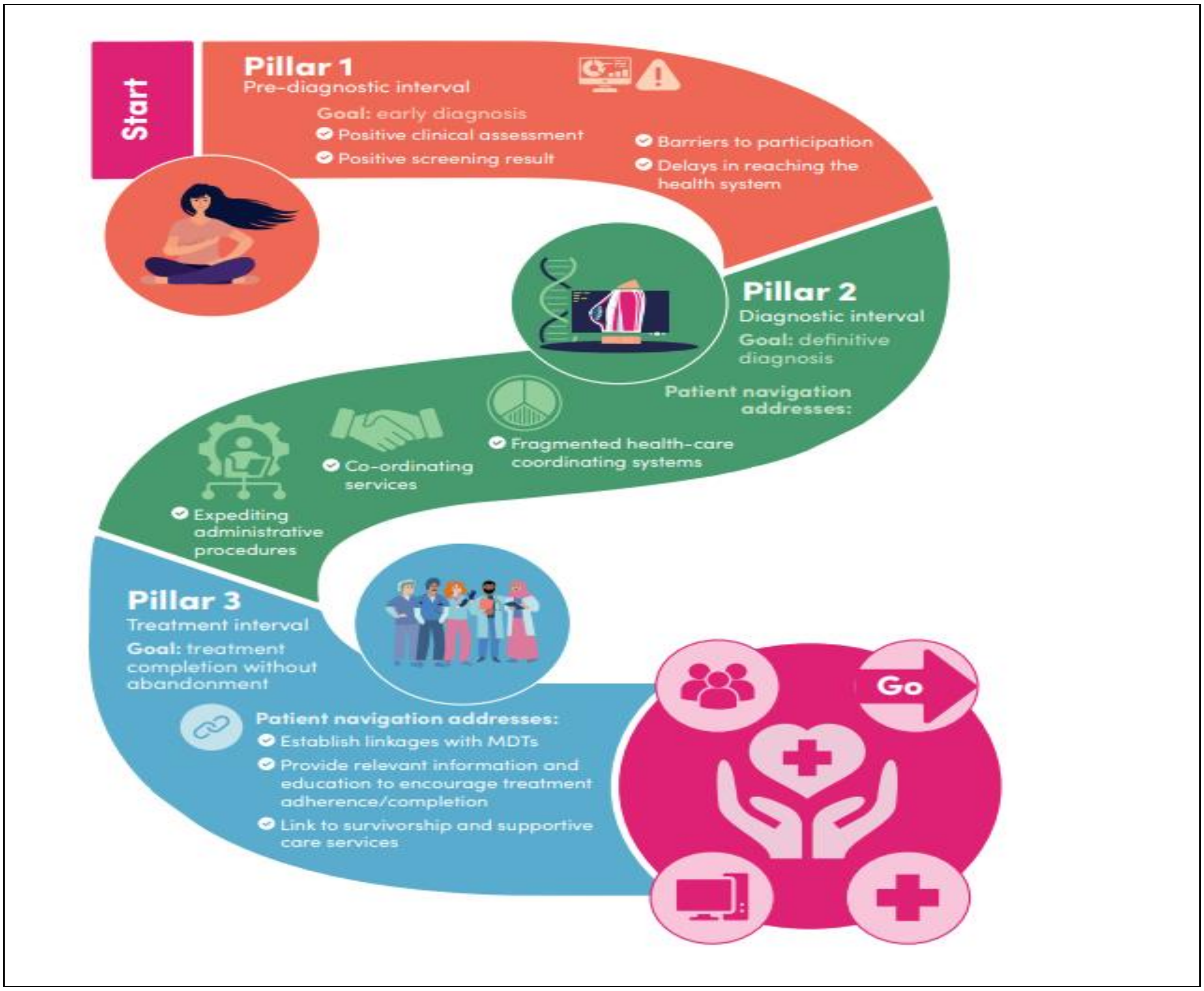


Source: Figure created by author. Information obtained from: American Joint Committee on Cancer https://www.cancer.gov/about-cancer/diagnosis-staging/staging

2.3 Early Detection of Breast Cancer

The United Nation's Sustainable Development Goals (SDGs) for 2030 calls for a reduction in premature mortality from non-communicable diseases (NCDs) by a third through prevention and treatment *[25]*. The early detection and screening for breast cancer is paramount for this SDG as it aims to reduce the mortality and morbidity pertaining to late diagnosis of the disease. In the literature, a breast cancer delay is defined as a time lag of more than 3 months between discovery of breast cancer symptoms and initiation of cancer treatment [26]. Breast cancer delays have been traditionally categorized as either patient delays or provider delays. Several cut off points have been proposed but traditionally – a patient delay is when 3 months elapse between discovery of symptoms and first medical consultation [27], [28]. On the other hand, a provider delay occurs between the first medical consultation and the start of treatment. The operational threshold for provider delay is 1 month although this varies across studies [29]. However, Walter et al. (2012) have questioned the term "delay" and argued that it is not only value laden, but it is also inaccurate. They suggested a more appropriate framework to describe the time intervals along the stages from symptom recognition to diagnosis and initiation of treatment (see *Figure **3***). The appraisal interval is defined to describe the time interval from detection or awareness of changes in the body to perceiving a reason to discuss the symptoms with a health care provider, the help-seeking interval describes the time interval from perceiving a reason to discuss symptoms with a health care provider to the first consultation with the health care provider about the symptoms. The diagnostic interval describes the time between first appointment and the time a formal cancer diagnosis is made, and this interval might involve referrals, several appointments, and investigations. The pre-treatment interval describes the interval between formal diagnosis and initiation of treatment[13].

Figure 3: Patient Navigation and the Three Pillars of Breast Cancer Patient Care Pathway



Source: WHO GBCI Implementation Framework (2024)[13]

In the HICs, early detection of breast cancer has resulted into favorable survival rates [30]. Early detection of breast cancer is intuitively appealing; identifying the disease at initial stage allows for better prognosis and may result in treatment savings especially for resource-constrained countries [31]. Systematic reviews and meta-analysis for breast cancer stage of diagnosis in Sub Saharan Africa suggest that strategies for early detection of breast cancer should be the major priority for cancer control programs in the Sub-Saharan African region [32]. Indeed, until there is a cure for breast cancer, the best way forward to curb mortality is a combination of early detection and effective treatment. If the overarching goal of any early detection initiative is to reduce mortality, then the detected cases must have access to effective and affordable treatment [20]. Therefore, however efficient early detection methods are, they are meaningless if there is no proper breast cancer treatment. As such, the establishment of a stage-appropriate treatment facility should precede any early detection initiative.

Approaches to breast cancer education

The Global Summit Early Detection Panel noted that education and awareness alone have the potential to result in a favorable shift in the stage of breast cancer at presentation. The panelists recounted that they "*consider it axiomatic that education about breast cancer is a right to all women*" [20]. Breast cancer education can be achieved with simple pervasive, popular, and cost-effective means for instance through television and radio programs and advertisements. However, the panel noted that it is important to tailor the education to the culture of the targeted population so that it can have the greatest benefit. The panel also highlighted the need to educate men as well because men can facilitate early detection in their partners and help to reduce the barriers to care. Healthcare providers such as physicians, nurses, midwives, traditional healers, etc. should also be educated [20]. Breast cancer education should stress the following:

- Signs and symptoms of breast cancer
- That breast cancer is fatal and can kill
- That breast cancer can be effectively treated and need not kill
- Seeking health care for a breast problem earlier is much better than later
- That most breast lumps are not cancerous
- That breast cancer is diagnosed by biopsy and not mastectomy

Very few empirical studies have evaluated the cost effectiveness of breast cancer education as an early detection tool for breast cancer in LMICs [33], [34], [35], [36]. In Ghana, Zelle et al. (2012) found that mass media awareness interventions were economically attractive at $1,364/DALY [35]. In Mexico, a study by Niens et al. (2014) found that at 95% coverage, a mass media awareness-raising program could be the most cost-effective breast cancer control intervention (ICER US$ 5,021/DALY) [34]. The two-breast cancer early detection interventions in the literature found to be cost effective are: Breast Awareness Raising (BAR) and Mass-media Awareness Raising (MAR) which, is BAR + a mass media campaign [35].

Tools for Screening of Breast Cancer

For LMICs, three methods have been commonly proposed and studied: Breast Self- Examination (BSE), Clinical Breast Examination (CBE) and mammography. In some low-income countries like Uganda, a proposed adjunct imaging method to mammography for symptomatic women with dense breasts is ultrasonography [37]. Table 2 below presents a summary description of the screening methods for breast cancer.

Table 2: Description and Effectiveness of Early Detection and Screening Methods

Early detection and Screening Methods	Description	Effectiveness of method
Breast Awareness Raising	Breast cancer education can be achieved with simple pervasive, popular, and cost-effective means for instance through television and radio programs and advertisements. However, it is important to tailor the education to the culture of the targeted population so that it can have the greatest benefit. It is also critical to educate men because they can facilitate early detection in their partners and help to reduce the barriers to care. Healthcare providers such as physicians, nurses, midwives, traditional healers, etc. should also be educated [20].	Few empirical studies have evaluated the cost effectiveness of breast cancer education as an early detection tool for breast cancer[33], [34], [35], [36]. In Ghana, a study found that mass media awareness interventions were economically attractive at $1,364/DALY [35]. In Mexico, a study by Niens et al. (2014) found that at 95% coverage, a mass media awareness-raising program could be the most cost-effective breast cancer control intervention (ICER US$ 5,021/DALY) [34]. The two-breast cancer early detection interventions in the literature found to be cost effective are: Breast Awareness Raising (BAR) and Mass-media Awareness Raising (MAR) which, is BAR + a mass media campaign [35].
Breast Self-Examination	Women are formally taught how to examine their breasts. Typically, women are taught to inspect their breasts preferably in front of a mirror for asymmetry and then by palpation examine the breast using the contralateral hand with the ipsilateral arm raised. A systematic BSE program entails at least one or more sessions for a group of women or with individual women taught by trained personnel.	The evidence of the efficacy for BSE has been shown to be inadequate [38]. Two randomized control trials were conducted, one in Shanghai China [39] and another in St. Petersburg Russia [40]. Both studies did not find taught BSE to reduce the risk of dying from breast cancer. A meta-analysis that included both randomized and non-randomized studies also found similar results that BSE has no effect on breast cancer mortality [41]. Based off this available evidence, the WHO International Agency for Research on Cancer (IARC) concluded back in 2002 and again in 2014 that there is inadequate evidence to support the notion that BSE has the potential to reduce breast cancer mortality [38]. However, a deeper analysis of the data from the Shanghai study by Smith et al. found that a large proportion of the women in the control arm were very responsive to symptoms of breast cancers yet they didn't receive the formal instruction in BSE [42] (Smith et al., 2003). The plausible explanation for this was said to be the high level of population awareness for breast cancers and this suggests that in cases where the population has good knowledge and awareness of breast cancer, the efficacy of BSE further shrinks.
Clinical Breast Examination	This is a standard clinical procedure where a healthcare provider examines women's breasts, chest wall and axillae. The healthcare provider looks out for signs and symptoms of breast cancer such as asymmetry, oedema, dimpling and erythema. This is then followed by systematically palpating both breasts and axillae in prostate and sitting positions.	Evidence from three trials found that women who were randomly assigned to receive CBE had less advanced stage cancer detected, and the tumors were of small size compared to women who didn't receive any screening [43], [44]. In a Canadian study where women were randomly assigned to CBE in one study arm and CBE plus mammography in another found that women in both arms had a similar rate of breast cancer mortality and nodal involvement rate at diagnosis [45]. Through this indirect evidence, it is suggested that CBE can do as well as mammography. Evidence from observational studies mostly conducted in the 1970s also found that combining CBE with mammography increased the rate to detect breast cancer by 5 to 10% points as compared with using mammography alone [38]. Although the WHO IARC has found there to be inadequate evidence that CBE reduces breast cancer mortality, it has found there to be sufficient evidence that CBE shifts the stage distribution of breast cancer tumors to lower stages

		[38]. The Global Summit Early Detection Panel also recommended that CBE should be integrated in routine health examinations to work as either a screening or diagnostic tool. The panel also noted that CBE would be most beneficial in countries where women typically present with late-stage disease[20].
Mammography	A standard mammography that has dual views (mediolateral oblique and carniocaudal) is used to screen both breasts. The age of women, interval of screening and frequency of conducting mammography on women at risk of breast cancer is a point of debate and as a result consensus has not been reached globally. Different contexts therefore have varying guidelines.	The WHO-IARC reviewed all the randomized control trials on mammography and found that there is sufficient evidence that mammography is an efficient method used to reduce breast cancer mortality especially for women between 50-69 and 70-74 years [38]. Evidence from cohort studies reviewed by the IARC showed that in HICs countries, screening by mammography reduced breast cancer mortality by 23% for women between 50-69 years invited for the screening and a 40% reduction was reported for the women who attend the screening. However, overall, consensus was not reached on the most appropriate screening interval, which age groups to target and other logistics of implementing and quality assuring a breast cancer-screening program [38]. While mammography was found to be an effective screening method, there are some harms and limitations associated with the method. The method is associated with 3 identified harms in the literature: (a) false positives, (b) overdiagnosis and (c) possible radiation-induced cancer [38], [46]. Overall, studies showed that false positive mammogram results have short-term negative psychological consequences on the women [38]. Regarding overdiagnosis, the term refers to the discovery of tumors that histologically fulfill the criteria for cancer but would not become clinically apparent in a woman's lifetime [46]. Some studies have shown that the proportion of women treated needlessly ranges from 10% to 30% dependent on the age and interval of screening [47]. The WHO-IARC reported an overdiagnosis rate of 6.5% (range, 1 to 10%) based on data from European studies and controlled trials also found similar results (4 to 11%) [38]. For possible radiation-induced cancer, the cumulative risk of death is from breast cancer attributed to radiation resulting from mammography is 1 to 10 per 100,000 women and this is dependent on the age of the woman, the frequency and duration of the screening [38]. For LMIC settings, mammography has two major limitations: firstly, it is a very high-cost method and, secondly, performing the procedure as well as interpreting the results could be technically complex [20]. As a result, the Global Summit Early Detection Panel recommended that mammography might not be an appropriate screening method for LMICs [20].
Ultrasonograph y (US)	Ultrasonography is a targeted examination commonly done using a handheld ultrasound scans. Ultrasonography is commonly used to detect palpable masses not visible on mammograms as well as to assess for non-palpable masses detected by mammograms. The method has also been found to contribute to differentiation in benign, intermediate, and malignant masses. However, ultrasonography is unable to demonstrate microcalcifications and as such the method cannot replace mammography as a gold standard.	Empirical evidence on the effectiveness of breast ultrasounds is limited to women with dense breasts on mammography or at an increased risk for breast cancer [48]. Ultrasounds may detect 3 to 4 additional breast cancers per 1000 women with an increased risk of the disease; however, there is no data on the use of ultrasonography in the general population [49]. As a potential screening tool, breast ultrasound scans have a couple of limitations including examination techniques are not standardized, no standardized criteria to guide interpretation of results, inability to detect microcalcifications, and a higher rate of false positives [49]. The false positive rate based on solid lesion for ultrasound ranged from 2.4% to 12.9% for ultrasound while for mammography it ranged from 0.7% to 6% [48]. The WHO-IARC panel concluded that there is inadequate evidence that ultrasonography neither reduces mortality or the rate of interval cancer. The panel also concluded that there is sufficient evidence, which shows that ultrasonography, increases the proportions of false positive outcomes [38].

2.4 Breast Cancer and Resource Allocation

The Breast Health Global Initiative developed guidelines to assist policymakers prioritize resource allocation for early detection of breast cancer in LMICs [50]. The panel provided guidelines for health systems based on varying level of resources and four categories were considered: basic level, limited level, enhanced level, and maximal level.

- ***Basic level*** – refers to the core services that are an absolute necessity and are typically provided in a single clinic visitation. At this level, the emphasis on conducting a physical examination and obtaining a history of the breast cancer symptoms. Imaging services are not expected to be available at this level.
- ***Limited level*** – refers to second tier services that can be provided in single or multiple clinical interactions. The emphasis at this level is to improve on clinical outcomes of the patients for instance, increase survival in the underlying context of few resources and modest infrastructure. At this level, services provided include breast cancer education to targeted women and some diagnostic imaging for suspicious breast lesions e.g., ultrasound and mammography.
- ***Enhanced level*** – refers to third tier services that are optional but important such as mammographic screening and image-guided biopsy. At this level, the resources are expected to further improve clinical outcomes and should increase the number of patient choices as well as the quality of therapeutic options.
- ***Maximal level*** – refers to high level services that are typically available only in high resource settings and their success is dependent on the existence and functionality of all the lower-level resources. An example is to screen high-risk populations using breast magnetic resonance imaging (MRI). In resource-constrained settings, these services should be considered a lower priority than the lower-level services because of their high resource requirement. Table 3 below presents a summary of the recommended early detection method for each level of services.

Table 3: Early Detection and Resource Allocation

Level	Breast Education	Detection Method
Basic level	Provide educational programs to teach the importance of early detection, risk factors of breast cancer, and health awareness (education and self-examination). The messages should both be culturally and linguistically appropriate.	-Clinical history -CBE
Limited level	Provincial or district level targeted outreaches conducted by healthcare providers to encourage high-risk women to seek CBE. The messages should both be culturally and linguistically appropriate.	-Diagnostic breast ultrasound in women with positive CBE -If possible: diagnostic mammography in women with positive CBE -Mammographic screening of target group*
Enhanced level	Regional breast health awareness programs integrated with general health and women's health programs.	-Mammographic screening biennially for women 50-69. - Consider mammographic screening for women aged 40-49 every 12-18 months.
Maximal level	Use media campaigns to deliver national awareness regarding breast cancer.	- Annual mammographic screening women >40 years. - Use of other imaging techniques appropriate for high-risk women.

Source: Yip et al. (2008) and Horton and Gauvreau *2015[50] *Target group selection should consider the breast cancer demographics and resource constraints in the population.*

The evidence suggests that Clinical Breast Examination (CBE) is the most cost effective and affordable screening technique for LMICs. An economic overview by Horton and Gauvreau (2015) advocated for implementing clinical breast exams (CBE) in resource-constrained settings and mammography where feasible, particularly in upper-middle-income countries, to improve early detection and outcomes [51]. The overview also noted that as treatment for cancers is scaled up, screening becomes more important to stage-shift breast cancer prognosis. However, very few studies have examined the cost-effectiveness of early detection, screening, and breast cancer control interventions in low- and middle-income countries.

2.5 Breast Cancer Screening and Priority Challenges

Recent literature continues to emphasize the dynamic landscape of breast cancer screening, particularly in LMICs where the burden of late-stage diagnosis remains high. Studies published between 2020 and 2024 underscore key challenges such as: Limited access to screening remains a significant barrier, with only 2–5% of eligible women (aged 40–69) screened in LMICs compared to 60–80% in high-income countries[52]. In Uganda, access is hindered by having just four mammography units for ~7 million women, requiring long travels making it unaffordable for most women[18]. South Africa fares better with urban mammography availability, but rural uptake is lower in lower quintiles (Q1–Q3) due to transport costs and wait times[11], [14]. Low awareness and cultural barriers drive late-stage diagnoses (80–90% Stages III–IV in LMICs). In Uganda, stigma linking cancer to social taboos reduces uptake of services[18], while South African rural communities often prefer traditional healers, delaying care[53]. Resource constraints, including insufficient trained staff and infrastructure, limit program scalability. Alarmingly, uptake of breast cancer screening practices in LMICs remains low, with pooled prevalence of 22.7% for mammography, 23.1% for clinical breast examination, and 14.6% for breast self-examination[54]. Factors associated with lower uptake include rural residence, lower income and education levels, and lack of insurance[54], [55]. In South Africa, the South African Breast Cancer, and HIV Outcomes (SABCHO) study provides critical South African-specific insights on breast cancer and HIV-related factors. For instance, Mapanga et al. (2023) found that 58% of 1,011 women in the cohort were diagnosed at advanced stages (III–IV), driven by health system delays (e.g., fewer clinic visits) and individual factors (e.g., low education, HIV status), underscoring barriers to early detection[56]. Additionally, Ayeni et al. (2023) reported 45% multimorbidity (e.g., HIV, hypertension) in 3,261 women, reducing 3-year survival to 60.8% versus 72% without multimorbidity, highlighting the need for integrated care[57]. Treatment delays, noted in Mapanga et al. (2023), include diagnostic intervals of 3–6 months in rural settings, exacerbated by transport barriers[14]. A growing body of research has also explored different supplemental surveillance options such as contrast enhanced mammography and the integration of artificial intelligence in mammography interpretation to improve accuracy and reach in underserved settings[58]. However, concerns about algorithm bias and health system readiness persist[59]. Integrating advanced technologies like Artificial Intelligence and digital breast tomosynthesis (DBT) is challenging due to high costs and infrastructure gaps[60]. These findings underscore the urgent need for context-appropriate strategies to improve breast cancer screening and control in LMICs and these insights reaffirm the importance of balancing clinical efficacy, economic viability, and equity considerations when formulating national breast cancer screening policies.

2.6 Economic Overview for Breast Cancer Control Interventions in LMICs

This section presents a review of the studies that have either assessed costs and outcomes or costs only or outcomes only for interventions for breast cancer control applying various economic evaluation approaches.

Search Strategy

We systematically searched international databases, namely MEDLINE, Academic Search Premier, CINAHL, Africa- Wide information, SocINDEX, Health source and Web of Science using the EBSCOHOST and GOOGLE SCHOLAR platform to identify the studies to be reviewed. The search took place from July 2022 to May2025 and was not limited to any time frame. The following search terms were used using search terms of "Breast cancer" and "cost effectiveness" OR "Cost" OR "economic evaluation" OR "costing analysis" OR "economic model" OR "cost utility analysis" OR "cost benefit" OR "economic analysis". The reference lists of selected studies were also screened to identify additional articles of possible interest.

Study Eligibility

All relevant articles that were identified using the above criteria were collated and data was entered into a data management software and the duplicates were eliminated. We conducted a preliminary review based on title and abstract, after which a deeper review was performed to assess the full papers for inclusion. Studies were included if they met the PICOS eligibility criteria: 1) **P**opulation: women at risk of breast cancer aged 18 and above in low and middle- income countries (LMICs), as defined by the 2019 World Bank LMIC list; 2) **I**ntervention: awareness raising, screening and treatment purpose; 3) **C**omparison: no screening or other breast cancer control programs; 4) **O**utcome: Cost per life year saved (LYS), Cost per life year gained (LYG), cost per quality adjusted life year (QALY), and cost per disability adjusted life year (DALY) averted were included in the scope of cost-effectiveness analysis, incremental cost-effectiveness ratio (ICER) or average cost-effectiveness ratio (ACER); 5) Study design: economic evaluations (ie, cost-effectiveness, cost-utility, cost-benefit, cost-minimization).

Exclusion criteria were as follows: 1) studies not available in English, 2) non- Peer reviewed journal, 3) Not accessible and 4) if one of the data elements of PICO were excluded. The inclusion and exclusion criteria applied during the screening process are summarized in Table 4 below. The stepwise screening process is detailed in the PRISMA flow diagram in *Figure* ***4***.

Table 4: Inclusion and Exclusion Criteria for Economic Overview of Breast Cancer Control in LMICs

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Women at risk of breast cancer aged 18 and above in low- and middle-income countries (LMICs), as defined by the 2019 World Bank LMIC classification	Studies not focused on the target population or not situated in LMICs
Intervention	Awareness-raising, screening, or treatment interventions for breast cancer	Studies unrelated to breast cancer interventions
Comparator	No screening or no breast cancer control programs	Studies without a comparator or with irrelevant comparison arms
Outcomes	Cost per life year saved (LYS), cost per life year gained (LYG), cost per quality-adjusted life year (QALY), cost per disability-adjusted	Studies not reporting relevant economic or effectiveness outcomes

	life year (DALY) averted, incremental cost-effectiveness ratio (ICER), or average cost-effectiveness ratio (ACER)	
Study Design	Economic evaluations, including cost-effectiveness, cost-utility, cost-benefit, or cost-minimization analyses	Non-economic evaluation studies (e.g., purely clinical, epidemiological, or qualitative studies)
Language	English	Non-English publications
Publication Type	Peer-reviewed journal articles	Non-peer-reviewed sources (e.g., conference abstracts, reports, dissertations)
Accessibility	Full-text articles accessible for data extraction	Inaccessible articles or missing full text

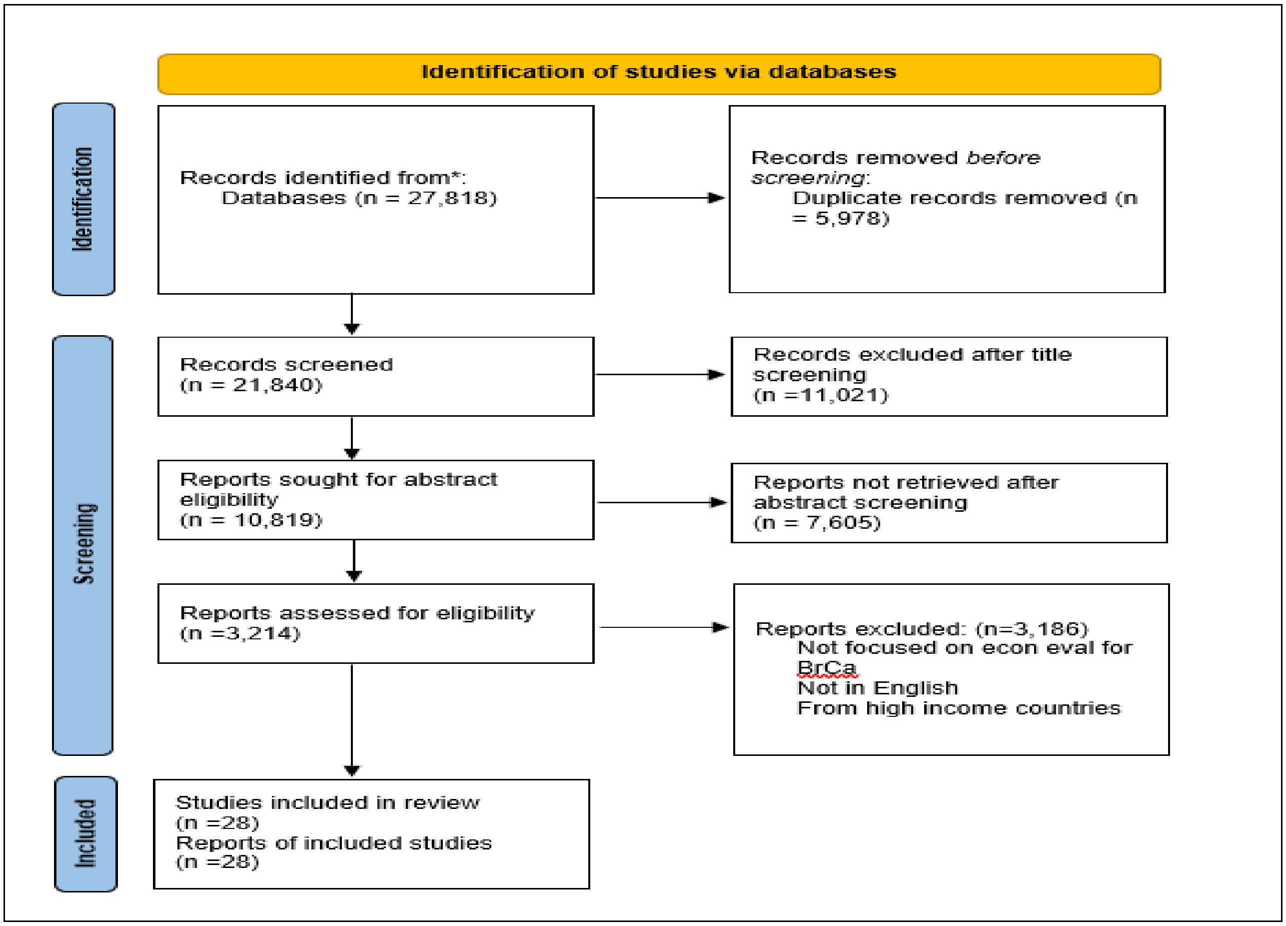
Assessment of quality of selected articles/studies

Drummond's checklist was used to assess the quality of economic evaluations. The quality assessment focused on the identification of fifteen key elements of economic evaluations and methodological characteristics that users may expect to find in comprehensive studies namely research question, description of study intervention, study design, identification, measurement and valuation costs and consequences, discounting, incremental analysis, presentation of results with uncertainty and sensitivity analysis and discussion of results. Although a valid threshold to classify evidence in terms of methodological quality is not available, we scored studies as 'high quality' if 11 or more elements from the Drummond checklist were reported. Studies were scored medium quality if 8 or 9 elements of the checklist were reported, or poor quality if < 8 elements of the checklist were reported.

Search Results

The initial electric search retrieved 27,818 articles all limited to peer reviewed, academic journals extracted from different database; 11,398 for MEDLINE, 9,403 from Academic Search Premier, 2,849 from CINAHL, 1,139 from SocINDEX, 428 from Health source, 730 from Web of Science, 539 from Scopus and 1332 from Google scholar. We screened these articles through four steps; **Step 1-** removed the duplicates, **Step 2 -** records excluded after title screening, **Step 3** - records removed after abstract screening and **Step 4 -** articles removed because they did not meet the inclusion criteria. We finally identified 28 articles that met our inclusion criteria.

Figure 4: PRISMA Flow Diagram for Study Selection



Study Characteristics

Table 7 defines the baseline characteristics of the 28 articles from LMICs incorporated in the study. Majority of the studies were from African countries (n=9) and multiple countries (n=8). The rest of the studies were from the Middle East countries (n=6), Asia (n=2) and Latin American countries (n=2).

Quality of the studies

Studies were scored against the fifteen questions from the Drummond's checklist for assessing economic evaluations. The quality analysis of the included articles ranged from a score 23% to 90%. Overall, 14 studies out 28 were of good quality (70% and above), 7 studies were of medium quality (63% -53%) and 7 (52% and below) were of poor quality. Table 6 summarizes the scores of studies measured against the appraisal checklist. Overall, half of the articles were of good quality and the other half were not of good quality. Additionally, 70% of the economic evaluations did not take into account any equity considerations.

Summary of findings on the economic overview of breast cancer control

Our results suggested that mammography screening was the most common screening intervention in the review. This screening approach was found to be the most cost effective in six studies compared to other studies. Similarly, cost-effective findings comparing Trastuzumab and other treatment interventions found Trastuzumab to be cost effective. These findings are echoed by [60] and [61]. Most studies assessed the different breast cancer treatment intervention and the following conclusions were reached; the base-case analysis suggested that AdjCT with Trastuzumab + chemotherapy was a cost-effective choice for patients with HER2-positive BC aged 70 years or older, the cost of utidelone per 30 mg was lower than $18.5 to obtain the cost-effectiveness in MBC patients resistant to anthracyclines and taxanes, the 6-month Trastuzumab is a cost-effective option when compared to 1-year Trastuzumab in patients with HER2 positive ABC in Egypt [62]. For LMICs, studies concluded that margetuximab plus chemotherapy is not cost-effective compared with Trastuzumab plus chemotherapy in pretreated patients with ERBB2-positive advanced breast cancer. To optimally assess cost-effectiveness, screening frequency and population age need to be considered. Studies included in this review evaluated multiple age groups, but mostly (85%) from the age between 40 and 70 years. They compared a range of screening frequencies (from annually to triennially). The studies by Sun et al. 2018 [65], Zehtab et al., 2016 (35-65 years) [66], Pascha et al., 2021 (40 and above) [67], and Zelle et al., 2012 (40 and above) [35] used biennial mammography screening for their program and found it cost-effective. Furthermore, Ginsberg et al., 2012 (40- 70) revealed that biennial screen-filmed mammography is more economically viable than annual screening (both strategies were cost-effective) [68]. Astim et al. 2011 found that biennial mammography (40 and above years) is more cost-effective.

On Breast Awareness Raising, the review highlighted that only two studies examined the cost-effectiveness of educational interventions for breast cancer awareness and early detection in LMICs[34], [35]. Table 5 provides a summary of the population, intervention, comparator, and outcome (PICOs) and the Template for Intervention Description and Replication (TIDieR) for the two studies

Table 5: PICOs and TIDieR Summary for Educational Interventions for Breast Cancer in LMICs

	Population (P)	**Intervention (I)**	**Comparator (C)**	**Outcome (O)**	**TIDieR: Who Delivered**	**TIDieR: Mode**	**TIDieR: Intensity**	**TIDieR: Setting**
Zelle et al., 2012[35]	Women aged 40–69 in Costa Rica and Mexico	Mass media + community-based education on breast cancer awareness and early detection	No educational intervention	Cost per DALY averted; reduction in breast cancer mortality	Trained health educators, community workers	Community outreach, printed materials, radio campaigns	Multiple sessions over several months	Community settings, primary healthcare centers
Niëns et al., 2014 [34]	Low-income households in LMICs	Educational outreach and materials on essential medicine use, availability, affordability	No educational outreach	Reduction in catastrophic health expenditure; improved access to essential meds	Community health workers, NGOs	Community meetings, brochures, radio announcements	Single or repeated sessions over targeted timeframe	Community hubs, local health clinics

Table 6 presents the quality of the assessed articles, Table 7 presents the characteristics of the CEA studies evaluated, and Table 8 presents the objectives, the main comparators and the key conclusions of the studies included.

Table 6: Quality Assessment of Included Studies

Study No.	Author	Does the economic evaluation state a well-defined objective?	Is the perspective of the analysis is clearly stated and appropriate?	Does the economic evaluation include strong evidence of the initiative's effectiveness?	Is a description of the initiative and the comparator clearly stated and appropriate?	Is the time horizon selected for the analysis is clearly stated and appropriate?	Is the target group selected for the analysis is clearly stated and appropriate?	Is the economic evaluation method selected clearly stated and appropriate?	Are all the relevant costs and outcomes for the initiatives identified?	Are costs measured in appropriate units and valued accurately?	Are outcomes measured in appropriate units and valued accurately?	Does the economic evaluation adequately account for equity considerations?	Are adjustments made for costs and outcomes that occur in the future using a discount rate?	Has an incremental analysis of costs and outcomes of initiatives been performed?	Is uncertainty in the estimates of costs and outcomes adequately taken into account?	(Are the findings from the economic evaluation translatable to your context or setting?	Total score	% Score
1	Birnbaum et al. 2018[69]	2	0	2	2	0	1	1	1	0	2	0	0	0	0	1	12	40
2	Barfar et al. 2014[70]	2	2	2	2	2	2	2	2	1	2	0	0	0	2	1	22	73
3	Niens et al 2014[34]	2	2	2	2	2	2	2	2	2	2	0	2	2	2	1	27	90
4	Nooshin Zehtab et al.2016[71]	1	1	1	2	1	1	2	2	2	2	0	0	2	0	2	19	63
5	Guzha et al. 2020[72]	2	2	0	1	2	1	1	1	2	0	0	0	0	0	2	14	47
6	Nnaji C et al. 2020[73]	1	0	0	0	1	1	1	1	0	1	1	1	2	2	2	14	47
7	Ifeoma Jovita Nduka et al. 2022[74]	1	0	0	0	1	1	0	1	0	1	0	0	0	1	1	7	23

8	Alshreef K et al. 2019[75]	2	2	2	2	2	0	2	2	2	1	0	0	1	2	2	22	73
9	Gihan Hamdy Elsisi et al. 2020[62]	2	1	1	1	2	1	1	0	1	1	2	2	2	1	2	20	67
10	Yeong et al. 2023[10]	2	0	0	1	1	2	2	1	1	1	0	0	0	0	1	12	40
11	Addo et al. 2021[76]	2	2	2	2	2	2	2	2	1	2	0	0	2	2	1	24	80
12	Ali Aboutorabi et al. 2014[77]	2	2	2	1	1	1	1	2	2	2	1	1	1	2	1	22	73
13	Navid Omidifar et al 2022[78]	2	2	0	2	0	2	1	2	2	0	1	1	1	1	1	18	60
14	Masuku et al 2025[79]	2	2	2	2	2	1	2	2	1	2	0	2	2	2	2	26	86
15	Ajeng VIcanervilia et al. 2022[60]	1	2	1	0	1	2	0	1	1	2	2	0	1	1	0	15	50
16	Parsa Erfani et al.2021[80]	2	2	1	1	1	1	2	1	2	1	2	2	1	1	2	22	73
17	Lince-Deroche et al. 2021[80]	2	2	0	1	2	1	2	2	2	1	0	0	0	2	2	19	63
18	Greshon et al. 2019[81]	2	2	2	2	2	1	2	1	2	2	0	2	2	1	1	24	80
19	Groot et al. 2006[82]	1	1	1	2	2	2	2	2	1	1	2	1	1	1	2	22	73
20	Zelle et al. 2012[35]	2	2	2	2	2	2	2	2	2	2	0	2	2	2	1	27	90

21	Ginsberg et al. 2012[68]	2	2	2	2	1	1	1	2	2	1	1	1	2	2	2	24	80
22	Boutayeb et al. 2010[83]	2	1	1	2	2	1	2	2	2	2	1	2	2	2	2	26	87
23	Okonkwo et al. 2008[84]	1	1	1	1	0	1	1	1	1	1	0	0	0	1	1	11	37
24	Hutchinson et al. 2024[12]	1	2	2	2	2	1	1	2	2	2	0	0	0	0	2	19	63
25	Zehtab et al. 2016[71]	1	1	2	1	2	2	1	1	1	1	1	1	1	2	1	19	63
26	Zelle. 2013[36]	2	2	2	2	2	2	2	2	2	2	0	2	2	2	1	27	90
27	Nguyen et al. 2018[85]	1	1	1	2	1	2	1	2	1	1	2	2	2	2	1	22	73
28	Ralaidovy el al. 2018[86]	2	2	2	2	1	2	1	1	1	1	0	2	2	0	2	21	70

Table 7: General characteristics of the included articles

	Author	Country	Study Population	Economic Evaluation Type	Study Design	Perspective	Time frame	Effectiveness Outcome(s)	Source effectiveness data	Discount Rate	Sensitivity Analysis	Incremental analysis
1	Birnbaum et al. 2018[69]	Eastern Africa and Colombia	Women at the age of 30-49 or 50-69	Microsimulation model	State transition microsimulation model	N/A	Not Clear	Lives Saved	Secondary data	NA	NO	NO
2	Barfar et al. 2014[70]	Iran	Women over 35 years of age	Cost effectiveness analysis	Decision tree model based	Provider	30 years	Cases Detected	Primary data collection	NA	Yes	No
3	Niens et al 2014[34]	Costa Rice and Mexico	Simulated Populations of women above 40	CEA	Markov Model based	Provider	100 years	DALYs	Secondary data collection	3% on both cost and come outs	Yes	Yes
4	Nooshin Zehtab et al.2016[71]	South East Iran	35–69-year-old women	CEA	Decision tree model based	Provider	Not Clear	DALYs	Secondary data collection	3%, 5% and 7% on cost	Yes	No
5	Guzha et al. 2020[72]	South Africa	Women of 40 years and above	Costing	Retrospective Cost Analysis	Provider	8 months	N/A	Primary data collection	NA	NO	NO
6	Nnaji C et al. 2020[73]	LMICs	NA	CEA	systematic review and Meta-Analysis	Provider	Not Clear	Not clear	Secondary data collection	NA	No	No
7	Ifeoma Jovita Nduka et al. 2022[74]	LMICs	NA	NO	Systematic Review	Provider	31 years	Not clear	Secondary data collection	NA	NA	NA
8	Alshreef K et al. 2019[75]	South Africa	Not Clear	CUA	Markov model based	Not Clear	35 years	QALYs	Secondary data collection	Not Clear	Yes	Yes
9	Gihan Hamdy Elsisi et al. 2020[62]	Egypt	women with HER2 +ve ABC	CEA	Markov model based	Provider	10 years	QALYs	Secondary data collection	NA	Yes	Yes

	Author	Country	Study Population	Economic Evaluation Type	Study Design	Perspective	Time frame	Effectiveness Outcome(s)	Source effectiveness data	Discount Rate	Sensitivity Analysis	Incremental analysis
10	Yeong et al. 2023[10]	Multiple	Female patients with breast cancer	NA	Systematic Review	NA	21 years	Effectiveness of the program	Secondary data collection	NA	NA	NA
11	Addo et al. 2021[76] Click or tap here to enter text.	Ghana	Women of 49 years and above	CEA	Markov model based	Provider	15 Years	QALYs	Secondary data collection	NA	Yes	Yes
12	Ali Aboutorabi et al. 2014[77]	Iran	Women of average age of 50 years	CEA	Markov model based-Randomized controlled trials	Provider	Over 20 years	QALYs	Secondary data collection	3% on both cost and outcome	Yes	Yes
13	Navid Omidifar et al 2022[78]	Iran	Women for BC surgery in 2019	CEA	cross-sectional study	Patient	3 years	Mean costs	Primary data collection	NA	NA	NA
14	Masuku et al 2025[78]	South Africa	Women aged 40 - 69 years old.	CEA	Decision Tree Model	Provider	Lifetime	DALYs	Secondary data collection	YES	YES	YES
15	Ajeng VIcanervilia et al. 2022[60]	LMICs	Women of 50 to 59 years	CEA, CUA, & CBA	Systematic review study	Provider	Not Clear	Life Years Gained, Life Years Saved, QALYs and DALYs	Secondary data collection	NA	NA	NA
16	Parsa Erfani et al.2021[80]	LMICs	Women aged 18 years and older	CUA	Systematic Reviews and Meta-Analyses	Provider	Not Clear	QALYs	Secondary data collection	NA	Yes	Yes
17	Lince-Deroche et al. 2021[80]	South Africa	NA	Cost Analysis	Clinical Cohort Micro Costing Study	Provider	1 Year	Costs	Primary data collection	NA	YES	NO

	Author	Country	Study Population	Economic Evaluation Type	Study Design	Perspective	Time frame	Effectiveness Outcome(s)	Source effectiveness data	Discount Rate	Sensitivity Analysis	Incremental analysis
18	Greshon et al. 2019[81]	Sun-Saharan Africa	Women aged 45 years.	CEA	Markov model based	Societal	45 years	QALYs	Secondary data collection	3% discount on both costs and outcome	Yes	Yes
19	Groot et al. 2006[82]	Sub-Saharan Africa	Women at risk of BC	CEA	Markov model based	Provider	100 years	DALYs	Secondary data collected	3% discount on both costs and outcome	Yes	Yes
20	Zelle et al. 2012[35]	Ghana	Women at risk of BC	CEA	Simulation Model	Provider	100 years	DALYs	Primary data collected	3% discount on both costs and outcome	Yes	Yes
21	Ginsberg et al. 2012[68]	Sub-Saharan Africa and South East Asia	Women at risk of BC	CEA	Markov model based	Provider	100years	DALYs	Secondary data collected	3% discount on both costs and outcome	Yes	Yes
22	Boutayeb et al. 2010[83]	Morocco	Women with Early-stage breast cancer	CEA	Observation study	Provider	1 year	Life Years Saved	Secondary data collected	NA	No	No
23	Okonkwo et al. 2008[84]	India	Women at rise of BC	CEA	Deterministic State Transition Model	Provider	25 years	Life years saved	Secondary data collected	3% discount on both costs and outcome	NA	NA
24	Hutchinson et al. 2024[12]	Kenya	Women at rise of BC	CBA	Cohort study	Provider	40 years	Net Economic Benefits and DALYs	Secondary data collected	NA	NO	No
25	Zehtab et al. 2016[71]	Iran	Women at risk of BC	CEA	Markov Model	Provider	Not clear	DALYs	Expert opinion	3% discount rate on outcomes	No	Yes
26	Zelle. 2013[36]	Peru	Women of 35 years of age	CEA	Markov Model	Provider	10 years	DALYs	Secondary data collected	3% discount on both cost and outcome	Yes	Yes

	Author	Country	Study Population	Economic Evaluation Type	Study Design	Perspective	Time frame	Effectiveness Outcome(s)	Source effectiveness data	Discount Rate	Sensitivity Analysis	Incremental analysis
27	Nguyen et al. 2018[85]	VietNam	Women of 45 to 69 years of ag	CEA	Markov Model	Provider	15 years	Life years saved	Expert opinion	NA	NA	NA
28	Ralaidovy el al. 2018[86]	Southeast Asia and Sub-Saharan Africa	Not Clear	CEA	Markov Model	Provider	Not clear	Healthy Life Years (HLYs)	Secondary data sources	3% discount on both cost and outcome	No	Yes

Table 8: Objectives, comparators, and main conclusions of the included CEAs

	Author	Intervention compared	Study objective	Conclusion of the study
1	Birnbaum et al. 2018[69]	Early detection strategies alone vs in combination with three systemic treatment programs	To estimate the outcomes of different early detection strategies in combination with systemic chemotherapy in the East African region and Colombia	Best outcomes were observed in settings where access to both early detection and adjuvant therapy is improved
2	Barfar et al. 2014	Mammography vs no screening	To assess the cost effectiveness of case-fining method mammography vs no screening	Case finding mammography was not cost-effective
3	Niens et al 2014[34]	Cost-effectiveness analysis of breast cancer control interventions in Mexico and Costa Rica	Comparing a series of breast cancer control interventions vs, no intervention.	Mammography was found to be very cost effective in both countries. However, CBE in Costa Rica and MAR in Mexico were both more cost effective than Mammography.
4	Nooshin Zehtab et al.2016[71]	The cost-effectiveness of breast cancer screening compared with no- screening	To analyze the cost-effectiveness of breast cancer screening using mammography in 35–69-year-old women in an Iranian setting	The screening intervention is more cost-effective than no- screening, however including it in health insurance package may not be recommended as long as the target group has a low participation rate.
5	Guzha et al. 2020[72]	Costing analysis for breast cancer treatment with chemotherapy	To develop a method to determine the cost of breast cancer treatment with chemotherapy per episode of care	The total direct medical cost for treatment of breast cancer at GSH for 200 patients was ZAR3 154 877, and the average episode-of-care cost per patient was ZAR15 774. The average cost of management of adverse events arising from the various treatment modalities was ZAR13 133 per patient. It was found that the cost of treating a patient with adverse events was 1.8 times higher than the cost of treating a patient without adverse events.
6	Nnaji C et al. 2020[73]	Compared the cost effectiveness of interventions for improving timely diagnosis of BC	To systematically synthesize available evidence on the nature and effectiveness of interventions for improving timely diagnosis of breast and cervical cancers in LMICs.	Not clear

	Author	Intervention compared	Study objective	Conclusion of the study
7	Ifeoma Jovita Nduka et al. 2022[74]	Not clear	To identify interventions that increase mammography screening uptake among women living in LMICs	Not clear
8	Alshreef K et al. 2019[75]	Cost-Effectiveness of Docetaxel and Paclitaxel for Adjuvant Treatment of Early Breast Cancer	To assess the cost-effectiveness of docetaxel and paclitaxel-containing chemotherapy regimens (taxanes) compared with standard (non-taxane) treatments in South Africa	The incremental cost per patient for the docetaxel regimen compared with standard treatment was R6774. The incremental quality-adjusted life years (QALYs) were 0.24, generating an incremental cost-effectiveness ratio of R28430 per QALY.
9	Gihan Hamdy Elsisi et al. 2020[62]	Compared a 6-month versus 1-year trastuzumab treatments in HER2 +ve ABC patient.	This study evaluates the cost-effectiveness of 6-month versus 1-year trastuzumab treatments.	The 6-month trastuzumab is a cost-effective option when compared to 1-year trastuzumab in patients with HER2 þve ABC in Egypt.
10	Yeong et al. 2023[10]	Systematic review of cost effectiveness analyses of breast cancer early detection programs	Systematic review to analyze the cost effectiveness of various breast cancer early detection programs in LMICs	Adopting an age-and-risk-based mammography screening can be viable in countries with limited resources.
11	Addo et al. 2021[76]	The study compared adjuvant tamoxifen treatment of hormone receptor positive early breast cancer among PPM Ghanaian women	To evaluate the cost effectiveness of of tamoxifen compared with no tamoxifen for adjuvant treatment of hormone receptor positive early breast cancer	Tamoxifen provides additional benefits to PPM Ghanaian women with HR+ EBC and is cost-effective compared with no tamoxifen.
12	Ali Aboutorabi et al. 2014[77]	The study compared adjuvant trastuzumab therapy with AC-T regimen in early breast cancer in Iran	To estimate cost-effectiveness of adjuvant trastuzumab therapy compared to ACT regimen in early breast cancer in Iran	12 months trastuzumab adjuvant chemotherapy is not a cost-effective therapy for patients with HER2-positive breast cancer in Iran.
13	Navid Omidifar et al 2022[78]	They compared individuals who received frozen counseling during surgery, and individuals who did not receive it.	To determine the cost-effectiveness of intraoperative frozen section analysis in women with breast cancer.	the study showed that performing frozen sections during surgery in women with breast cancer was more cost-effective than ignoring them
14	Masuku et al 2025[79]	The study compared different coverage scenarios for CBE vs the current baseline.	To assess the cost-effectiveness of CBE interventions in South Africa.	The findings suggested CBE efficiently saves lives but is not cost effective in South Africa
15	Ajeng VIcanervilia et al. 2022[60]	They compared mammography screening only to no strategy, mammography screening plus treatment and mammography, risk-based assessment, and ultrasound/CBE to no strategy	To assess whether mammography is a cost-effective breast cancer screening method in LMICs.	Mammography screening appeared to be a cost-effective strategy in LMICs, particularly in Upper MICs
16	Parsa Erfani et al.2021[80]	The cost of breast cancer care in LMICs	To describe the scope of the literature on the cost of breast cancer care in low- and middle-income countries	Not clear

	Author	Intervention compared	Study objective	Conclusion of the study
17	Lince-Deroche et al. 2021[80]	The study estimated the average costs for breast cancer conditions in SA as well as the financial implication of shifting to lower cost imaging options.	To estimate average costs for breast cancer conditions in SA as well as the financial implication of shifting to lower cost imaging options.	The average cost per initial consultation/examination was (USD 2015) $10.14. Mammography cost $59.96 and ultrasound $21.11 per patient.
18	Greshon et al. 2019[81]	The study compared the cost effectiveness and affordability of trastuzumab in SSA for early stage HER2 positive breast cancer	To assess the costs and benefits associated with trastuzumab treatment over a lifetime horizon in 11 African countries	Trastuzumab was not found to be cost effective in the African countries analyzed and would require significant discounts for it to be cost-effective.
19	Groot et al. 2006[82]	Individual stage I to IV treatment compared with an extensive mammography screening control program	To assess the cost-effectiveness of breast cancer control that covers various interventions in different settings	Stage I treatment and an extensive screening control program are the most cost-effective interventions
20	Zelle et al. 2012[35]	Treatment interventions, biennial mammography and CBE screening interventions, awareness raising inter- ventions, palliative care interventions compared with no scenario	To analyze the cost, effects, and cost-effectiveness of breast cancer control interventions in Ghana, and identify the optimal mix of interventions to maximize population health	Both screening by clinical breast examination and mass media awareness raising seem economically attractive interventions. Mammograph by screening is not cost-effective
21	Ginsberg et al. 2012[68]	Stage 1 to 4 treatment individual, treatment of all stages, biennial mammography screening 50 to 70 compared with no scenario	To determine the cost-effectiveness of 81 interventions to combat breast, cervical and colorectal cancer at different geographic coverage levels, to guide resource allocation decisions in LMIC	For breast cancer, although expensive, mammography screening in combination with treatment of all stages is cost-effective in both regions. More cost-effective than treating late-stage disease
22	Boutayeb et al. 2010[83]	Three chemotherapy regimens, AC, AC & taxanes and AC & taxanes & trastuzumab	To evaluate the total cost of chemotherapy in early-stage breast cancer	Moroccan health authorities need to devote between US$13.3 to 28.6 million to treat women by chemotherapy every year
23	Okonkwo et al. 2008[84]	Mammography screening, CBE screening among different age groups and in different frequencies	To assess the screening program that should be used in India.	CBE screening in India compares favorably with mammography screening in developed countries
24	Hutchinson et al. 2024[12]	Early diagnosis vs screening with CBE vs screening with mammography	To assess the cost benefit of expanding breast cancer prevention and treatment services in Kenya	All three strategies were found to be economically efficient in the long run with CBE providing the highest net economic benefits
25	Zehtab et al. 2016[71]	Compared mammography screening with no screening	To assess the cost effectiveness of screening using mammography in rural Iran.	Not clear

	Author	Intervention compared	Study objective	Conclusion of the study
26	Zelle. 2013[36]	Different breast cancer control interventions in Peru	To assess the cost effectiveness of different breast cancer control interventions in Peru.	Effort should be made toward early detection through a combination of mobile and fixed mammography triennially for women aged 45-69 years. However, the most feasible and cost-effective intervention in non-urban settings is a phased introduction of triennial CBE screening (40-69 years) with upfront FNA. In urban areas it is a combination of CBE (40- 49years) and mammography (50-69 years).
27	Nguyen et al. 2018[85]	The different screening program in Vietnam	To evaluate the cost effectiveness of a breast cancer screening program in Vietnam	Screening for breast cancer using CBE for women aged 40-55 years was found to be very cost effective. Early initiation into the program (35 years) increased the ICER
28	Ralaidovy el al. 2018[86]	Treatment of breast cancer for stages I&II, screening with mammography, and basic palliative care for cancer	To calculate the new WHO-CHOICE cost effectiveness results for breast, cervical, and colorectal cancer	For breast cancer, the treatment of breast cancer, stages I and II, with surgery ± systemic therapy, at 95% coverage, was found to be the most cost-effective intervention

Conclusion on the cost effectiveness for Breast Cancer Control Interventions in LMICs
This section synthesizes the findings from the reviewed economic evaluations of breast cancer control interventions in low- and middle-income countries (LMICs). Given the diversity of settings, methodologies, comparators, time horizons, and outcome measures used in these studies, direct comparisons of cost-effectiveness results across all interventions and countries are not appropriate. Instead, this synthesis highlights broad patterns in the types of interventions evaluated, their contextual relevance, and the conclusions drawn by the original study authors regarding cost-effectiveness

The review noted that there is insufficient good quality economic evidence on breast cancer control in LMICs, with 28 economic evaluation studies identified from 20 countries. While the review highlighted a high number/quantity of economic evaluations on breast cancer (28 articles), most of the studies are very limited in generalizability and relevance to East and South African countries., For instance, only three studies were from South Africa and none from Uganda. Moreover, only half of the total studies reviewed were of good quality. As such, these findings highlight a limited evidence base hence limiting the generalizability of these findings to other Low middle income countries (LMIC) such as Uganda.

Several studies concluded that early detection and screening strategies, such as clinical breast examination (CBE) or mammography screening, were cost-effective compared to no intervention, particularly when targeted to specific age groups or implemented at defined frequencies. While the reviewed studies generally support the cost-effectiveness of certain early detection, screening, and treatment strategies for breast cancer in LMICs, variation in study design and assumptions precludes drawing firm comparative conclusions. Further, there remains a need for more robust and locally calibrated economic evaluations, particularly those incorporating equity, financial risk protection, and distributional consequences.[20]

In the review, we also note that 85% of the studies included in the review targeted breast cancer control interventions towards women aged 40-70 years. Only one study assessed breast cancer screening from the age of 18 years and above, whereas four studies assessed breast cancer screening from the age of 30 years. However, there is clear uncertainty about the magnitude of over diagnosis among both younger and older women.

The other factor that influenced the cost effectiveness of the study was the duration and frequency of the intervention. For instance, most of the included studies specified the screening interval from 1 to 2 years, which was generally found to be cost-effective. When a comparison was made between biennial screening and annual or triennial screening, a biennial interval was found to be more cost-effective than the other screening interval strategies. This was in line with WHO recommendation of a screening interval of two years among women aged 50-69 years in well-resourced settings or limited resource settings with relatively strong health systems [9]. However, the recommendation was based on modeling studies and further analysis of trials showed that screening every two years seems to provide the best trade-off between benefits (mortality reduction) and harms (over diagnosis or overtreatment).

From the evaluation, only two studies assessed the cost effectiveness of breast cancer promotion awareness and self-breast examination (SBE) which may not be representative of LMICs such as Uganda and South Africa therefore there is need for studies to assess the different primary prevention strategies/interventions for breast cancer that increase breast cancer awareness.

The quality of these studies varied with 50% of the studies not good. Nearly all studies with good quality were model based. However, in some cases, the lack of model validation may have influenced the ICER results and therefore affect the extent to which results can serve as a solid basis for decision making. The findings from this review suggest the need to adhere methodological standards for economic evaluation analyses, or the development of such standards specifically for breast cancer research.

2.7 Equity, Financial Protection, and Breast Cancer

This sub-section focuses on the equity and financial protection considerations associated with breast cancer early detection and screening in LMICs. The inclusion of this section is directly aligned with one of the study's key objectives: to assess not only the cost-effectiveness but also the potential financial risk protection and equity-enhancing benefits that could result from publicly financing breast cancer control interventions. Examining equity and financial protection in breast cancer control is critical for ensuring that scarce health resources are allocated in ways that maximize population health gains while reducing disparities in access and outcomes. Inequities in screening, diagnosis, and treatment reflect underlying weaknesses in health financing and service delivery systems, leading to delayed care and catastrophic expenditures for affected households. Framing breast cancer control within the broader health system and resource allocation context therefore highlights the need for policies that promote equitable access, financial risk protection, and efficient investment across the continuum of cancer care. This section therefore aims to review the complex interplay between social factors, healthcare systems, and health outcomes, and to inform efforts to promote health equity and reduce disparities in breast cancer care. It will further review interventions and policy approaches aimed at reducing disparities in breast cancer screening and improving financial protection for underserved populations and evaluate the effectiveness of strategies such as subsidized screening programs, outreach initiatives targeting vulnerable communities, and policies to eliminate cost-sharing for preventive services.

From the perspective of breast cancer screening, equity involves ensuring that all individuals, regardless of their socioeconomic background or other factors, have equal opportunities to access screening services and receive timely and appropriate follow-up care if abnormalities are detected [20]. Financial protection ensures that the cost of breast cancer screening and related diagnostic procedures does not pose a barrier to access for those who need these services, thus contributing to equitable access to early detection and treatment of breast cancer [88].

Cancer is a high-cost illness that has been a high-ranking cause of catastrophic health expenditures, which can push households into poverty [89], [90], [91]. Moreover, in most LMICs where health insurance is out of reach for many households, cancer healthcare is paid for largely through out-of-pocket payments [92]. Breast Cancer in South Africa exhibits pronounced disparities in breast cancer services across ethnic and socioeconomic lines [93]. Colored and black women present with more aggressive tumors and with more advanced disease presentation [94]. Socio-economic factors greatly contribute to this pattern as they limit access to healthcare services and screening especially in the rural areas [93], [95]. Furthermore, the intersection between breast cancer and HIV/AIDS further exacerbates the challenge especially among the black population[95].

Universal public finance is a financing option which implies that the government finances an intervention irrespective of who delivers or receives the service [88]. The heuristic power of universal public finance lies in its ability to (a) increase coverage and access to the poor population groups thus increasing health gains, (b) reduce a household's expenditure on health care and this provides some form of insurance to cover households against financial ruin or impoverishment and (c) potential positive financial consequences like cost savings resulting from crowding out of private expenditure on the health intervention [96]. This is also in line with the holistic move toward universal health coverage. The extended cost-effectiveness analysis (ECEA) method can be used to evaluate equity and financial protection consequences of publicly financing a health intervention [97].

A review of the existing literature was conducted across PubMed, Scopus, and Web of Science to identify empirical studies published between 2000 and 2024 examining equity and financial protection externalities associated with publicly financing interventions for breast cancer control in LMICs. Search terms combined MeSH and free-text keywords related to "breast cancer," "equity," "financial protection," "public financing", "extended cost effectiveness", "distributional consequences" and "sub-Saharan Africa." Only English-language empirical studies were considered, while reviews, commentaries, and studies outside the region or disease focus were excluded. While this search identified some empirical studies that had assessed inequities in breast cancer treatment in sub-Saharan Africa and the socioeconomic impact of breast cancer on young women [3], [97], [98], [99], the search did not find any empirical studies that have evaluated the equity and financial protection positive externalities that would result from publicly financing interventions for breast cancer control in LMICs.

2.8 Conclusion and Priorities for Future Research

Although it has been well established that the key determinant of successful breast cancer outcome in any population is early detection of the disease, few good quality studies have evaluated the costs and effectiveness of breast cancer early detection methods in LMICs.

The findings of this review highlight the potential benefits of implementing early detection strategies, including screening programs and improved access to essential treatments, in reducing the overall burden of breast cancer in LMICs. These interventions not only lead to better health outcomes for individuals by enabling early diagnosis and timely treatment but also offer substantial economic benefits by avoiding the high costs associated with advanced-stage cancer care.

However, amidst these promising findings, it is crucial to acknowledge the significant challenges that hinder the successful implementation of breast cancer interventions in LMIC settings that include, limited financial resources, inadequate infrastructure, and sociocultural barriers [9], [20], [69].

Moreover, disparities in access to healthcare, particularly among marginalized populations, exacerbate the burden of breast cancer and perpetuate existing inequalities in health outcomes.[11]

Moving forward, it is imperative to prioritize further research initiatives aimed at enhancing the effectiveness, equity, and sustainability of breast cancer interventions in LMIC contexts. Through evidence-based interventions and targeted policy interventions, we can pave the way towards a future where breast cancer is no longer a pervasive threat to the health and well-being of women in LMICs and beyond. After a review of literature (presented above), the following areas were highlighted as the main priorities for future economic analyses for breast cancer research in LMICs:

- Develop dynamic simulation models to predict shifts in stage distribution of Breast Cancer as a result of implementing early detection and treatment interventions for breast cancer in LMICs.
- Conduct cost analyses for various early detection methods in LMICs and especially in Sub Saharan Africa.
- Perform full economic evaluations comparing multiple early detection interventions for breast cancer in LMICs especially in Sub Saharan Africa. These can include cost effectiveness analyses, cost benefit analyses or cost utility analyses.
- Considering UHC aspirations, there is a need to investigate the distributional impact on equity and financial protection of publicly financing early detection methods for breast cancer in LMICs.

To conclude, this literature review indicated that early detection and treatment of breast cancer in LMICs was a cost-effective strategy. However, there is a paucity of good quality evidence on the same in the LMICs. Moreover, not a single full economic evaluation comparing multiple breast cancer early detection and screening interventions has been conducted in the Eastern or Southern African countries. Furthermore, no study (both in the developing and developed countries) has investigated equity and financial protection aspects associated with publicly financing interventions for early detection of breast cancer. Thus, this literature review concludes that the overall aim of this thesis remains unanswered:

- To assess the cost effectiveness and distributional impact of publicly financing interventions for early detection, screening, and breast cancer control in Uganda and South Africa.

CHAPTER

3

"… but the people who know their God shall be strong and carry out great exploits…" Daniel 11:32

Chapter 3: Study Design and Overview of Methods

3.1 Introduction

This study was conducted in two countries in the Sub-Saharan African region (Uganda and South Africa) given the increasing trajectory of breast cancer incidence and mortality in LMICs. The global statistics for the year 2022 indicate that female breast cancer is the second leading cause of global cancer incidence with an estimated 2.3 million cases, and it is the fourth leading cause of mortality worldwide with 665,684 deaths [1]. Among women, it is the most frequently diagnosed cancer and is the leading cause of cancer death among women in 157 countries [1].

In Uganda, breast cancer is the second most diagnosed female cancer after cervical cancer, with an estimated age-standardized incidence and mortality rate of 21.3/100,000 and 10.3/100,000 respectively [6]. These high mortality rates can be interpreted as almost half of Ugandan women diagnosed with breast cancer die from the disease. This high mortality rate is predominantly attributed to late-stage diagnosis of the disease: up to 89% of the women with breast cancer in Uganda present with stage III or IV [107]. Such late-stage presentation fundamentally permits the breast tumors to advance in stage when prognosis is poor. A population-based study in Uganda put the five-year breast cancer survival rate at 44% [108] and this low survival rate is predominantly attributed to late-stage diagnosis of the disease. Other probable reasons for presentation with advanced stage cancers include lack of breast cancer screening services [109], barriers in access to health care [26], lack of awareness [110], and biological tumor factors [111]. As is the case with other black women in developing countries a significant proportion of the Ugandan women who die from breast cancer are 40 years old or younger and the mean age is 45 years [112]. Ugandan women who die from breast cancer are 40 years old or younger and the mean age is 45 years [112] and another study reported the peak age for Ugandan women to be 30-39 years [108]. A comprehensive review of the breast cancer early detection and diagnostic capacity for Uganda reported deficits in recognition of signs and symptoms for breast cancer, centralization of diagnostic tests, limited number of trained professionals, and severe underuse of clinical breast examination as a vital screening tool [18].

In South Africa, breast cancer incidence has steadily increased, and the absolute number of new cases has doubled over the last 20 years accounting for 14-30% of all cancers affecting women [113]. In 2020, South Africa reported 15,491 new breast cancer cases and although overall, the age standardized rate (ASR) shows a slight increase, there has been a marked increase in the ASR for South Africans of European decent [95]. Regarding the lifetime risk of breast cancer in South Africa, it varies greatly by race with white women (1 in 13), Colored women (1 in 18), Asian women (1 in 25) having a higher lifetime risk compared to black women with a 1 in 81 lifetime risk[93], [114]. Regarding geographically distribution of breast cancer cases, the Eastern Cape Province has registered significant increases in the number of breast cancer cases reporting a 61% increase in the cases between 1998 – 2012 [115]. More patients present with late-stage disease (stage III or IV) and the evidence indicates that on average, 54% of the patients present with late-stage disease [116], [117]. Moreover, there are ethnic disparities in the late presentation with patients of African/black ancestry more likely to present with advanced-stage disease while patients of European ancestry are more likely to present with early-stage disease[118].

The National Department of Health in South Africa has declared Breast Cancer a priority for the country and National Breast Cancer Policy guidelines were developed although they remain to be fully implemented [95]. The policy guidelines note that breast cancer screening is the most viable strategy for breast cancer control through early detection interventions and effective treatment. The guidelines recommend that screening for Breast Cancer should start at the age of 40 years [119]. The new policy document provided a new standard of care guideline that is summarized in *Table* ***9***. Regarding mammography the new policy states that "*lack of resources and infrastructure in the South Africa public healthcare system render this strategy untenable. Presently MMG should be performed on symptomatic and identifiable high-risk patients at specialist breast units*" (NDoH, 2017)p.28.

Table 9: Standard guidelines for screening and early diagnosis of breast cancer in South Africa

Standard 1.1	Women over 40 years attending a Primary Health Clinic will have a clinical breast examination (Provider Initiated Screening Clinical Breast Exams – PISCBE) biannually.
Standard 1.2	All women attending Primary Health Clinics will be given opportunistic breast education including printed education materials and taught breast self-examination.
Standard 1.3	Awareness messages should be disseminated for communities and healthcare workers that any woman who notices a change in breast should report promptly to a health facility for further assessment.

Source: National Department of Health: Breast Cancer Prevention and Control Policy, 2018

Although it has been well established that the key determinant of successful breast cancer outcomes in any population is early detection of the disease [9], very few studies have evaluated the downstaging effect of these interventions and the associated costs and effectiveness of these methods in LMICs [34], [35], [36], [69]. Moreover, not a single full economic evaluation for breast cancer control has been conducted in Uganda or South Africa. Furthermore, no study (both in the developing and developed countries) has investigated equity and financial protection aspects that might arise from publicly financing interventions for early detection and screening of breast cancer. This chapter presents a summary of the early detection and screening approaches, the overall aim and objectives of this study, the conceptual framework, and an overview of the methods applied to answer each study objective.

3.2 Early Detection and Screening Interventions

The Global Summit Early Detection Panel led by Anderson et al. (2003) defined "*early detection"* as the identification of breast cancer in its infancy natural history where treatment has a very high potential for cure with very minimal physical effect. The distinctive mark for early detection is that woman with symptoms of breast cancer approach health workers for diagnosis and medical intervention. On the other hand, "*screening*" of breast cancer requires the use of a test on asymptomatic women not seeking medical intervention or on women who are unaware of the breast cancer condition [20].

Early detection alone without screening entails the provision of education to the population at risk of breast cancer as well as to the providers of health care services to enable them to recognize and respond to the first symptoms of breast cancer [20]. This education and knowledge for both parties could potentially result into timely diagnosis of the cancer especially for LMICs where women commonly present with very advanced breast cancer. Early detection methods that don't entail screening have also been found to require lower resources and therefore are a logical and appropriate first step for countries with fewer resources [20]. In fact, the Global Summit Early Detection Panel reached consensus that all countries should promote public education and awareness of breast cancer regardless of their resource level [20]. However, the panel retaliated that these efforts must be combined with established diagnosis and treatment programs. The Global Summit Early Detection Panel noted that education and awareness alone have the potential to result in a favorable shift in the stage of breast cancer at presentation. The panelists recounted that they "*consider it axiomatic that education about breast cancer is a right to all women*"[20]. However, it is important to highlight that early detection of breast cancer is meaningless if there is no subsequent proper breast cancer treatment is administered. If the overarching goal of any early detection initiative is to reduce mortality, then the detected cases must have access to effective and affordable treatment.

Screening on the other hand can be broadly categorized into two types – *opportunistic screening* and *organized screening [20]*. *Opportunistic screening* is when an individual seeks screening services including screening initiated by health care providers during routine or unrelated care encounters outside of the formal screening program. While this might increase the odds of early detection through discovery of non-palpable tumors, it only benefits affluent women who can afford to get tested and pay for necessary follow-up diagnostic tests [20], [38]. *Organized screening* on the other hand entails the creation of a formal screening program by either the government, a health facility or an institution for a targeted population (Anderson et al., 2003). Organized screening has the highest potential for early detection for a large proportion of the population at risk but it's also the most resource intensive approach [20], [38]. The well-established screening techniques for breast cancer include Breast Self-Examination (BSE), Clinical Breast Examination (CBE), and Mammography. In some low-income countries like Uganda, a proposed adjunct imaging method to mammography for symptomatic women with dense breasts is ultrasonography [37].

The study compared scenarios of universally providing the either Awareness raising, OR Clinical Breast Examination (CBE), OR Mammography to the status quo. The modelled scenarios also included treatment and palliative care where applicable to all the patients correctly detected as having breast cancer. *Table **10*** presents a list of interventions that were modelled in the three scenarios. The breast cancer interventions included in this study were selected based on the World Health Organization (WHO) Breast Cancer Initiative recommendations, which outline evidence-based strategies for breast cancer control across different resource settings[20], [51]. To ensure local relevance, these interventions were further tailored through a comprehensive review of national breast cancer management guidelines from Uganda and South Africa[119], alongside relevant published literature as described and summarized in Chapter 2 of this thesis.

Baseline / Business as Usual Breast Cancer Contexts for Uganda and South Africa

Furthermore, the baseline scenario of the model was to the degree possible parametrized using country specific coverage rates for identified interventions. The baseline scenario assumes that current incidence rates of breast cancer continue, and that these breast cancer diagnoses present at the current proportion of early stage for South Africa (46%) and late stage (54%) breast cancers [116], [117] and for Uganda 11% early presentation and 89% late presentation. While the breast cancer implementation guidelines in both countries provide an aspirational framework, their implementation is still subpar. For instance, in Uganda, access is hindered by having just four mammography units for ~7 million women, requiring long travels making it unaffordable for most women[18]. South Africa fares better with urban mammography availability, but rural uptake is lower in lower quintiles (Q1–Q3) due to transport costs and wait times[11], [14]. Low awareness and cultural barriers also drive late-stage diagnoses (80–90% Stages III–IV in LMICs). In Uganda, stigma linking cancer to social taboos reduces uptake of services[18], while South African rural communities often prefer traditional healers, delaying care[53]. Therefore, the model's baseline comparator captures the average observed system performance as reflected in current national epidemiological data, not the ideal or fully realized implementation of policy recommendations.

This approach ensured that the interventions modeled in the study reflect not only globally recommended best practices but also those that are currently available, accessible, and routinely used within the local healthcare delivery systems for Uganda and South Africa.

Table 10: Definition and classification of breast cancer interventions

Early Detection/screening interventions	Awareness Raising Interventions: Training of primary health workers + outreaches by primary health workers to raise breast cancer awareness + enhanced media activities including mass media campaigns
	Clinical Breast Examination (CEB): Biennial CBE screening in asymptomatic women aged 40 – 75 + outreaches by primary health workers to raise breast cancer awareness + limited media activities
	Mammography (MG): Biennial MMG screening in asymptomatic women aged 40 – 75 + outreaches by primary health workers to raise breast cancer awareness + limited media activities
Treatment of Breast Cancer at different stages	Treatment for stage1: Lumpectomy with axillary dissection, radiotherapy, tamoxifen, or chemotherapy for eligible patients
	Treatment for stage 2: Lumpectomy with axillary dissection, radiotherapy, tamoxifen, or chemotherapy for eligible patients
	Treatment for stage 3: Mastectomy, adjuvant chemotherapy, radiotherapy, and tamoxifen for eligible patients
	Treatment for stage 4: adjuvant chemotherapy, radiotherapy (10 Gy), and eligible patients are given tamoxifen and total mastectomy
Palliative Care	Training for palliative care community nurses + home-based visits + pain medication for eligible patients (morphine, palliative radiotherapy (8 Gy in 1 fraction), and laxatives

**Down-staging interventions cause a shift in the stag distribution of cancer and will only be modeled in combination with treatment of all stages (I-IV). Palliative care interventions are only given to stage III and IV patients and in some cases they substitute stage IV treatment.*

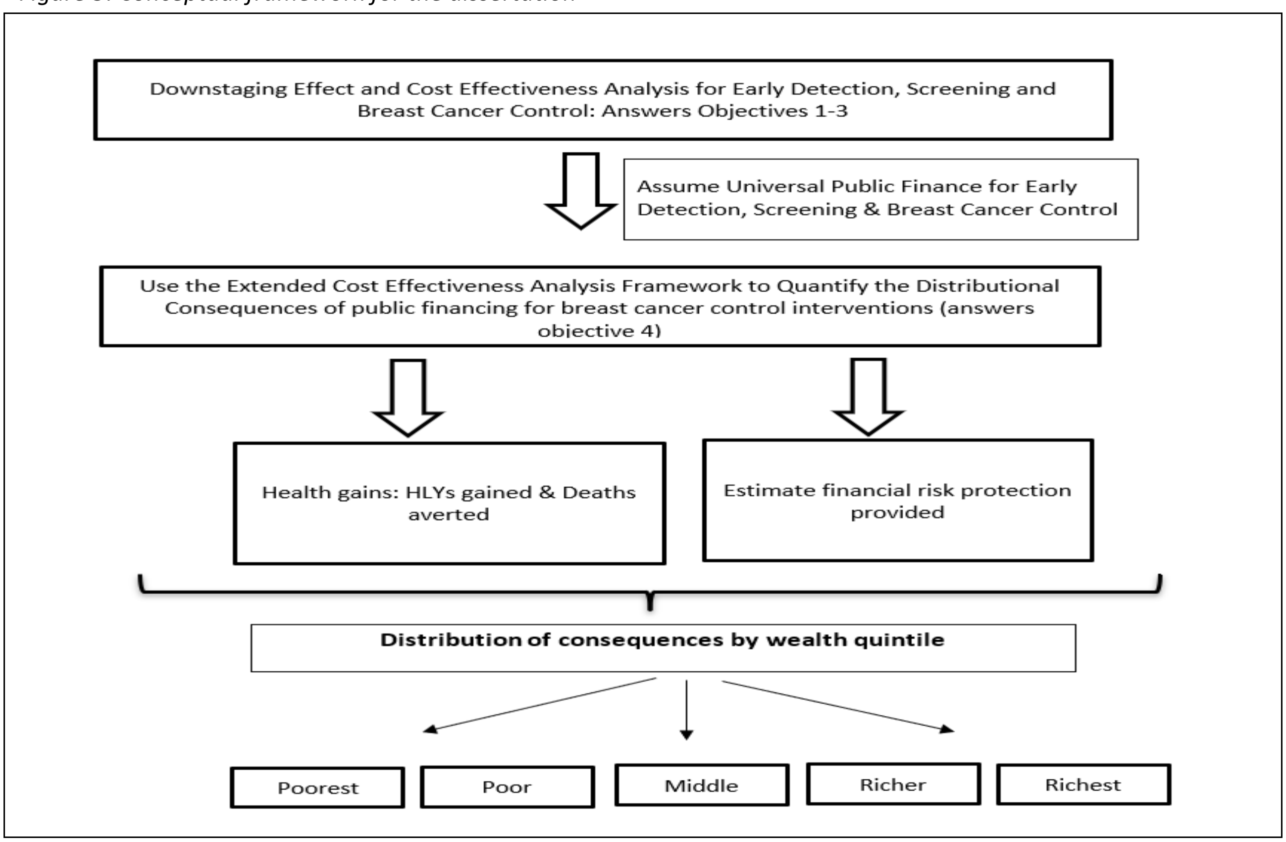
3.3 Thesis Conceptual Framework

For study objectives 1 - 3, this study constructed a dynamic state transition model to estimate and predict down-staging of breast cancer as result of breast cancer awareness raising and screening strategies in Uganda and South Africa over a period of 40 years. The dynamic state transition model was also used to estimate the cost effectiveness associated with the early detection and screening strategies. An extended cost effectiveness analysis (ECEA) was conducted to answer study objective 4. The ECEA fundamentally builds on the conventional cost-effective analysis (CEA) and utilizes standard

CEA results [97]. The ECEA permits for the inclusion of non-health benefits such as financial risk protection and other equity considerations into the evaluation of public health interventions. This makes the ECEA method very appealing given that the criteria for resource allocation in LMICs is usually very complex and cannot be guided by a mere cost per QALY/DALY typically generated by the conventional CEA.

Using the classical CEA method, this study estimated the costs and effectiveness (Healthy life years gained) for the 3-breast cancer early detection and screening interventions. The CEA included treatment costs for individuals who are accurately detected to have breast cancer by the different early detection methods. Considering universal health coverage aspirations for the two countries under assessment, this study then assessed the possible distributional impact of utilizing universal public financing as a tool to increase access and coverage of breast cancer early detection interventions in LMICs. Therefore, assuming a case of publicly financing breast cancer interventions considered in objectives 1 - 3, the study employed the ECEA method to quantify the distributional consequences of publicly financing early detection and breast cancer control interventions across socioeconomic strata in Uganda along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through catastrophic health expenditure cases averted. In other words, which wealth quintile benefits the most (health gains) and averts the most private expenditures due to publicly financing the different early detection methods. Is it the rich or the poor? This answered study objective 4.

Figure 5: Conceptual framework for the dissertation



3.4 Overview of Study Methods

Using a dynamic state transition model, we estimated and quantified the down-staging impact associated with early detection and screening strategies in Uganda and South Africa for a period of 40 years A dynamic state transition model is a mathematical framework that simulates how individuals or cohorts move between distinct health states over time, while accounting for changes in population-level factors such as incidence, mortality, and program coverage [120], [121]. Unlike static models, which assume a fixed population structure and constant transition probabilities, dynamic models incorporate feedback mechanisms and time-dependent interactions, making them especially suitable for evaluating interventions where disease dynamics, population growth, or health system interactions evolve over time [120], [121].

Using the dynamic state transition model and following the WHO standardized guidelines on how to conduct a CEA[19], the study conducted a conventional cost effectiveness analysis (CEA) for early detection, screening, and treatment of breast cancer in the two countries. The results from the cost effectiveness analysis were used in the extended cost effectiveness analysis, which incorporates financial consequences and equity aspects to the cost effectiveness analysis results. The ECEA method has been described in detail elsewhere [97]. The present study considered a provider's perspective for costing, and this implies that only the health provider costs were estimated. Costs and benefits were discounted at 3%. Multivariable sensitivity analysis was conducted to assess for uncertainty in some key variables that influence costs and effectiveness parameters. Specifically, the multivariable sensitivity analysis involved simultaneously varying multiple key input parameters within plausible ranges to assess how combined uncertainties affect model outputs. These parameters were varied across plausible ranges (based on published literature or assumed ±25% uncertainty) to evaluate their joint impact on cost-effectiveness outcomes and the robustness of the study's conclusions. A detailed description of the parameters, their sources, and the ranges used has been added to the methods section of chapter 5 and 6. All costs are presented in United States Dollars and in each country's local currency.

Overview of Methods for Study Objective 1

We constructed a dynamic state transition model to estimate and predict down-staging of breast cancer as result of early detection and screening strategies for breast cancer control. This dynamic state transition modelling approach was selected for the current study because it enables a more realistic evaluation of the population-level impacts and cost-effectiveness of breast cancer control interventions under varying program scales, coverage levels, and resource constraints, particularly in low- and middle-income country settings. Compared with decision trees or static cohort models, the dynamic state transition model is better suited to capturing the long-term health and economic outcomes of screening and treatment programs, accounting for repeated screening cycles, stage shifts, and mortality over time [120], [122]. Additionally, dynamic models can integrate changes in population demographics [120], [121], which is critical for informing scalable and context-relevant policy decisions in Uganda and South Africa.

Our model is an empirical model based on stage distribution at diagnosis and how early detection and screening interventions (awareness raising, clinical breast examination and mammography) can improve stage distribution through downstaging over a time horizon of 40 years. As such, this thesis does not model the natural history of disease progression which is the approach widely used to simulate cancer progression pathways. The decision to reject the natural history model was not solely based on data scarcity but on the degree and type of data required: natural history models rely heavily on detailed longitudinal epidemiological data, such as age-specific progression rates, time between preclinical and clinical stages, and survival distributions by treatment, which are largely unavailable or unreliable in these contexts.

Given these limitations, this thesis adopts the proportional performance rate (PPR) approach (Zelle et al., 2015), which offers a more pragmatic modelling framework. Our model applied the proportional performance rate (PPR) framework developed by Zelle et al. (2015), which calculates a proportional shift in stage distribution (Z) based on key screening performance indicators, including test sensitivity, attendance rates, screening frequency, and mean sojourn time. This method offers a pragmatic, aggregated approach to estimating stage shifts when detailed individual-level natural history data are unavailable, as is often the case in low- and middle-income countries (LMICs) like Uganda and South Africa. This approach also provides a feasible alternative to individual level data-intensive methods, such as the microsimulation framework used by Birnbaum et al. (2018), which models individual disease trajectories and treatment effects on survival. Given the individual level data limitations in the Ugandan and South African contexts, the proportional performance rate approach was selected as the most suitable method for this thesis, allowing the integration of available population-level screening data into the model while still providing meaningful estimates of potential stage shifts and their impact on cost-effectiveness.

Although the proportional performance rate approach also requires several assumptions and the use of cross-country parameter estimates, it relies primarily on available screening performance metrics, such as test sensitivity, attendance rates, and sojourn time, rather than attempting to reconstruct full individual-level disease trajectories. This makes the proportional performance rate approach more feasible and transparent in data-limited settings, providing robust, policy-relevant estimates of the potential impact of early detection and screening interventions on stage distribution and cost-effectiveness outcomes. The selection of this modelling approach reflects a balance between methodological rigor and contextual feasibility, ensuring that the results produced are meaningful and actionable within the realities of low- and middle-income country healthcare systems.

To parametrize the model, we used a mixture of empirical estimates from Uganda and South Africa, as well as contextually relevant assumptions from low-and middle-income countries. The model imposes normative assumptions about ideal scenarios of three early detection and screening interventions: awareness raising campaigns, clinical breast examination, and mammographic screening and compares these scenarios to the current business-as-usual scenario (hereafter, the “baseline” scenario). The study population was the population of Uganda and South Africa, and in particular, the female population of the two countries.

Overview of Methods for Study Objectives 2 and 3

Estimation of Costs and Effectiveness

The study considered a provider's perspective i.e., healthcare provider costs only were considered. A normative costing based on the national breast cancer norms, policies and guidelines was done. An ingredients-based approach to costing was used. Ingredients based approach entailed three steps: the first was identification of all required resources or inputs, second was to quantify the required resources and last step was the valuation of these resources based on their current replacement value [123]. The cost analysis focused on estimating the recurrent and capital costs separately, which were then summed up to give the total cost. Capital costs were annualized using a discount rate of 3% at the appropriate life years and the unit of analysis was cost per breast cancer case detected and treated.

The effectiveness of each early detection and screening intervention method was due to changes in (i) down-staging or stage-shift distribution (resulting from an increase in awareness and from earlier disease presentation due to early detection and screening interventions), (ii) disability weights i.e. health state valuations (HSVs), (iii) from case fatality resulting from improved survival due to the treatment provided. Each early detection and screening intervention was implemented for 40 years. The effectiveness outcome measure was expressed in Healthy years lived because breast cancer interventions affect both the mortality (case fatality) and morbidity (disability weights).

Cost effectiveness analysis and sensitivity analysis

Interventions that were found to be less costly and more effective are called "dominant" interventions. Using the rule of simple dominance, incremental analyses were performed by rank ordering strategies. Incremental Cost Effectiveness Ratios (ICERs) were calculated for each strategy (costs divided by benefits) compared with the baseline scenario [123]. The extended dominance rule of thumb held where interventions with a higher ICER dominated interventions with a previous non-dominated ICER. [124]. To interpret the cost-effectiveness results generated by this study, we carefully considered current best practices and recent methodological developments regarding cost-effectiveness thresholds, particularly for low- and middle-income countries (LMICs). Historically, the World Health Organization (WHO) proposed heuristic thresholds based on multiples of a country's GDP per capita (e.g., an intervention was considered highly cost-effective if the incremental cost-effectiveness ratio [ICER] was less than one times GDP per capita)[117]. However, the WHO has formally withdrawn these GDP-based thresholds, recognizing that they may misrepresent local opportunity costs and distort national health priority-setting[117].

For South Africa, we apply the country-specific cost-effectiveness threshold empirically estimated by Edoka and Stacey (2020), which places the opportunity cost-based threshold at USD 3,015 per disability-adjusted life year (DALY) averted at 53% of GDP per capita. This threshold reflects the marginal productivity of the South African health system and provides a robust benchmark for interpreting ICERs relevant to local decision-making.

For Uganda, we reference the cross-country estimates provided by Woods et al. (2016)[148] and by Pichon-Riviere et al (2023) [149] which suggest that low-income countries (LICs) may have thresholds as low as USD 16 – 537 per DALY averted or as 1% - 54% of GDP per capita. While we acknowledge the uncertainty and limitations of applying general cross-country estimates, these thresholds offer a pragmatic interim benchmark grounded in the opportunity cost-based framework [150], and importantly, we avoid applying outdated GDP-based multiples and explicitly highlight the need for future research to generate precise Uganda-specific empirical thresholds. For all the key parameters that influence the final result (ICER), multiple variable sensitivity analysis was carried out to assess for robustness of the values used to estimate the ICER. This is particularly important regarding proxies or data extracted from literature. The parameters considered for sensitivity analysis included: the case fatality rates, disability weights, sensitivity of MMG and CBE, treatment costs and screening costs.

Overview of Methods for Study Objective 4

This study assessed the equity implications that are associated with universally and publicly funding breast cancer early detection interventions. This study objective is premised on the application of universal public financing as a tool to move towards universal health coverage. We conducted an extended cost effectiveness analysis (ECEA) of a policy to publicly finance early detection and breast cancer control interventions in South Africa and Uganda.

Extended Cost-Effectiveness Analysis provides a comprehensive framework for evaluating the impact of health interventions on both health and financial outcomes, with a particular emphasis on equity and financial risk protection, making it particularly relevant for informing policy decisions in LMICs where considerations of equity and financial protection are crucial [97].

For any health intervention, priority setting should seek to achieve health system goals, broadly defined as (i) maximization of health, (ii) reduction of inequities in health, and (iii) financial protection against the costs of ill health [98]. The main approach to establishing health priority setting -- cost-effectiveness analysis, addresses only the first objective of maximizing health outcomes. How governments balance health maximization with equity and financial protection has far-reaching implications for what health priorities are agreed and pursued [99].

A systematic review conducted in 2012 on whether cost effectiveness analysis could integrate equity concerns found that three viable techniques ranging from descriptive to quantitative existed [100]. These methods included: the integration of distributional concerns through equity weights and social welfare functions, the use of mathematical modeling to explore opportunity costs of alternative policy options and the use of multi-criteria decision analysis. As a result, analytical frameworks that attempted to account for the intricate multiple criteria decision-making process have been developed [100]. A couple of mathematical models have been developed to either: (a) explicitly incorporate equity parameters into decision making scenarios or (b) present disaggregated findings in the form of a dashboard [101]. Nonetheless, most of these methods could not additionally consider the multiple dimensions and outcomes that result from health interventions or polices. Such multiple dimensions include the private expenditures averted due to government providing a health intervention and the financial risk protection that ensues from prevention of poverty resulting from illness [101].

The extended cost effectiveness analysis (ECEA) method was conceived and developed to evaluate health and financial consequences of health policies or interventions in four domains: (a) evaluate health gains of an intervention (b) the financial risk protection i.e. prevention of impoverishment that results from illness, (c) to estimate the costs of the intervention or policy to the decision maker and (d) the distributional consequences of the intervention across socioeconomic strata [97], [101]. As such, ECEA highlights the return on investment in the dimension of financial risk protection and equity, in addition to the health gains associated with a health intervention [101]. In other words, ECEA is a novel method that augments the conventional cost effectiveness analysis method to consider non-health benefits such as financial protection and equity.

Despite the importance of considering financial risk protection and equity aspects when conducting economic evaluations, a paucity of research has done so using the ECEA method in low and middle-income countries [96], [102], [103], [104], [105], [106]. This analysis aimed to estimate the extended cost effectiveness analysis of publicly financing early detection and screening interventions for breast cancer control in South Africa and Uganda.

The ECEA has been described elsewhere in detail and applied in various low- and middle-income countries [97]. Extended Cost Effectiveness Analysis augments the traditional cost effectiveness analysis method by considering non-health benefits such as financial protection and equity by quantifying: 1) the distribution of health benefits across wealth strata, 2) the cases of catastrophic health expenditure averted by a policy and 3) the financial protection provided by a policy [97].

In this analysis, we quantified the distributional consequences of publicly financing early detection and breast cancer control interventions across socioeconomic strata in South Africa along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through cases of catastrophic health expenditures averted.

3.5 Way Forward

This research is envisaged to add to the anecdotal evidence base of economic analyses for early detection and screening of breast cancer in LMICs. Furthermore, the application of the extended cost effectiveness analysis method is envisaged to methodologically add value to the classical cost effectiveness analysis. This is mainly because the extended cost effectiveness method does not only consider maximization of health but also minimization of unfair variation in health benefits and financial burden across the different socioeconomic classes [97]. This also implies that findings from an extended cost effectiveness analysis combine two of the three goals of universal health coverage. This study will add to the evidence base in the following ways:

- Predict and quantify the down-staging effect of early detection and screening interventions for breast cancer control in LMICs.
- Provide a better understanding of the cost effectiveness of early detection, screening, and management of breast cancer in LMICs.

- Estimation of the cost and health gains associated with early detection and screening of breast cancer interventions in LMICs.
- The financial protection consequences (catastrophic health expenditure cases averted) that result from publicly financing breast cancer control interventions in LMICs.
- Findings from this study will also provide guidance to priority setting for breast cancer control with emphasis on ensuring that households are not exposed to financial hardship due to seeking breast cancer healthcare services.

CHAPTER 4

"…For thus says the Lord: 'You shall not see wind, nor shall you see rain; yet that valley shall be filled with water…" II Kings 3:17

Chapter 4: Predicting down-staging of breast cancer due to early detection and screening strategies: case studies of South Africa and Uganda

Abstract

Background

Late-stage presentation and delayed treatment are major contributors to poor breast cancer survival rates in low- and middle-income countries (LMICs). Improved early detection interventions for breast cancer can lead to earlier breast cancer detection, lower costs, and improved outcomes. We aimed to predict and quantify the downstaging associated with three early detection and screening interventions in one low-income country (Uganda) and one middle income country (South Africa).

Methods

We constructed a dynamic state transition model to estimate and predict down-staging of breast cancer as result of early detection and screening strategies for breast cancer control. Our model is premised on a comprehensive mathematical framework that estimates the stage shifts in early versus late stages of breast cancer diagnosis based on proportional performance rates (Z's) of three early detection and screening interventions (awareness raising, clinical breast examination and mammography) over a 40-year time horizon.

Results

For Uganda, we estimate that the three early detection and screening interventions are associated with a 66% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease for over the period of 40 years. For South Africa, we report a 32% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease over the 40-year period. Awareness raising interventions have similar downstaging effect in both countries (9% in Uganda and 8% in South Africa) while Clinical Breast Examination (CBE) has a stronger effect in Uganda (21%) than in South Africa (9%). In both countries, mammography led screening is reported to have the strongest down-staging effect of 36% in Uganda and 15% in South Africa. From our analysis, we note that early detection and screening interventions have almost double the impact in settings where late-stage presentation of breast cancer disease is very prevalent (Uganda) as compared with settings where late-stage presentation of the diseases is not as prevalent (South Africa).

Conclusions

Our study predicts significant down-staging associated with early detection and screening interventions for breast cancer in Uganda and South Africa. The down-staging effect is stronger in Uganda where late-stage presentation of breast cancer is very high. LMICs should therefore consider improving and enhancing investments in early detection and screening interventions as they can yield substantial down-staging for breast cancer. The implementation of early detection and screening interventions however should follow very comprehensive systematic and phased planning to ensure that the health system can ably and effectively manage the increased number of breast cancer cases owing to enhanced early detection. Our model can guide pragmatic decision making and can easily be adapted to other LMICs settings to facilitate the identification of resource-appropriate early detection and screening interventions.

4.1 Background

The global statistics for the year 2022 indicate that female breast cancer is the second most diagnosed cancer worldwide with an estimated 2.3 million cases. [1]. This disease burden is particularly severe in regions such as Africa and Asia where the cancer mortality rates are disproportionately greater than the corresponding cancer incidence rates [2] suggestive of a gap in treatment and survival outcomes. Among women, breast cancer remains the most frequently diagnosed cancer and is the leading cause of cancer-related death among women in 157 countries [1] reflective of a global health challenge.

While global variations exist in breast cancer incidence, mortality, and survival rates vary considerably between the global regions up to approximately fourfold [5]but what has been unequivocally consistent across the regions is that the incidence of breast cancer is increasing, and in regions without early detection programs, mortality is also increasing [1]. Late-stage presentation and delayed treatment are major contributors to poor breast cancer survival rates in low- and middle-income countries (LMICs) [2], [5].

Early detection coupled with appropriate treatment is the most effective strategy for breast cancer control as demonstrated largely by evidence from high income countries [9]. However, there is limited empirical evidence in LMICs on the impact of the various early detection and screening modalities on breast cancer control [10].

Given the constrained fiscal space that LMICs operate within, the need to strategically prioritize and optimize the allocation and utilization of finite resources for health is paramount[69]. To guide policy makers on the appropriate early detection and screening interventions to implement, we constructed a dynamic state transition model to estimate and predict down-staging of breast cancer associated with early detection and screening strategies in Uganda and South Africa. Down-staging is a critical indicator of the effectiveness of early detection and screening techniques and their subsequent impact particularly in LMIC where late-stage presentation of breast cancer is very prevalent [9], [69], [125].

Our model assessed the performance of three early detection and screening interventions (awareness raising campaigns, clinical breast examination, and mammography) and quantified their ability to shift breast cancer cases that would have otherwise been diagnosed as “late stage” to an “earlier stage” at the time of diagnosis. The model was also used to estimate the costs and effectiveness of the three early detection and screening interventions as presented in Chapter 5 and Chapter 6 of this thesis.

4.2 Methods

We constructed a dynamic state transition model to estimate the down-staging effect of three breast cancer early detection and screening interventions in Uganda and South Africa for a time horizon of 40 years. We used a mixture of empirical estimates, and assumptions from low-income countries to populate parameters in the model. The model imposes normative assumptions about ideal scenarios of three early detection and screening interventions: awareness raising campaigns, clinical breast examination, and mammographic screening and compares these scenarios to the current business-as-usual scenario (the “baseline” scenario).

4.2.1 Model Philosophy

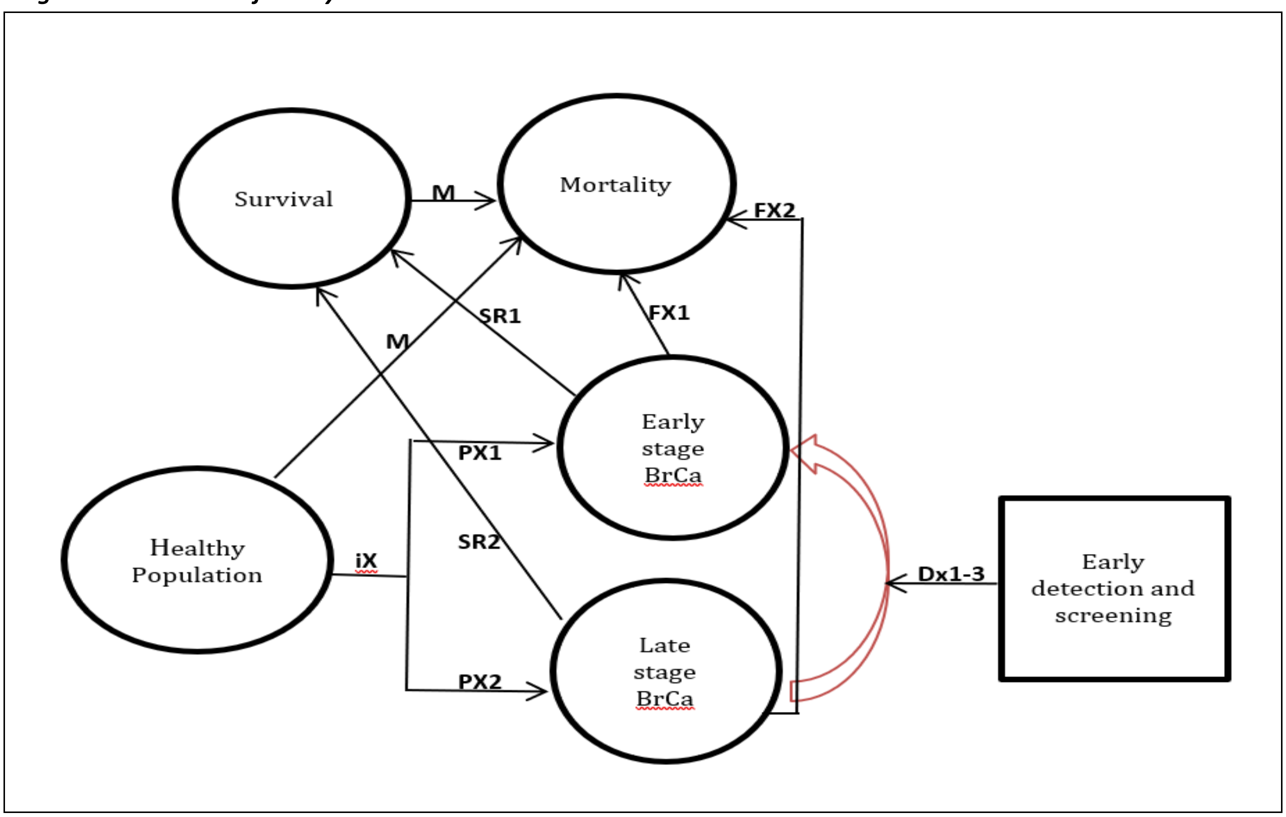
We developed a model based on available published data from LMICs that were relevant to breast cancer disease. As such, we did not estimate model parameters. For parameters such as preclinical sojourn time and screening test sensitivity, we constrained our values to fall within the average range of published estimates. We model early detection and screening interventions as shifting breast cancer cases that would have otherwise been diagnosed as “late stage” to an “earlier stage” at diagnosis, and this stage-shift improves prognosis that is associated with lower breast cancer management costs. Thus, early detection interventions downstage breast cancer disease, requiring less systemic treatment which is very costly for most LMICs [9]. Regarding the model philosophy, we made minimal assumptions about the natural history of breast cancer. All aspects of breast cancer were modelled by stage; early stage (stage I & II), and late sage (stage III & IV). This key assumption underpins the implication that any effect of early detection and screening interventions is a result of downstaging or stage shifting of the breast cancer disease. As such, our model is an empirical model based on stage distribution at diagnosis and how early detection and screening interventions can improve stage distribution through downstaging.

This model philosophy we have adopted is aligns with the views of other Breast Cancer researchers who argue that predictive models based on the natural history of the disease are inherently prone to greater error. This is because these predictive models require very accurate data from observational studies on the frequency and timeline for progression from "stage I" to "stage IV" disease which largely remain unavailable for LMICs [69]. Furthermore, predictive models based on natural history of the disease assume a uniform, linear progression from localized to metastatic disease with cancers starting nicely as localized disease, then gradually progress to node positive disease, and finally end up with metastatic cancer. However, this oversimplifies the reality of breast cancer progression, which varies with the tumor subtype [126]. Furthermore, the natural history of breast cancer is not always predictable. For instance, a 2cm triple negative cancer may already be node positive and will progress or metastasize in a short period of time (less than a year) while a 2cm estrogen receptor-positive (ER+) screen detected breast cancer may remain localized and node negative for 1 - 2 years. This stark variation in tumor behavior demonstrates that disease progression is highly individualized and heavily influenced by biological factors, making a model based on the natural history of the disease less applicable to diverse populations with varying tumor types and treatment access. Consequently, models that do not rely on these assumptions offer a more adaptable and realistic framework for predicting breast cancer outcomes in LMICs[68].

4.2.2 Model Overview/Structure

Using a dynamic state transition model, we yielded a set of breast cancer records for a population that was constructed using the following assumptions. First, we initialized the model with the populations of South Africa and Uganda in 2024 by age and sex (ages 0 through 100 inclusive) [127]. Second, each year, we allowed women to give birth in accordance with the estimated age-specific fertility rates for South Africa and Uganda [128]. Women gave birth to males and females as determined by the sex ratio at birth [129]. The model assumed that fertility rates for women with and without breast cancer was the same as the age-specific fertility rates of the broader Ugandan and South African populations. These rates were uniformly applied to all women of reproductive age in the simulation, irrespective of their breast cancer status. Healthy persons (i.e., persons not diagnosed with breast cancer, or recovering from breast cancer) died at rates determined by the Lifetable Mortality rates (M) [130], [131]. The population increases or decreases in accordance with the net migration rate [132], and the population is also affected by the fertility and mortality rates which determine the number of women reaching the ages of 40 – 75 years, the target population for the cost effectiveness analysis (chapters 5&6 of this thesis). The model utilized official net migration estimates for Uganda and South Africa, applying these rates yearly to the simulated population. It assumed that migrants entering or exiting these populations shared the same health conditions, risks, and access to health services, including breast cancer screening under the proposed intervention, as the resident population.

Figure 6: Schematic of the dynamic state-transition simulation model



ix represent breast cancer incidence rate; PX1 represent the proportion of breast cancer patients in early stage, PX2 represent the proportion of breast cancer patients in late stage; (Dx1–3) represents the down-staging effect of *awareness raising interventions, CBE, and Mammography; (Fx1 and Fx2) represents the case fatality rates, (SR1 and SR2) represents the survival rates, M represents background mortality.*

Population of Interest

The target population for the intervention (breast cancer screening and subsequent treatment) was women between the ages of 40-75 years. The model simulated dynamic population demographics based on changing birth and mortality rates to mimic the proportion of women who would be eligible for screening at age 40-75 years over the study time horizon. The Healthy Life Years (HLYs) were calculated for all individuals within this simulated population based on their health states and associated disability weights. This comprehensive demographic model was necessary to:

- Accurately project the number of women entering and aging through the eligible screening ages over the long-time horizon.
- Account for competing risks of mortality from other causes for the entire population.
- Provide a stable demographic denominator for epidemiological rates. Male offspring were included as part of the general demographic simulation (e.g., through the application of sex ratios at birth) to ensure overall population dynamics were correctly represented.

The direct health gains from the breast cancer intervention (i.e., reduced morbidity and mortality specifically from breast cancer) accrued to women ONLY. Any differences observed in the total HLYs for males between the intervention and baseline scenarios would be an indirect consequence of the intervention, primarily resulting from changes in the overall number of births if more women survived their reproductive years due to earlier cancer detection and treatment.

It is therefore important to draw a distinction between (a) the modelled population (entire Ugandan and South African population for demographic integrity and comprehensiveness) and (b) the primary population directly benefiting from the intervention (women at risk of or with breast cancer). Therefore, the economic evaluation's interpretation of cost-effectiveness (e.g., cost per HLY gained specifically from averting breast cancer burden) focused on the health gains experienced by women. The annual incidence (women diagnosed with breast cancer) was determined using age specific incidence from 2022, from the IARC Globocan Today database [7]. The age specific incidence was divided by the age specific population in Uganda and South Africa in 2024, to determine the incidence rate. Diagnosed women were also categorized as Early Stage, or Late Stage. The baseline proportion of women diagnosed as Early Stage or Late Stage was taken from empirical estimates for South Africa [56], [109], [138], [139] and Uganda [107], [108].

4.2.3 Modelled Interventions for Early Detection, Screening, Treatment, and Palliative Care

Baseline Scenario Description

We compared three early detection and screening interventions against a baseline scenario. The baseline scenario assumes that current incidence rates of breast cancer continue, and that these breast cancer diagnoses present at the current proportion of early stage for South Africa (46%) and late stage (54%) breast cancers [116], [117] and for Uganda 11% early presentation and 89% late presentation.

While the breast cancer implementation guidelines in both countries provide an aspirational framework, their implementation is still subpar. For instance, in Uganda, access is hindered by having just four mammography units for ~7 million women, requiring long travels making it unaffordable for most women[18]. South Africa fares better with urban mammography availability, but rural uptake is lower in lower quintiles (Q1–Q3) due to transport costs and wait times[11], [14]. Low awareness and cultural barriers also drive late-stage diagnoses (80–90% Stages III–IV in LMICs). In Uganda, stigma linking cancer to social taboos reduces uptake of services[18], while South African rural communities often prefer traditional healers, delaying care[53]. Therefore, the model's baseline comparator captures the average observed system performance as reflected in current national epidemiological data, not the ideal or fully realized implementation of policy recommendations. Furthermore, the baseline scenario, assumes a continuation of current breast cancer incidence patterns, stage distribution at diagnosis, assuming no additional investment is made into early detection and screening interventions of any kind for the time horizon considered in this analysis. In the baseline scenario, total breast cancer control costs come only from treating the cases that present (with no investment in screening or awareness).

Description of the modelled intervention scenarios

All modeled improvements under the intervention scenarios (awareness raising, CBE, mammography) are calculated relative to the empirical baseline. Under the intervention scenarios, we model an immediate scale-up to 100% coverage of the screening program among the target age group (which translates to 50% of women screened each year biennially). We assume the quality of screening/treatment under the intervention is ideal – e.g., all detected cases get full treatment per guidelines. This effectively simulates the best-case impact of implementing these interventions compared to the baseline of no additional intervention

The first comparator is an "awareness/early diagnosis" scenario which focuses on implementing awareness campaigns and training primary health workers to promote awareness on breast cancer. The second is a "CBE led screening" scenario, where clinicians are trained to identify breast lesions through clinical breast examination. The third comparator is a "Mammographic led Screening" scenario, whereby, mammographic screening is implemented and scaled up, capturing additional cases of breast lesions which would have been undetected by CBE.

The CBE and Mammography led scenarios assume that, in the first year of the model runtime, a screening intervention is implemented. This screening intervention targets women aged 40 to 75 years old, and screens them biennially. It assumes an immediate coverage of 100%, meaning that, on average, 50% of the population of women aged 40 to 75 are screened every year. In all scenarios, women who get diagnosed are treated for breast cancer. Women are assumed to be treated over the course of a year, and after this period enter a "recovery" period. The recovery period has separate case fatality rates for early-stage disease vs late-stage disease taken from Ralaidovy et al. [86]. Furthermore, in the model, women that have been diagnosed with breast cancer are excluded from screening while the disease is being treated and they re-enter the general population for screening after a period of 5 years. At that point they are assumed to be part of the healthy population again, and the model assumes the same incidence rates as the general population.

Table 11: Operational Definitions for Breast Cancer Control Measures Considered in the Analysis

Early Detection/screening interventions	**Awareness Raising Interventions:** Training of primary health workers + outreaches by primary health workers to raise breast cancer awareness + enhanced media activities including mass media campaigns
	Clinical Breast Examination (CEB): Biennial CBE screening in asymptomatic women aged 40 – 75 + outreaches by primary health workers to raise breast cancer awareness + limited media activities
	Mammography (MG): Biennial MMG screening in asymptomatic women aged 40 – 75 + outreaches by primary health workers to raise breast cancer awareness + limited media activities
Treatment of Breast Cancer at different stages	**Treatment for stage1**: Lumpectomy with axillary dissection, radiotherapy, tamoxifen, or chemotherapy for eligible patients
	Treatment for stage 2: Lumpectomy with axillary dissection, radiotherapy, tamoxifen, or chemotherapy for eligible patients
	Treatment for stage 3: Mastectomy, adjuvant chemotherapy, radiotherapy, and tamoxifen for eligible patients
	Treatment for stage 4: adjuvant chemotherapy, radiotherapy (10 Gy), and eligible patients are given tamoxifen and total mastectomy
Palliative Care	Training for palliative care community nurses + home-based visits + pain medication for eligible patients (morphine, palliative radiotherapy (8 Gy in 1 fraction), and laxatives

Source: WHO[13] and country specific guidelines for Uganda and South Africa [112]

4.2.4 Model Parameters

The model parameters were informed through a structured process designed to maximize relevance and applicability to the Ugandan and South African contexts. First, we conducted a comprehensive review of peer-reviewed literature (presented in chapter 2 of this thesis), national breast cancer guidelines, Ministry of Health reports, and relevant global health sources (e.g., WHO, GLOBOCAN, GBD). For each parameter, we prioritized the use of country-specific data where available; when such data were unavailable or incomplete, we used regional estimates (e.g., sub-Saharan Africa averages) or international evidence judged to be applicable to similar healthcare settings. In cases where multiple published estimates were identified, selection was guided by several criteria: (1) methodological rigor of the original study, (2) population similarity to the Ugandan or South African context, and (3) alignment with other epidemiological data. Where significant uncertainty remained, we conducted sensitivity analyses to assess the robustness of model results across plausible parameter ranges. Expert consultations with oncologists and public health specialists from both countries and other global public health experts were also incorporated to validate parameter choices and ensure local relevance.

The incidence and mortality data used in this analysis were obtained from the IARC Global Cancer Observatory (GLOBOCAN) database, which compiles standardized cancer statistics for countries worldwide. For South Africa, the incidence data reported in GLOBOCAN are based on national estimates derived from the South African National Cancer Registry (NCR), a population-based registry with national coverage. In contrast, the incidence data for Uganda are based on aggregated estimates from two subnational population-based cancer registries: the Kampala Cancer Registry and the Gulu Cancer Registry. These regional registries cover specific catchment areas and are used by GLOBOCAN to generate national estimates for Uganda due to the absence of a fully national registry.

Description of Model Parameters

- **Population Demographics:** The population distribution was obtained and from the UN population projections for South Africa and Uganda (by age and sex for 2024 and projected forward 40 years). These data provided the initial population age structure ("population distribution") for the model. The population is dynamically updated each year via births, deaths (using country-specific fertility rates and life tables) and net migration.
- **Breast Cancer Incidence and Stage Distribution:** We used age-specific breast cancer incidence rates for 2022 from GLOBOCAN. These rates (per 100,000) were applied to our simulated population to generate new breast cancer cases each year. Table 12's "incidence distribution" row had no single value because it's a set of age-specific rates.
- For the **baseline stage distribution** of cancers: for South Africa, approximately 46% early-stage vs 54% late-stage, based on averaging published data; for Uganda, 11% early vs 89% late. These percentages (with sources) are included in Table 12. These baseline stage distributions were the starting point for down-staging calculations. Furthermore, we defined early stage as the patients with Stage I & II while late stage was for patients with Stage III & IV.
- **Proportional performance rates for the three early detection interventions (Mass awareness, CBE, and MMG):** We adapted the mathematical framework developed by Zelle et al. 2015 described elsewhere in detail [138]. Zelle et al. described the creation of a "Z-index", which is an estimate of the success rate of an early detection or screening policy. Zelle *et al.* related this index to empirical stage distributions from the Nijmegen Study [140] using an Ordinary Least Squares Regression and provided regression coefficients and intercepts for estimating the proportion of early-stage diagnoses. Using this approach, we computed country-specific Z-indices for South Africa and Uganda based on local incidence estimates and published values for sojourn time and test sensitivity [138]. We then interpolated the coefficients to match observed baseline proportions of late-stage diagnoses (54% in South Africa and 89% in Uganda). For awareness-raising interventions, we applied a fixed 10% downstaging effect, consistent with evidence from similar LMIC studies [34], [35].
- **Sensitivity of CBE and MMG:** Estimated the average from the published global evidence. The test sensitivity is simply a parameter used as an input to calculate the performance of the screening interventions and to determine the probability that a cancer is detected at an early or late stage. It is important to note that in the model, the sensitivity of a screening test (CBE or mammography) directly influences the probability that a breast cancer case is detected at an early stage *versus remaining undetected until later*. The model uses the test sensitivity as an input to the **"**Z-index" calculation (per Zelle et al.) that determines the expected shift in stage distribution. A higher sensitivity increases the down-staging effect represented in Figure 6. Figure 6's "(Dx1–Dx3)" nodes as the downstaging effects for awareness, CBE, and mammography are functions of the screening test sensitivity (as well as sojourn time and baseline incidence). Thus, for instance, a mammography sensitivity of 70% means a greater fraction of cancers can be caught in early stages compared to a test with 50% sensitivity (CBE), all else equal, and the model accounts for this when computing the new stage distributions under each intervention scenario.

- **Mean Sojourn time (MMG):** Obtained from Zelle et al. 2015 from a proof of concept for predicting the stage shift because of breast cancer screening in LMICs.
- **Mean Sojourn time (CBE):** Obtained from Zelle et al. 2015 from a proof of concept for predicting the stage shift because of breast cancer screening in LMICs.
- **Effect size of awareness raising interventions:** Obtained from similar studies from LMICs. The 10% downstaging effect is expressed in terms of ten percentage points and not as a proportion of cases.
- **Mortality Rates:** We obtained country-specific life tables (overall mortality rates by age and sex) from the UN life tables. These rates were used to model background (non-breast cancer) mortality in the dynamic population. We applied the life table mortality to all individuals without modification (since our model does not further stratify by other health conditions).
- **GBD Disability Weights (Late and Early Stage BrCa):** Obtained from the 2021 Global Burden of Diseases and the disability weights represent a health-related quality of life decrement due to breast cancer. The disability weight was applied to the Uganda and S. Africa specific breast cancer incidence described above.
- **Case Fatality Rate (Early Stage BrCa):** Obtained from Ralaidovy et al 2018 and for early stage taken as an average between the case fatality rate for stage I (0.01) and Stage II (0.02).
- **Case Fatality Rate (Late Stage BrCa):** Obtained from Ralaidovy et al 2018 and for late stage taken as an average between the case fatality rate for stage III (0.08) and Stage IV (0.27).

To calculate the performance of early detection and screening interventions, we utilized the parameters presented in *Table 12*.

Table 12: Model Parameters and Values

Model Parameter	**Parameter Value**	**Reference/Source**	**Means for Calculation**
Population Distribution		[127]	Obtained Uganda specific and South Africa specific population projections from 2024 for 40 years by age and sex (ages 0 through 100 inclusive) from the UNDP world population projections
Incidence Distribution		[7]	The annual incidence (women diagnosed with breast cancer) was determined using age specific incidence from 2022, from the IARC Globocan Today database [100]. The age specific incidence was divided by the age specific population in Uganda and South Africa in 2024, to determine the incidence rate.
Proportion of cases that are early stage (stage I & II) – South Africa	46%	[56], [109], [138], [139]	Estimated an average from the published South African evidence
Proportion of cases that are early stage (stage I & II) – Uganda	11%	[107], [108]	Estimated an average from the published Ugandan evidence

Sensitivity (MMG)	70%	[35], [36], [133], [134], [135], [136], [137], [138]	Estimated the average from the published global evidence. The test sensitivity is simply a parameter used as an input to calculate the performance of the screening interventions and to determine the probability that a cancer is detected at an early or late stage.
Sensitivity (CBE)	50%	[35], [36], [133], [134], [135], [137], [138]	Estimated the average from the published global evidence. The test sensitivity is simply a parameter used as an input to calculate the performance of the screening interventions and to determine the probability that a cancer is detected at an early or late stage.
Mean Sojourn time (MMG)	2 years	[138]	Obtained from Zelle et al. 2015 from a proof of concept for predicting the stage shift because of breast cancer screening in LMICs
Mean Sojourn time (CBE)	1.5 years	[138]	Obtained from Zelle et al. 2015 from a proof of concept for predicting the stage shift because of breast cancer screening in LMICs
Effect size of awareness raising interventions	10%	[34], [35]	Obtained from similar studies from LMICs. The 10% downstaging effect is expressed in terms of ten percentage points and not as a proportion of cases.
Lifetable mortality rates		[131]	Obtained Uganda specific and South Africa specific life mortality rates from the UNDP life tables for males and females
GBD Disability Weights (Early Stage BrCa)	0.039	[8]	Obtained from the 2021 Global Burden of Diseases and the disability weights represent a health-related quality of life decrement due to breast cancer. The disability weight was applied to the Uganda and S. Africa specific breast cancer incidence described above.
GBD Disability Weights (Late Stage BrCa)	0.451	[8]	Obtained from the 2021 Global Burden of Diseases and the disability weights represent a health-related quality of life decrement due to breast cancer. The disability weight was applied to the Uganda and S. Africa specific breast cancer incidence described above.
Case Fatality Rate (Early Stage BrCa)	0.020	[86]	Obtained from Ralaidovy et al 2018 and for early stage taken as an average between the case fatality rate for stage I (0.01) and Stage II (0.02).
Case Fatality Rate (Late Stage BrCa)	0.18	[86]	Obtained from Ralaidovy et al 2018 and for late stage taken as an average between the case fatality rate for stage III (0.08) and Stage IV (0.27).
Beta coefficient for screening interventions for South Africa	0.7944	Author's computation	Author's computation following the Zelle et al 2015 proportional performance rates approach

Beta coefficient for screening interventions for Uganda	1.6	Author's computatio n	Author's computation following the Zelle et al 2015 proportional performance rates approach
Y-intercept for screening interventions South Africa	0.46	Author's computatio n	Author's computation following the Zelle et al 2015 proportional performance rates approach
Y-intercept for screening interventions Uganda	0.11	Author's computatio n	Author's computation following the Zelle et al 2015 proportional performance rates approach
Baseline coverage for CBE for South Africa	22.7%	[16]	Obtained from the literature for LMICs countries
Baseline coverage for CBE for Uganda	10%	[18]	Obtained from a Uganda specific analysis on the diagnostic capacity for breast cancer in country
Baseline coverage for MMG for South Africa	20%	[16]	Obtained from the literature for LMICs countries
Baseline coverage for MMG for Uganda	0.01%	[139]	Obtained from a Uganda specific analysis

4.2.5 Effectiveness of early detection and screening interventions

The effectiveness of each early detection and screening intervention method was because of changes in (i) down-staging or stage-shift distribution, (ii) disability weights i.e., health state valuations (HSVs), (iii) from reduced case fatality resulting from improved survival due to the treatment provided. The effectiveness outcome measure was expressed in Healthy years lived because breast cancer interventions affect both the mortality (case fatality) and morbidity (disability weights).

To quantify the downstaging from late stage to early-stage breast cancers related to early detection and screening interventions, we based our model on a mathematical framework by Zelle et al. 2015 described elsewhere in detail [138]. Zelle et al. described the creation of a "Z-index", which is an estimate of the success rate of an early detection or screening policy. This success rate is a function of the mean sojourn time of the method (awareness raising, or CBE or Mammography), the sensitivity of that method, and the incidence of breast cancer before the early detection or screening policy was introduced. Zelle et al. then relate this Z-index to empirical estimates of stage distribution provided by the Nijmegen Study [140] using an Ordinary Least Squares Regression. Usefully, Zelle et al. provided a table transforming the regression coefficients to different y-intercepts (the proportion of women diagnosed with early-stage breast cancer). Therefore, we calculated the Z-index for South Africa and Uganda using mean sojourn time and sensitivity provided by [138], and incidence using our model (described above). We then impute the annual proportion diagnosed with breast cancer using the y-intercept and coefficients provided by [138], which we linearly interpolated to derive the coefficients which would match our estimate of the starting proportion of late diagnoses of 54% in South Africa and 89% for Uganda. For the awareness raising interventions, we assumed a flat 10% downstaging effect similar studies in LMICs[34], [35].

The primary analysis of the model summed Healthy Life Years (HLYs) across the entire simulated population, incorporating children born during the simulation period due to the dynamic demographic modeling over the time horizon. The model disability weights linked to each health state, computing HLYs as (1 - Disability Weight) × Life Years for everyone in each state, with annual summation.

Regarding inclusion of Healthy Life Years from “new people”, our primary analysis summed Healthy Life Years (HLYs) across the entire simulated population.

4.2.6 Model Access and User Interface

We used the Botech protocol and software (which uses python coding language) to develop a dynamic state transition model that was run under the four scenarios described above. We developed a dynamic state transition model because we believe it best captures the trade-off between complexity and legibility. The Botech protocol is a protocol to create dynamic state transition models, which was created by Forecast Health Australia in collaboration with the World Health Organization. A protocol in this sense, is a set of rules about how a model should be created, what actions occur when a model is run, and how a model’s results should be recorded and interpreted. The model is available for viewing and running: https://botech.forecasthealth.org/?userId=standard&modelId=uga_cbe

4.3 Results

We report the magnitude of downstaging in breast cancer distribution (i.e., the shift in the proportion of early vs. late-stage breast cancer) projected after implementing three awareness raising and screening interventions for breast cancer in Uganda and South Africa for (i) awareness raising, (ii) Clinical Breast Examination (CBE) led screening, and (iii) Mammography led screening, among the population of women aged 40 to 75. It is important to highlight that the figures presented in *Table 14* (e.g., number of patients diagnosed early or late) represent the modeled outcomes under each separate intervention scenario. They are not additive across interventions as each intervention was modeled independently compared to the baseline (business-as-usual) scenario.

In Uganda, the baseline distribution was 11% of breast cancer patients presenting with early stage of the disease and 89% presenting with late-stage disease [108], [109]. The implementation of awareness raising campaigns across the country coupled with training of health workers to create awareness for early detection of breast cancer shifts the proportion of the women presenting with early stage from 11% to 20%, translating into 25,038 women over 40 years shifting from late stage to early-stage. The scaling up of clinical breast examination has a stronger effect as it shifts 21% (59,800) breast cancer patients to present in the early stage of the disease over the 40-year period. Mammography has the strongest downstaging effect of 36% (100,840) of the breast cancer patients presenting in the early stage. Cumulatively, we estimate that the three early detection and screening interventions in Uganda are associated with a 66% stage-shift of breast cancer patients from late-stage to early-stage of the disease over the 40-year period.

Table 13: Predicting down-staging of breast cancer presentation in Uganda over a 40-year period

	40-year period		**Downstaging effect**
Screening Intervention	**# Of patients in early stage**	**# Of patients in late stage**	
Baseline	30,914.62	250,127.39	
Awareness Raising	55,952.48	225,162.72	9% (25,038 women)
CBE	90,746.23	190,452.58	21% (59,831 women)
Mammography	131,764.05	149,542.97	36% (100,849 women)
Total downstaging effect of the 3 interventions			**66%**

Figure 7: Predicting stage-shifting of breast cancer in Uganda

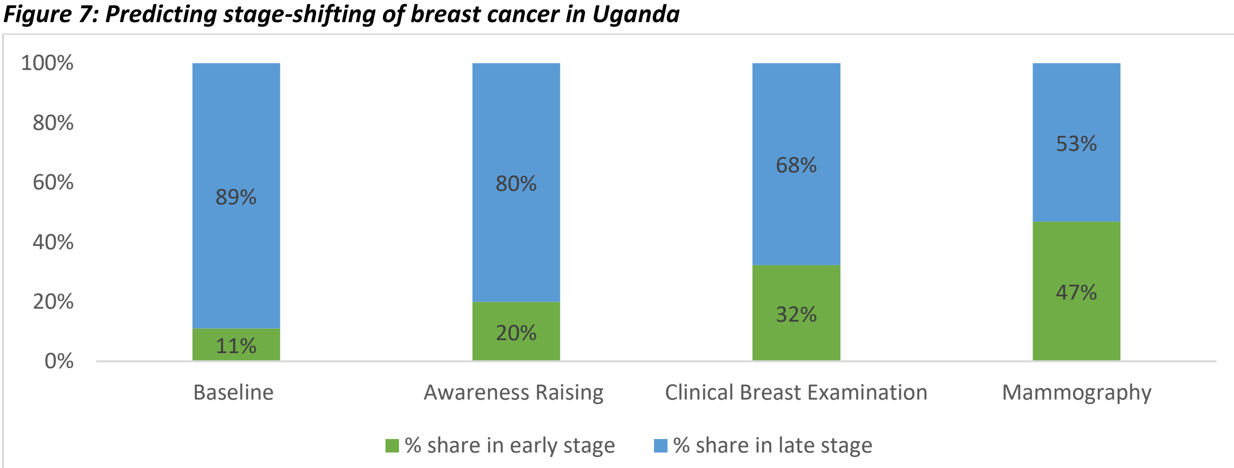
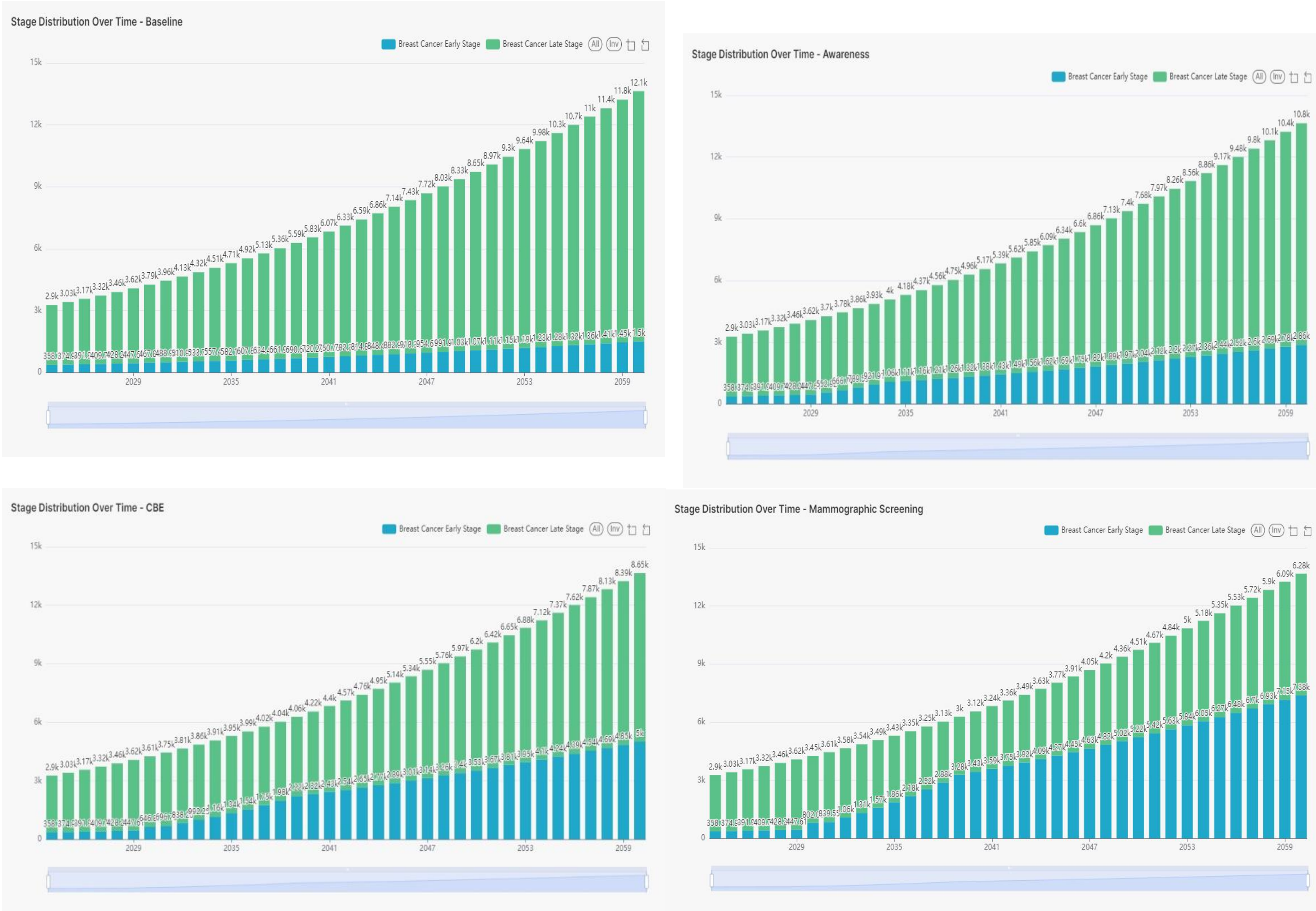


Figure 8: Predicting down-staging of breast cancer presentation in Uganda over a 40-year period



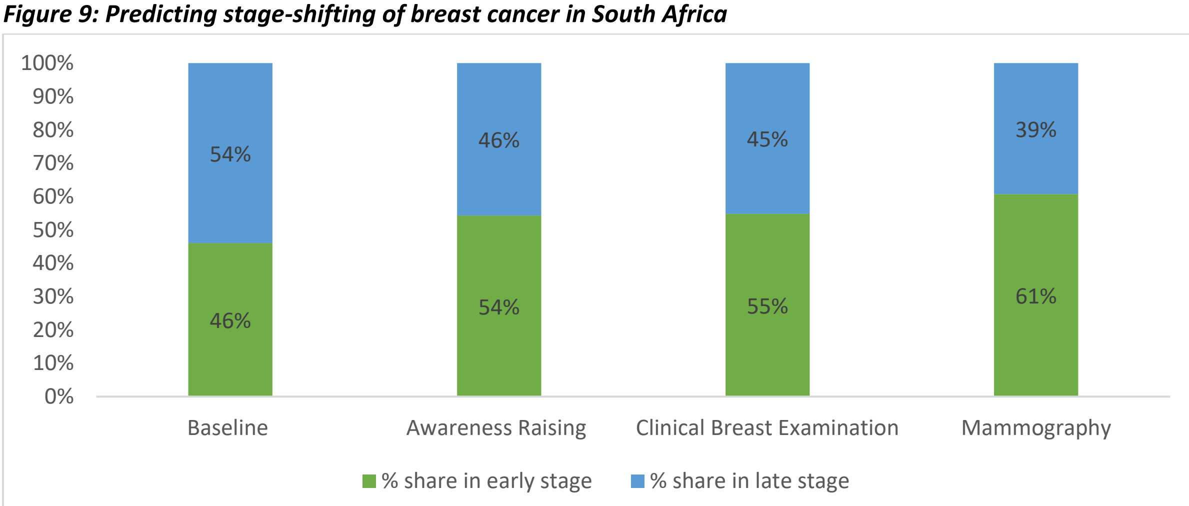
In South Africa, the implementation of awareness raising campaigns across the country coupled with training of health workers to create awareness for early detection of breast cancer shifts the proportion of the women presenting with early stage by 8% (73,719). The scaling up of clinical breast examination has an almost equal effect as the awareness raising campaigns as it shifts the stage distribution of the breast cancer patients presenting in the early stage of the disease by 9% (78,167). Mammography on the other hand has the strongest stage shift effect of 15% (130,487) of the breast cancer patients presenting in the early stage.

Cumulatively, we estimate that the three early detection and screening interventions in South Africa are associated with a 32% stage-shift of breast cancer patients from late-stage to early-stage of the disease for over the period of 40 years.

Table 14: Predicting down-staging of breast cancer presentation in South Africa over a 40-year period

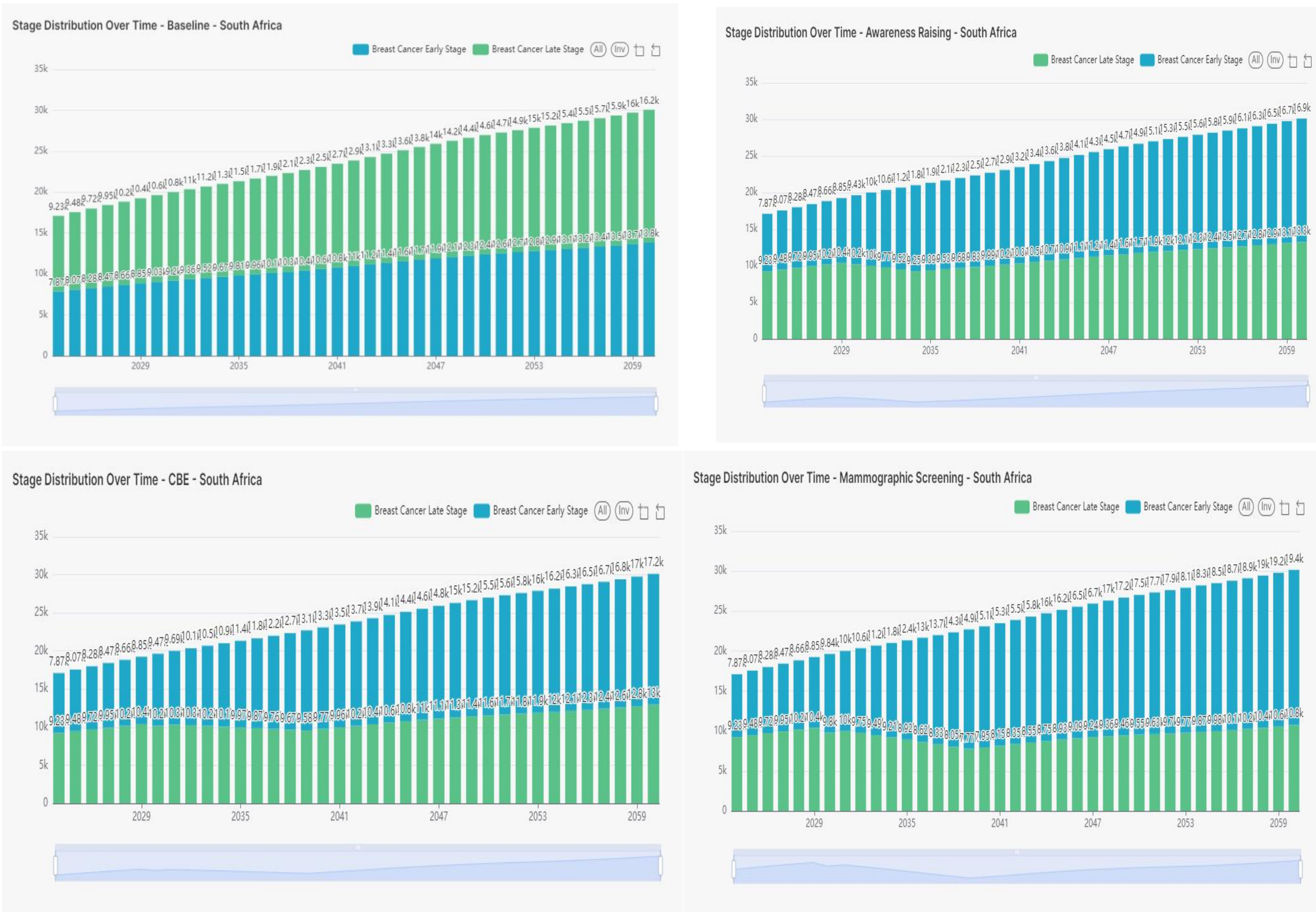
	40-year period		**Downstaging effect**
Screening Intervention	**# Of patients in early stage**	**# Of patients in late stage**	
Baseline	406,158.24	476,794.47	
Awareness Raising	479,877.52	403,680.78	8% (73,719 women)
Clinical Breast Examination	484,325.24	399,223.98	9% (78,167 women)
Mammography	536,645.80	347,305.35	15% (130,487 women)
Total downstaging effect of the 3 interventions			**32%**

Figure 9: Predicting stage-shifting of breast cancer in South Africa



Awareness raising has similar downstaging effect in both countries (9% in Uganda and 8% in South Africa) while CBE has a stronger effect in Uganda (21%) than in South Africa (9%). In both countries, mammography led screening is reported to have the strongest down-staging effect of 36% in Uganda and 15% in South Africa. Overall, early detection and screening interventions have a stronger downstaging effect in Uganda which has a higher incidence of late-stage presentation than South Africa.

Figure 10: Predicting down-staging of breast cancer presentation in South Africa over a 40-year period



4.4 Discussion

We developed a model to predict and quantify the effect of early detection interventions on downstaging breast cancer diagnosis in South Africa and Uganda. Our findings demonstrated that the three early detection and screening interventions assessed have a stronger impact in settings where late-stage presentation of breast cancer is very prevalent. For Uganda, we report a cumulative downstaging effect of 66% and 32% for South Africa for the three early detection interventions over a period of 40 years. In both countries, awareness raising interventions have similar downstaging effect (9% in Uganda and 8% in South Africa), while CBE has a stronger effect in Uganda (21%) than in South Africa (9%). In both countries, mammography led screening is reported to have the strongest down-staging effect of 36% in Uganda and 15% in South Africa.

For Uganda we report a cumulative 66% down-staging effect, and this is corroborated by WHO/IARC's breast cancer screening viewpoint which notes that organized mammographic screening reduces the portion of late-stage presentation by at least 60% which ultimately reduces breast cancer mortality by 20% [38]. Another study reported that for LMICs, 60% of breast cancer cases in early stage should nominally be obtained through a breast cancer screening program [138]. For South Africa, our findings of a 32% cumulative downstaging effect are in line with results from comparator middle-income countries in the region. For instance, a study from Kenya reported that increasing breast cancer awareness within the population and training of primary health care workers to recognize symptoms and administering clinical breast exams increased the number of women diagnosed with cancer by about 20%[12]. Another study from Ghana found that interventions to raise awareness and screening interventions were very effective for breast cancer control, with biennial CBE screening of women aged 40-69 as the optimal choice [35].

Furthermore, the stage-shift results presented in this chapter align with existing evidence from prior modelling studies, particularly those by Zelle et al. (2015) [140] and Birnbaum et al. (2018)[68], both of which are modelling frameworks to assess the impact of early detection strategies on breast cancer outcomes in LMICs. Zelle et al. (2015) employed a proportional performance method to estimate stage distribution shifts from early detection, albeit with a natural disease history model, which may explain their smaller projected impact compared to our study. Birnbaum et al. (2018), in contrast, did not use a natural disease model (aligned to this thesis), however, they used an individual level micro-simulation Markov model calibrated to sub-Saharan African settings and similarly projected substantial gains in early-stage diagnoses following mammographic screening and CBE. The study presented in this thesis distinguishes itself by borrowing aspects from the Zelle model (use of proportional performance rates) and aligns with the Birnbaum model (by not using a natural disease model), but unlike Birnbaum who used individual level micro-simulation that requires more granular individual-level data, our model simulates a cohort level population over a 40-year horizon. These methodological strengths better account for demographic transitions, screening coverage trajectories and requires less granular data required by microsimulations. The larger estimated impact on early-stage diagnosis observed in our study may be attributable to the modelling approach but also to the assumption of idealized implementation scenarios, which represent normative aspirations rather than current practice. This contextual nuance is important in interpreting the results in light of real-world constraints and underscores the value of modelling aspirational benchmarks for policy evaluation.

Due to constrained fiscal spaces for health in LMICs, the quantification of potential down-staging for breast cancer diagnosis has implications for policy and pragmatic planning. Now more than ever, there is a need to optimally utilize available resources to benefit the largest proportion of the population. Easy to use models like the one we have developed will be very useful in generating robust evidence to identify resource-appropriate interventions and to guide the allocation of scare resource in LMICs. Furthermore, our analysis confirms that countries with high prevalence of late-stage presentation could greatly benefit from institutionalizing early detection and screening interventions through increasing access to breast cancer diagnosis and prompt cancer management. While our findings confirm a strong downstaging effect associated with early detection and screening interventions, it is important to note that careful and well-thought-out planning should precede the full roll out and expansion of early detection and screening interventions. This is because early detection and screening interventions will cause a surge in the number of women seeking breast cancer services, and if this surge is not met with the expected diagnostic and effective treatment capacity, the benefits of early detection will be negated. Furthermore, this can increase mistrust in the public health system and result in an increase in health care costs through the private sector [9].

As with any other modelling exercises, our model has limitations worth highlighting. Firstly, our model is not a dynamic simulation of individual patients but is rather based on cohort age-specific parameters. As such, we were not able to model very advanced nuanced scenarios. Nevertheless, it is well established that more advanced individual simulation models require advanced information that is not readily available in most LMICs at the expense of their usefulness for decision makers[69]. Secondly, our model doesn't consider other contextual factors like obesity rate, insurance coverage, and the level of poverty and yet these contextual constructs could have an altering effect on breast cancer control in the two countries assessed. Thirdly, our model doesn't account for the harms associated with breast cancer screening (e.g., false positives, and over-diagnosis) and the impact of breast cancer diagnosis and treatment on fertility. Future model refinements could incorporate stage specific or treatment-specific fertility modifiers as the data becomes progressively available. Fourthly, the architecture of the model doesn't treat women who have previously had a breast cancer episode as having an elevated risk and after they have survived, they re-enter the health population assuming the same incidence rates as the healthy population. We acknowledge that evidence suggests that breast cancer survivors have a fourfold increased risk of having breast cancer again[58] and future models should permit for accommodation of such nuances. Fifth, the degree to which breast cancer early detection and screening interventions are beneficial to Uganda and South Africa cannot merely depend on estimated stage-shifting as quantified by our model. Other critical criteria such as affordability (budget impact), value for money, safety, and other political economy concerns should be considered. lastly, the cancer registries in both Uganda and South Africa were not fully functional and therefore critical local data on breast cancer epidemiology and stage distribution were obtained from literature sources.

Despite these shortcomings, the above limitations fit within the overall aim of this study which was to provide broad indication rather than very precise estimates of the impact of early detection and screening interventions on downstaging of breast cancer in LMICs. Our study also had several strengths. Firstly, our model doesn't include the natural history of the underlying breast cancer disease, but rather, it focuses on the observable events in disease progression, implying fewer inputs, transparency in the model and higher generalizability to other contexts. Secondly, our model utilizes country-specific parameters and to the degree possible, the parameters obtained from existing literature have been adjusted to better reflect the Ugandan and South African context where this model has been applied and sensitivity analysis performed to check for robustness of findings. Thirdly, our model predicts the amount of stage-shifting associated with early detection and screening interventions for breast cancer and this is a powerful indicator for the effectiveness of a screening program especially for LMICs where late-stage presentation of the disease is very prevalent. Fourthly, our model can further support the estimation of the cost-effectiveness of the early detection and screening interventions by attaching potential costs or effects associated with the quantified downstaging impact of the proposed interventions.

In conclusion, our analysis predicts significant down-staging associated with early detection and screening interventions for breast cancer in Uganda and South Africa. In countries where late-stage presentation of breast cancer patients is very prevalent like Uganda, early detection and screening interventions have almost double the impact as compared with settings where late-stage presentation of the diseases is not as prevalent like in the case of South Africa. LMICs should therefore consider improving and enhancing investments in early detection and screening interventions as they can yield substantial down-staging for breast cancer. The implementation of early detection and screening interventions however should follow very comprehensive systematic and phased planning to ensure that the health system can ably and effectively manage the increased number of breast cancer cases owing to enhanced early detection. Our model can guide pragmatic decision making and can easily be adapted to other LMICs settings to facilitate the identification of resource-appropriate interventions.

CHAPTER

5

"Oh, the depth of the riches both of the wisdom and knowledge of God! How unsearchable are His judgments and His ways past finding out!" Roman 11:33

Chapter 5: Cost-Effectiveness of Early Detection, Screening and Breast Cancer Control Interventions in South Africa

Abstract

Background

Early detection of breast cancer is known to improve its prognosis. However, women in most low- and middle-income countries, including South Africa, do not detect it early hence present at an advanced stage. Improved early detection interventions for breast cancer can lead to earlier breast cancer detection and improved outcomes. This study aimed to estimate the costs and effectiveness of early detection and treatment interventions for Breast Cancer in South Africa.

Methods

We constructed a dynamic state transition model to estimate the cost-effectiveness of early detection and screening interventions for breast cancer control. Our model is premised on a comprehensive mathematical framework that estimates the stage shifts in early versus late stages of breast cancer diagnosis based on proportional performance rates (Z's) of three early detection and screening interventions (awareness raising, clinical breast examination and mammography) from 2024 to 2060.

Results

Interventions to raise awareness combined with treatment of all stages, will avert 16,006 incremental deaths, and provide 267,635 incremental Healthy Life Years. Biennial Clinical Breast Examination (CBE) coupled with treatment of all stages will avert 34,663 incremental deaths and provides 537,816 incremental Healthy Life Years. Mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 57,821 incremental deaths and provides 899,450 incremental Healthy Life Years. The Average Cost Effectiveness Ratios (ACERs) range from $377 per death averted for awareness raising interventions to $634 per death averted for Mammography. Biennial CBE coupled with treatment interventions for all stages is cost-effective for South Africa with an ICER of $2,782 per healthy life year gained. Awareness raising interventions were also found to be cost effective with an ICER of 3,204 per health life year gained. Mammography screening combined with treatment for all stages was not found to be a cost-effective intervention for South Africa with an ICER of $8,492 per healthy life year gained.

Conclusion

Our findings indicate that biennial CBE (ages 40-75) and awareness raising interventions are cost effective and feasible option for South Africa and MMG was not found to be a cost-effective option. For the short to medium term, we recommend a combination of nation-wide phased scale up of biennial CBE for women aged 40-75 and awareness raising interventions to facilitate timely diagnosis, referral, and treatment. A combination of fixed and mobile MMG should be considered in the medium to long term as more resources become available. For sustainability and affordability purposes, LMICs should implement awareness raising and screening interventions in an integrated manner with other non-communicable diseases such as cervical cancer in a phased manner with robust monitoring and evaluation.

5.1 Background

Global data for 2022 shows that female breast cancer ranks as the second most common cancer worldwide, with an estimated 2.3 million, and it is the fourth leading cause of mortality worldwide with 665,684 deaths[1]. Among women, it is the most frequently diagnosed cancer and is the leading cause of cancer death among women in 157 countries[1]. In the Africa, breast cancer incidence and mortality are rising, with projections suggesting that cases will double in Sub-Saharan African by 2050[2].

In South Africa, breast cancer incidence has steadily increased, and the absolute number of new cases has doubled over the last 20 years accounting for 14-30% of all cancers affecting women [113]. In 2020, South Africa reported 15,491 new breast cancer cases and although overall, the age standardized rate (ASR) shows a slight increase, there has been a marked increase in the ASR for South Africans of European decent [95]. Regarding the lifetime risk of breast cancer in South Africa, it varies greatly by race with white women (1 in 13), Colored women (1 in 18), Asian women (1 in 25) having a higher lifetime risk compared to black women with a 1 in 81 lifetime risk[93], [114]. Regarding geographical distribution of breast cancer cases, the Eastern Cape Province has registered significant increases in the number of breast cancer cases reporting a 61% increase in the cases between 1998 – 2012 [115].

The cancer mortality in the African region and in South Africa is disproportionately greater than the incidence burden in the region and this is mostly attributed to late-stage presentation of the disease[1]. More patients present with late-stage disease (stage III or IV) and the evidence indicates that on average, 54% of the patients present with late-stage disease [56], [109], [138], [139]. Moreover, there are ethnic disparities in the late presentation with patients of African/black ancestry more likely to present with advanced-stage disease while patients of European ancestry are more likely to present with early-stage disease[118].

The National Department of Health in South Africa has declared Breast Cancer a priority for the country and National Breast Cancer Policy guidelines were developed although they remain to be fully implemented[95]. The policy guidelines note that breast cancer screening is the most viable strategy for breast cancer control through early detection interventions and effective treatment. The guidelines recommend that screening for Breast Cancer should start at the age of 40 years [119].

To address the too frequent challenge of late-stage presentation, early detection and screening interventions are necessary for shifting breast cancer cases that would have otherwise been diagnosed as "late stage" to an "earlier stage" at diagnosis, and this stage-shift improves prognosis that is associated with lower breast cancer management costs. For South Africa, to the best of our knowledge, there is no empirical evidence to estimate the cost effectiveness of the down-staging early detection and screening interventions for Breast Cancer to date. This study aims to estimate the cost effectiveness of three early detection and screening interventions (awareness raising campaigns, clinical breast examination, and mammography) for South Africa.

5.2 Methods

We constructed a dynamic state transition model to estimate the cost effectiveness of three breast cancer down-staging interventions in South Africa for a time horizon of 40 years. We used a mixture of empirical estimates, and assumptions from low-income countries to populate parameters in the model. The model imposes normative assumptions about ideal scenarios of three early detection and screening interventions: awareness raising campaigns, clinical breast examination, and mammographic screening and compares these scenarios to the current business-as-usual scenario (the "baseline" scenario). The model philosophy, structure, the population of interest, the model parameters, the process to quantify the effectiveness of early detection and screening interventions, are presented in Chapter 4 of this thesis and will not be repeated in this chapter. Furthermore, the modelled interventions for early detection, screening, treatment, and palliative care are also presented in chapter 4, section 4.2.3 and will not be repeated in this chapter.

5.2.1 Costs

The study considered a provider's perspective i.e., healthcare provider costs only were considered. The rationale for the provider's perspective aligns with the primary interest of the study for estimating the resource and budgetary implications for the public health system in South Africa. A normative costing based on the national breast cancer norms, policies and guidelines was done from 2022 for a time horizon of 40 years. An ingredients-based approach to costing was used. Ingredients based approach entailed three steps: the first was identification of all required resources or inputs, second was to quantify the required resources and last step was the valuation of these resources based on their current replacement value [123]. The cost analysis focused on estimating the recurrent and capital costs separately, which were then summed up to give the total cost. Capital costs were annualized using a discount rate of 3% at the appropriate life years and the unit of analysis was cost per breast cancer case detected and treated. The cost analysis included only the direct medical costs (early detection activities, diagnostic tests, and treatment including surgery, chemotherapy, and radiotherapy), personnel, supplies, equipment, utilities, stationery, and building space. It's worth noting that the analysis excluded future unrelated healthcare costs for individuals whose lives are extended due to early detection and screening interventions, but for conditions unrelated to breast cancer. As de Vries et al. (2019) point out, omitting these future unrelated medical costs may underestimate total lifetime healthcare expenditure, especially in models where interventions prolong life[148]. This exclusion was due to the lack of reliable data to estimate such costs in the South African setting.

At the program level, the following resources were considered: administrative and managerial costs, media costs, and costs to train healthcare providers. Diagnostic test costs were applied to all individuals undergoing testing, including both true-positive and false-positive cases. The model estimated the number of women receiving follow-up diagnostic procedures based on test performance parameters notably sensitivity of screening interventions in combination with the age-specific incidence of breast cancer. This approach ensured that cost estimates for diagnostic services accurately captured the system's diagnostic workload by reflecting the total number of tests generated under each intervention scenario. For all the screening interventions, the cost of diagnostic tests for women who tested negative for all stages of breast cancer were included and a ratio of 16.4:1 was estimated and utilized, consistent with previous similar studies for those that tested negative vs. tested positive [33], [35], [138][35], [36], [125] Unit costs of patient services in this study were estimated using a combination of micro-costing principles and available cost data from literature. Where feasible, detailed resource utilization patterns and unit prices were used, based on treatment protocols identified in the literature and contained in the two countries breast cancer policies, cost analyses from comparable low- and middle-income country (LMIC) settings, and consultation with local experts [35], [36], [125]. Cost inputs obtained from the literature were adjusted for inflation using the 2020 Consumer Price Index for South Africa (sourced from Statistics South Africa) and converted to 2022 values using exchange rate (US $1 = ZAR 18) obtained from the OANDA database (www.oanda.com).

In instances where local or regional data were unavailable, estimates from the WHO-CHOICE database were employed[141], particularly for standardized medical procedures such as lumpectomy and mastectomy. These estimates provided detailed information on required quantities of consumables, staff time, and infrastructure use, which were then valued using South African input prices (e.g., wages, drug prices, equipment costs), with appropriate adjustments for transport and distribution for drugs and supplies.

To estimate total patient costs, these unit costs were multiplied by the projected number of patients requiring each service under each intervention scenario. The total number of patients and their stage-specific treatment requirements were generated from the dynamic model, while the breakdown of services used (e.g., diagnostics, surgery, radiotherapy, systemic therapy) was informed by published treatment protocols and expert consensus.

5.2.2 Estimation of Healthy Life Years (HLYs)

Healthy Life Years (HLYs) were estimated as the primary health outcome metric in this analysis, capturing both the quantity and quality of life gained from the interventions. HLYs were calculated by first estimating the number of life years gained from averted premature deaths due to breast cancer, based on the difference in breast cancer mortality under each intervention scenario compared to the baseline. These life years were then adjusted for disability using stage-specific disability weights obtained from the Global Burden of Disease Study[8]. Specifically, for each averted breast cancer death, the corresponding life expectancy was calculated and weighted by the average health-related quality of life associated with the cancer stage at diagnosis. We summed HLYs across the entire modelled population, which, due to the dynamic demographic simulation over the time horizon, included children born during this period. The model tracked disability weights associated with each health state.

Therefore, HLYs were calculated as: **(1 - Disability Weight) × Life Years** for everyone in each state and summed annually.

All future health benefits were discounted at a 3% annual rate, consistent with standard economic evaluation guidelines.

5.2.3 Cost Effectiveness Analysis

The cost-effectiveness analysis in this thesis adopted a pair-wise comparison of each breast cancer screening and early detection intervention against the current “business-as-usual” scenario. This approach was selected to reflect the policy context in low- and middle-income countries, where new interventions are typically introduced progressively rather than as mutually exclusive alternatives. Conducting pair-wise comparisons allows for independent assessment of the incremental costs and health gains of each strategy relative to existing practice, providing decision-makers with flexible evidence to support either stand-alone adoption or phased integration of multiple cost-effective interventions within constrained health budgets. For chapter 5& 6 of this this, we computed Incremental Cost Effectiveness Ratios (ICERs) were calculated for each strategy (costs divided by benefits) compared with the baseline scenario [123]. Additionally, we computed Average Cost-Effectiveness Ratios (ACERs) for each intervention, defined as the total cost of the intervention divided by the total health outcomes (e.g., HLY gained, or deaths averted) achieved by that intervention. The extended dominance rule of thumb held where interventions with a higher ICER dominated interventions with a previous non-dominated ICER. [124]. To interpret the cost-effectiveness results generated by this study, for South Africa, we apply the country-specific cost-effectiveness threshold empirically estimated by Edoka and Stacey (2020), which places the opportunity cost-based threshold at USD 3,015 (ZAR 38,500) or at 53% of GDP per capita, per disability-adjusted life year (DALY) averted[142].

5.2.4 Sensitivity Analysis

For all the key parameters that influence the results (ICERs), multivariable sensitivity analyses were carried out to assess for robustness of the values used to estimate the ICER. The cost effectiveness analysis chapters of this thesis (5&6) utilized a multivariable sensitivity analysis over the probabilistic sensitivity analysis. A full probabilistic sensitivity analysis was not conducted for the CEA due to limited data on parameter distributions and for model feasibility; instead, a multivariable deterministic sensitivity analysis was carried out. The multivariable deterministic sensitivity analysis is a reasonable approach to test the influence of each parameter on results given uncertainty, especially in low-data settings. For this thesis, this is particularly important given the proxies and data extracted from literature. The multivariable sensitivity analysis involved simultaneously varying multiple key input parameters within plausible ranges to assess how combined uncertainties affect model outputs. These parameters were varied across plausible ranges (based on published literature or assumed ±25% uncertainty) to evaluate their joint impact on cost-effectiveness outcomes and the robustness of the study’s conclusions. The parameters considered for sensitivity analysis are presented in *Table 15*.

Table 15: Parameters Varied by Multivariable Sensitivity Analysis for South Africa

Parameter	Baseline Value used in analysis	Lower bound parameter	Upper bound parameter	Source
Sensitivity (MMG)	70%	86.3%	87.60%	A study from Kenya [125]
Sensitivity (CBE)	50%	40%	70%	A study from Kenya [125]
Mean Sojourn time (MMG) **++**	2 years	1.5 years	2.5 years	Lower and upper bounds were defined as ±25% of the base value

Mean Sojourn time (CBE) ++	1.5 years	1 year	2 years	Lower and upper bounds were defined as ±25% of the base value
Effect size of awareness raising interventions	10%	7.5%	25%	A study from Malaysia [143]
Case fatality rate (early stage)	0.020	0.006	0.063	A study from Ghana [35]
Case fatality rate (late stage)	0.18	0.093	0.300	A study from Ghana [35]
Disability weights (early stage)	0.039	0.035	0.043	Global Burden of Diseases Study [8]
Disability weights rates (late stage)	0.451	0.265	0.527	Global Burden of Diseases Study [8]
Treatment unit costs as estimated by author (early stage) in 2022 USD++	951	926.74	974.26	Lower and upper bounds were defined as ±25% of the base value
Treatment unit costs as estimated by author (late stage) in 2022 USD++	1,131	1,106.74	1,154.26	Lower and upper bounds were defined as ±25% of the base value
Discount Rate	3%	0%	5%	SA NDOH Recommendation for health technology assessments

++ Lower and upper bounds were defined as ±25% of the base value in the absence of empirical confidence intervals for mean sojourn time and treatment costs, Exchange rate (US $1 = ZAR 18)

Table 16: Unit Costs for Program Activities per Woman Screened, South Africa

Activity	Unit Cost per Woman 2022 (USD)	Source
Mammography	54.8	[80]
Core Biopsy	95.56	[80]
Ultrasound	20.28	[35], [125][10], [33], [36]
Clinical Breast Exam – Primary Care Facility	0.90	[80]
Clinical Breast Exam – Secondary level Facility	10.5	[80]
Follow up diagnostic visit	10.31	[35], [125][10], [33], [36]
Treatment Costs (Early Stage)	951	[80]
Treatment Costs (Late Stage)	1131	[80]
Governance and policy	0.19	[12]
Awareness raising	2.06	[12]
Training	2.95	[12]
M&E and research	0.57	[12]
Screening costs (baseline)	1.84	[78]

The unit costs presented in *Table 16* were originally sourced from a detailed costing study conducted in Kenya [12]and South Africa[78]. To ensure contextual relevance, the Kenyan unit costs were adjusted to 2022 South African Rand (ZAR). Inflation adjustments were made using the Consumer Price Index (CPI), with 2020 used as the base year for deflation, based on official CPI data from Statistics South Africa (Stats SA). Currency conversion from Kenyan Shillings to South African Rand was performed using average 2022 exchange rates obtained from the OANDA financial data platform www.oanda.com). The term “cost per woman” refers to the unit cost of service delivery per woman receiving a specific intervention. This reflects the average cost per service recipient. Table 18 below presents the average utilization of various inputs and unit costs used in the model. The totals for each procedure were derived by summing the costs of all listed procedures for the respective stages.

Table 17: Average utilization of diagnosis and treatment services inputs and unit costs for South Africa

Procedure	Ingredients	Stage 1	Stage 2	Stage 3	Stage 4	Palliative Care	Unit cost per patient per visit (ZAR)	Unit Cost per patient per visit (USD)	Source
Initial diagnosis and evaluation during treatment	No. of health centre visits	1	1	1	1		104.3	6.37	[80]
	No. of follow up hospital visits	3	3	3	3		122.9	7.51	[80]
	Bilateral mammography	1	1	2	0		1,003	54.48	[80]
	Complete blood count	7	7	7	7		227.80	13.93	[35], [125][10], [33], [36]
	FNA or core needle biopsy	1	1	1	1		1,564.8	95.56	[80]
	Liver function tests	8	8	8	8		99.39	6.08	[35], [125][10], [33], [36]
	Ultrasonography	1	1	1	1		331.68	20.28	[35], [125][10], [33], [36]
	Renal function tests	8	8	8	8		112.38	6.87	[35], [125][10], [33], [36]
	Bone scan	0	0	1	1		1,762.42	107.79	[35], [125][10], [33], [36]
	Chest X-ray	1	1	1	1		383.62	23.46	[35], [125][10], [33], [36]
	ECG	1	1	1	1		215.77	13.20	[35], [125][10], [33], [36]
	Total Initial Diagnosis and Evaluation Costs	436.99	436.99	599.26	490.3				
Non-breast cancer evaluation	No. of health centre visits	2	2	2	2		56.27	3.44	[35], [125][10], [33], [36]
	Bilateral mammography	1	1	1	1		879.77	53.80	[35], [125][10], [33], [36]
	Ultrasonography	0.28	0.28	0.28	0.28		331.68	20.28	[35], [125][10], [33], [36]
	FNA or core needle biopsy	0.02	0.02	0.02	0.02		1,564.8	95.56	[80]
	Total Non-breast cancer evaluations								
Treatment	No. of hospitalization days	2	2	6	6	6	168.64	10.31	[35], [125][10], [33], [36]
	No. of end-of-life hospitalization days				7	4.7	168.64	10.31	[35], [125][10], [33], [36]
	No. of OPD visits radiotherapy	30	30	30	30	1	84.32	5.16	[35], [125][10], [33], [36]
	No. of OPD visit chemotherapy	6	6	6	6	0	84.32	5.16	[35], [125][10], [33], [36]
	% Receiving surgical intervention	Lumpectomy 40%	Lumpectomy 30%	Lumpectomy 10%	Lumpectomy 0%	Lumpectomy 0%	2,506.89	153.32	[35], [125][10], [33], [36]
	% Receiving surgical intervention	Mastectomy 60%	Mastectomy 70%	Mastectomy 90%	Mastectomy 5%	Mastectomy 5%	13,500	766.8	[35], [125][10], [33], [36]
	% Receiving anesthesia	100%	100%	100%	5%	5%	2,192.53	134.09	[35], [125][10], [33], [36]
	% Receiving radiotherapy	40%	30%	100%	10%	0	600.83	36.75	[35], [125][10], [33], [36]
	% Receiving endocrine treatment	100%	100%	100%	40%	0	4.49	0.27	[35], [125][10], [33], [36]
	% Receiving chemotherapy	0	20%	60%	60%	0	6,503.84	397.76	[35], [125][10], [33], [36]
	% Receiving boost radiotherapy					41%	600.83	36.75	[35], [125][10], [33], [36]
	% Receiving home-based visits					75%	56.27	3.44	[35], [125][10], [33], [36]
	% Receiving morphine					84%	23.57	1.44	[35], [125][10], [33], [36]
	% Receiving laxative					50%	78.71	4.81	[35], [125][10], [33], [36]
	% Receiving ondansetron					36%	56.27	3.44	[35], [125][10], [33], [36]
	% Receiving amitriptyline					41%	0.32	0.02	[35], [125][10], [33], [36]
	% Receiving zelodronic acid					30%	1,742.70	106.58	[35], [125][10], [33], [36]
	Total Treatment Costs	900	1,001	1,131	1,130				

5.3 Results

We report 40-year cumulative breast cancer costs, effects, and cost-effectiveness projected after implementing early detection and screening interventions in South Africa through three scenarios: (i) awareness raising, (ii) Clinical Breast Examination (CBE) led screening, and (iii) Mammography led screening, among the population of women aged 40 to 75 biennially.

5.3.1 Intervention Effectiveness

Awareness Raising: By 2060, interventions to raise awareness combined with treatment of all stages, will avert 16,006 deaths incremental to the baseline scenario, and provide 267,635 Healthy Life Years incremental to the baseline scenario. Awareness raising interventions had minimal effect on down-staging for breast cancer with the number of women diagnosed with early-stage disease increasing by 8% translating into an additional 73,719.28 women presenting with early stage of breast cancer disease.

Clinical Breast Examination: By 2060, biennial CBE coupled with treatment of all stages will avert 34,663 deaths incremental to the baseline scenario and provides 537,816 Healthy Life Years incremental to the baseline scenario. The scaling up of clinical breast examination has an almost equal effect as the awareness raising interventions as it shifts the stage distribution of the breast cancer patients presenting in the early stage of the disease by 9% (78,167). When compared with awareness raising, CBE has a stronger down-staging effect by only 6%.

Mammography: Our analysis found that mammography coupled with treatment of all stages was the most effective breast cancer control intervention averting 57,821 deaths incremental to the baseline scenario and provides 899,450 Healthy Life Years incremental to the baseline scenario by 2060. Mammography led screening also had significant effect on down-staging for breast cancer with the number of women diagnosed with early-stage increasing by 15% translating into an additional 130,487 women presenting with early stage of breast cancer disease who would have otherwise presented with late stage of the disease. The results also suggest that mammography has a 67% stronger down-staging effect when compared to CBE and a 77% stronger down-staging effect when compared with awareness raising interventions.

Table 18: Effectiveness of Breast Cancer Control Interventions in South Africa

Intervention Scenarios	Incremental Deaths Averted	Incremental HLYs	Down-staging Effect
Awareness Raising	16,006	267,635	8%
CBE	34,663	537,816	9%
Mammography	57,821	899,450	15%

5.3.2 Costs

Basic awareness interventions coupled with treatment was the cheapest scenario with an annual average cost of $249Million. Biennial CBE coupled with treatment is associated with an annual average cost of $265 Million while mammography led screening coupled with treatment of all stages is the most expensive scenario with an average annual cost of $419 Million. For all the scenarios, the cost driver was treatment costs for late stage of the disease. However, we note a shift in the distribution of the costs once the effectiveness of the screening interventions kicks in from around year 5, where more women are diagnosed early therefore reducing the costs of treatment from late-stage disease by 12%. The costs presented were discounted at 3%.

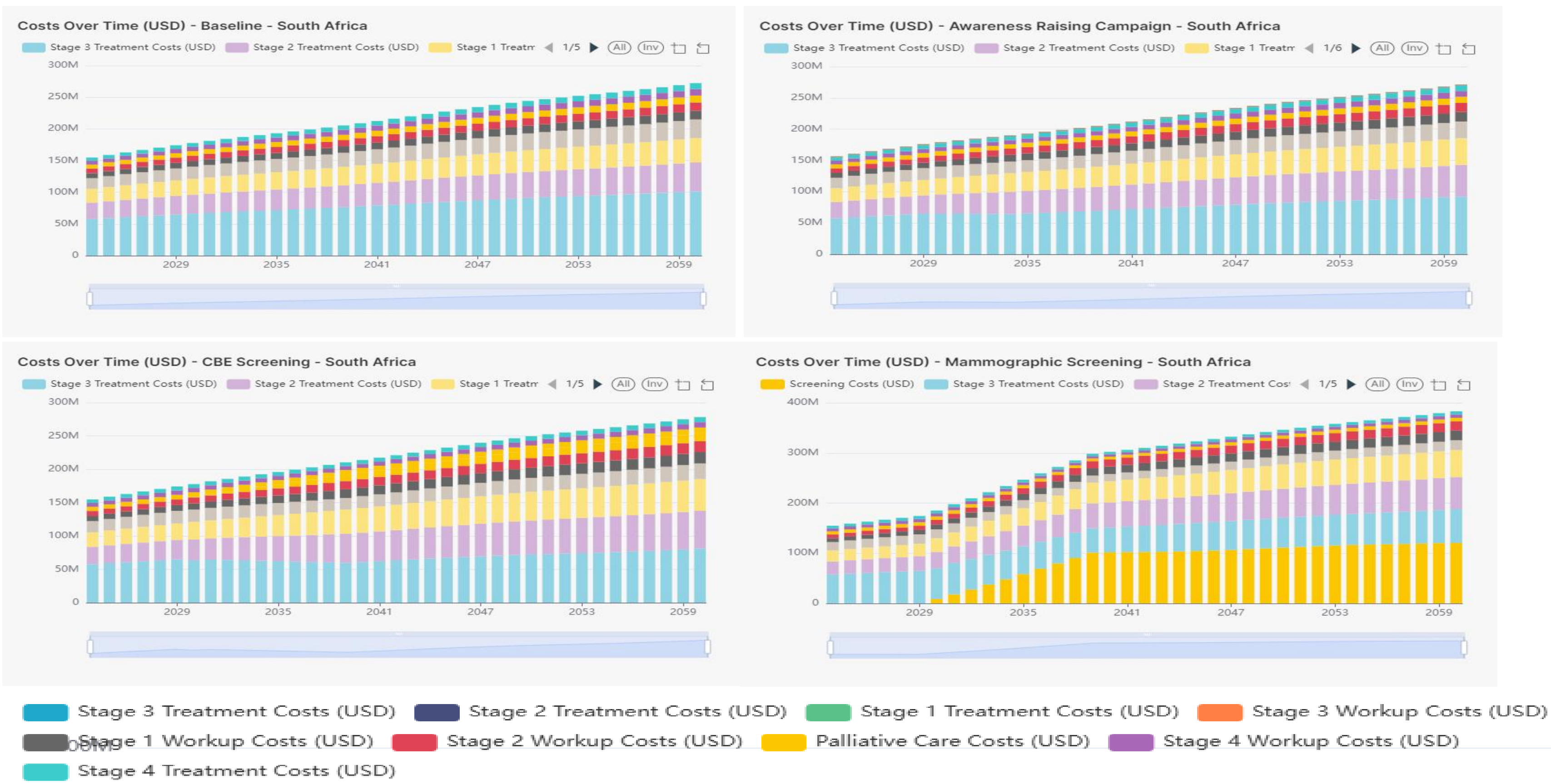
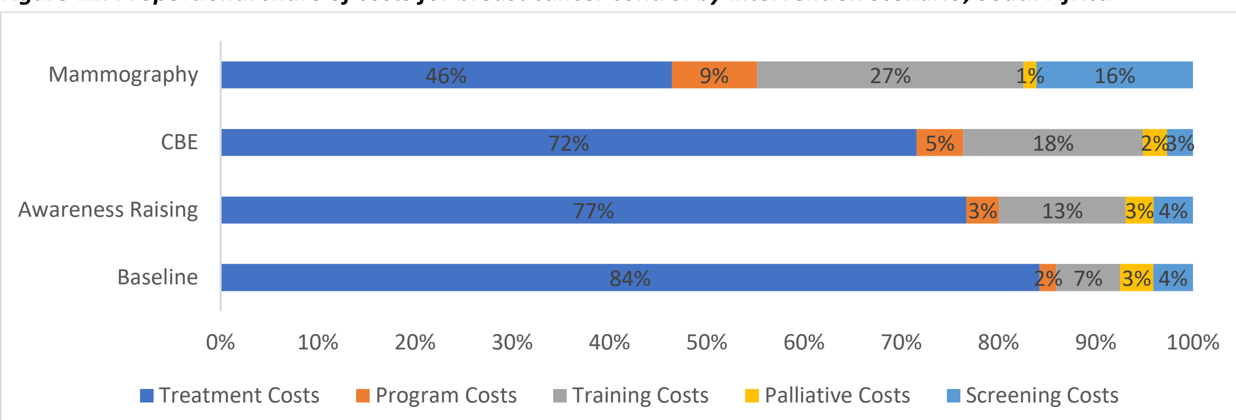


Table 19: Disaggregation of Breast Cancer Control Costs (Discounted) in USD for South Africa

Item	Total Costs (USD)			
	Baseline	**Awareness Raising**	**CBE**	**Mammography**
Treatment Costs	7,827,118,938	7,782,601,101	7,694,337,331	8,270,229,886
Program Costs	157,335,702	340,943,977	513,793,619	1,564,113,761
Training Costs	608,749,227	1,319,149,949	1,987,924,328	4,890,995,924
Palliative Costs	318,171,835	293,787,008	266,407,946	231,761,861
Screening Costs	378,532,300	410,136,755	284,098,090	2,869,494,916
Total Costs	9,289,908,002	10,146,618,790	10,746,561,314	17,826,596,348
Annual Average Cost	232,247,700	253,665,470	268,664,033	445,664,909
As a % of National Budget	*0.17%*	*0.19%*	*0.20%*	*0.32%*
As a % of Health Budget	*6%*	*6%*	*7%*	*10%*
As a % of GDP	*0.06%*	*0.07%*	*0.07%*	*0.12%*

Except for the mammography led screening scenario, treatment costs account for over 70% of the estimated costs in all scenarios. In the mammography led screening scenario, 27% of the costs are attributed to training and capacity building of the workforce while 16% of the total costs are attributed to screening costs due to the costly mammography resource inputs including equipment, and supplies. Treatment costs and palliative care costs are higher in the baseline and awareness raising scenarios because in these scenarios more patients present with late-stage disease which is more costly to effectively manage.

Figure 11: Proportional share of costs for breast cancer control by intervention scenario, South Africa



5.3.3 Cost Effectiveness Ratios

The Average Cost Effectiveness Ratios (ACERs) range from $377 per death averted for awareness raising interventions to $634 per death averted for Mammography. Using the Edoka and Stacey threshold which ranges between USD 3,015 - USD 3,223 (53% of GDP per capita for 2024)[142], our analysis shows that Biennial CBE coupled with treatment interventions for all stages is cost-effective for South Africa with an ICER of $2,708 per healthy life year gained. Awareness raising interventions were also found to be cost effective with an ICER of 3,201 per health life year gained. Mammography screening combined with treatment for all stages is not a cost-effective intervention for South Africa with an ICER of $9,491 per healthy life year gained.

Table 20: ICERs for early detection and screening interventions compared with baseline scenario in South Africa

Intervention Scenarios	Incremental Costs (USD)	Incremental HLYs	Incremental Deaths Averted	ICER**/HLYs Gained
Awareness Raising	856,710,788	267,635	16,006	3,201
CBE	1,456,653,313	537,816	34,663	2,708
Mammography	8,536,688,347	899,450	57,821	9,491

***ICER= (Cost of Intervention – Cost of Baseline Scenario)/ (Health Benefit of Intervention – Health Benefit of Comparator), Costs and HLYs discounted at 3%*

21: ACERs for early detection and screening interventions compared with baseline scenario in South Africa

Intervention Scenarios	Total Costs (USD)	Total HLYs	Total Deaths Averted	ACER*/HLYs	ACER/Death Averted
Awareness Raising	10,146,618,790	2,563,777,838	26,482,057	3.96	383
CBE	10,746,561,314	2,564,048,019	26,463,400	4.19	406
Mammography	17,826,596,348	2,564,409,653	26,440,242	6.95	674

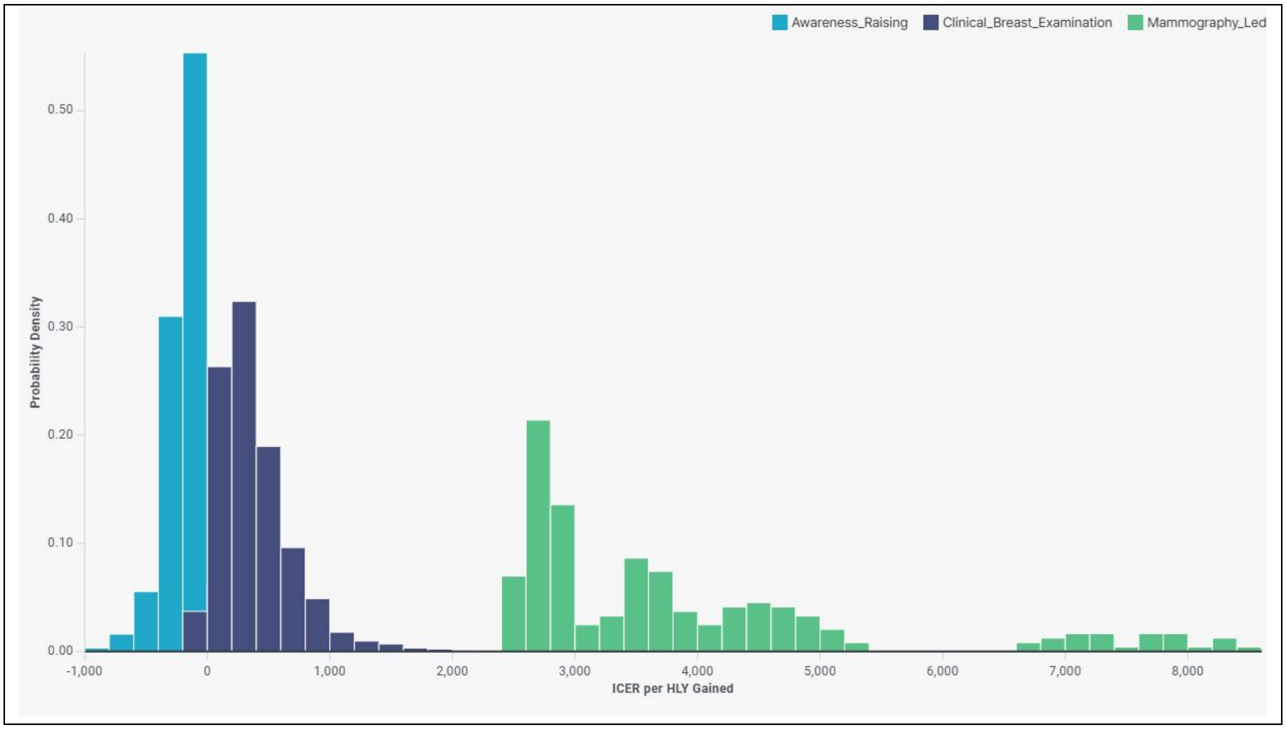
**ACER=Total Cost of Intervention/Total HLYs or/ Number of Deaths Averted,*

5.3.4 Sensitivity analysis

The histogram illustrates the distribution of cost-effectiveness results (expressed as cost per DALY averted) for three breast cancer early detection strategies in South Africa: awareness raising, clinical breast examination (CBE), and mammography-led screening. Each distribution represents the outcome of multiple simulations under varying input parameters in a multivariable sensitivity analysis. The awareness raising interventions shows a tightly clustered distribution centered around zero, with a large proportion of simulations indicating cost-saving results (i.e., negative or near-zero cost per HLY gained). This suggests that awareness campaigns are highly likely to be cost-effective or even cost-saving under a wide range of parameter uncertainties. The CBE interventions demonstrates a broader distribution, generally concentrated between 0 and 1,000 USD per HLY gained. While not as consistently cost saving as awareness interventions, CBE remains cost-effective across most simulations, indicating strong potential for efficient resource use in the South African health system context. By contrast, the mammography-led intervention displays a wide, right-skewed distribution ranging from approximately 2,000 to over 10,000 USD per HLY gained. This reflects considerable variability in its cost-effectiveness performance and a greater likelihood of exceeding typical cost-effectiveness thresholds. While mammography may offer clinical benefits, the economic results suggest that it may not be the most efficient investment in a setting like South Africa.

Overall, the sensitivity analysis supports the robustness of awareness raising and CBE as economically favorable strategies, while highlighting the fiscal and efficiency challenges associated with implementing mammography-led screening at scale.

Figure 12: Multi-Variable Sensitivity Analysis Histogram for South Africa



5.4 Discussion

We developed a model to estimate the cost effectiveness of early detection and screening interventions to downstage breast cancer diagnosis in South Africa. Over a 40-year time horizon, interventions to raise awareness combined with treatment of all stages, will avert 16,006 deaths incremental to the baseline scenario, and provide 267,635 Healthy Life Years incremental to the baseline scenario. Biennial Clinical Breast Examination (CBE) coupled with treatment of all stages will avert 34,663 deaths incremental to the baseline scenario and provides 537,816 Healthy Life Years incremental to the baseline scenario Our analysis found that mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 57,821 deaths incremental to the baseline scenario and provides 899,450 Healthy Life Years incremental to the baseline scenario by 2060. Furthermore, our analysis shows that Biennial CBE coupled with treatment interventions for all stages is cost-effective for South Africa with an ICER of $2,708 per healthy life year gained. Awareness raising interventions were also found to be cost effective with an ICER of 3,201 per health life year gained. Mammography screening combined with treatment for all stages was not found to be a cost-effective intervention for South Africa with an ICER of $9,491 per healthy life year gained.

Our findings align with and extend the existing body of literature, for instance, a study from India found biennial CBE was a cost-effective intervention with an ICER of $1,341 per life-year gained[84], another study from Ghana reported CBE as the most cost-effective intervention ($1,299 per DALY averted) and reported mass media awareness interventions as cost effective ($1,364 per DALY averted) [35]. Studies from central America (Mexico and Costa Rica) also found that awareness raising interventions were more cost effective than mammography [34]. Another study from China reported that CBE was cost effective when compared with no screening [144]. On the contrary, a cost effectiveness analysis for clinical breast examination in South Africa[78] did not find the intervention cost-effective and this divergent finding from our results could be attributed to differences in approach especially the time horizon as well as the idealized nature of our study interventions that assume 100% coverage within the first two years. Additionally, another study from China reported that a combination of CBE and ultrasound screening in rural areas was not a cost-effective intervention and the divergent results can be attributed to the fact that this study was set in a rural setting with low breast cancer incidence[145]. The observed incremental cost-effectiveness ratios (ICERs) in our study were higher than those reported in similar studies from India and Ghana. This could be attributed to differing baseline epidemiology (e.g., higher late-stage diagnosis rates in South Africa), differences in health system costs, or variances in the unit costs of implementation. Furthermore, the magnitude of health gains (i.e., deaths averted, and healthy life years gained) was larger in our model, likely due to the inclusion of a longer time horizon and the idealized nature of our study intervention scenarios. Importantly, our findings are also consistent with WHO-CHOICE estimates that emphasize the cost-effectiveness of non-mammographic interventions when implemented at scale and integrated with existing health system platforms[86].

Our analysis did not find mammography to be a cost-effective intervention for South Africa. Our findings are congruent with the evidence from sub-Saharan Africa suggesting that while mammography has led to mortality reduction in high income countries[15], it may not be the way forward for sub-Saharan Africa due to affordability and other technical concerns such as breast tissue density and an elevated harm to benefit ratio due to higher false positives and over diagnosis[16]. However positive research on clinical downstaging using CE and raising public awareness of breast cancer maybe a more appropriate and effective approach to clinical downstaging of the disease[16]. [34][84][71][85][36][70][70]
Our findings have policy implications for breast cancer control in South Africa. Our results highlight that breast cancer screening is vital for South Africa, and while there are already reasonable existing structures in place, ongoing challenges necessitate concerted efforts to ensure that all women have access to necessary screening services[95]. Firstly, our analysis shows that biennial CBE and awareness raising interventions are cost-effective for South Africa. These interventions have lower resource implications and are less complex to implement than MMG. Therefore, we recommend a combination of nation-wide scale up of biennial CBE for women aged 40-75 and awareness raising interventions to facilitate timely diagnosis, referral, and treatment. This nation-wide scale up should follow a phased approach and should align to the guidance provided by the WHO on how to implement a phased approach for breast cancer early detection [9].

Secondly, to better provide CBE and awareness raising interventions, an enabling environment comprising of critical socio-cultural and health systems factors (e.g., health worker attitudes, long queues, referral pathways, disparities in access to cancer services, etc.) should precede the roll out of nation-wide awareness raising and CBE interventions.

Third, our analysis did not find MMG to be a cost-effective intervention, however, we note that South Africa should continue to incrementally make investments to mammographic screening for diagnostic purposes and the scale up of these investments should be gradual and guided by disease burden with prioritization given to rural areas where disparities in access to breast cancer services is more pronounced. Furthermore, the South African Department of Health should consider scaling up of mobile MMG units to reach women in rural or remote locations where permanent screening facilities are not available. Mobile MMG are more accessible in rural areas, and they have the potential to address disparities in access. However, mobile MMG mobile units are more expensive than fixed MMG with the estimated cost per case screened increasing by at least 20% [36]. Therefore, the scale up of mobile MMG units should be carefully considered with a phased approach and the mobile units could also be used to deliver early detection activities for other priority communicable and non-communicable diseases.

Fourth, while our results show that CBE and awareness raising interventions are economically attractive, they require significant resources for implementation at scale and this warrants affordability concerns. Implementing the awareness raising interventions annually would require an additional 6% of the total health budget while CBE would require an additional 7% of the total health budget. For purposes of sustainability and affordability, we recommend that these early detection and screening interventions for breast cancer control are implemented in an integrated model along with other programs targeted at the same proportion of the demographic such as the cervical cancer program. Resource allocation to the integrated model can happen in a gradual and well sequenced manner over long-term budgetary commitments. An alternative cost-saving approach suggested in the literature is to use risk-based screening approaches which is targeted screening to high-risk groups only, however, the evidence suggests that 100% attendance rate is required for a risk-based screening approach to achieve the standard of cost-effectiveness [145]. In a complex healthcare setting like South Africa, achieving a 100% attendance rate could be very challenging.

As with any other modelling exercises, our study has limitations worth highlighting. Firstly, the cancer registry in South Africa is not fully functional and therefore this analysis relied on secondary data sources and global estimates for critical indicators such as case-fatality which may not be reflective of the reality thus biasing our estimates.

Secondly, this study considered a provider's perspective, excluding the costs to the patients including their productivity loss. We are cognizant of the fact that inclusion of these costs would have provided the complete and more accurate estimate of the resource requirement for breast cancer control in South Africa, especially owing to the high travel costs that have been associated with breast cancer treatment in South Africa. Additionally, the model excludes future unrelated medical costs due to unavailability of robust data to support their estimation in South Africa.

Thirdly, there is limited information on the effectiveness of awareness raising interventions and therefore our estimates for this scenario should be interpreted cautiously. Fourth, our model doesn't account for the harms associated with screening (e.g., false positives, and over-diagnosis). Additionally, the model doesn't predict the direct impact of screening on mortality. Furthermore, the model uses a simplifying assumption that all women diagnosed with breast cancer will receive treatment appropriate to their stage of disease. In South Africa, although breast cancer treatment services are recommended in national guidelines and generally available in tertiary centers, access remains highly unequal, especially for rural and uninsured populations with disadvantaged groups facing the greatest barriers to accessing cancer care[146]. The assumption in the model that all diagnosed women access and complete treatment therefore overstates real-world coverage but was necessary to enable full economic evaluation of each intervention scenario.

Fifth, the degree to which breast cancer early detection and screening interventions are beneficial to South Africans cannot only depend on the estimated cost-effectiveness based on down-staging as quantified by our analysis. Other critical criteria such as affordability (budget impact), value for money, safety, and other political economy concerns should be considered.

Despite these shortcomings, our study also had several strengths. Firstly, our analysis doesn't include the natural history of the underlying breast cancer disease, but rather, it focuses on the observable events in disease progression, implying fewer inputs, transparency in the model and higher generalizability to other contexts. Secondly, our dynamic state transition model incorporates the compounding effects of intervention scale-up over time and the long-term disease progression, offering a more nuanced projection of health outcomes over a 40-year horizon. Thirdly, to arrive at South African estimates for this study, we relied on a model that showed face validity confirmed by an expert panel. Moreover, despite our study limitations, our results are consistent with the results of studies from comparator countries. Fourth, while our findings reinforce the broader consensus that early detection is cost-effective in LMICs, the context-specific parameterization of our model for South Africa provides important empirical specificity and relevance to policymakers in country. Lastly, the above limitations do not greatly hinder the overall objective of this analysis which was to provide an indication of the cost-effectiveness of breast cancer early detection and screening interventions to inform policy decisions rather than to provide very precise estimate for each of the scenarios evaluated.

In summary, our findings indicate that biennial CBE (ages 40-75) and awareness raising interventions are a cost effective and feasible option for South Africa and MMG was not found to be a cost-effective option. For the short to medium term, we recommend a combination of nation-wide phased scale up of biennial CBE for women aged 40-75 and awareness raising interventions to facilitate timely diagnosis, referral, and treatment. A combination of fixed and mobile MMG should be considered in the medium to long term as more resources become available. Our results are consistent with those from other similar settings which have reported that awareness raising, and biennial CBE are not only crucial for down-staging breast cancer diagnosis but that they are also economically attractive and viable for low- and middle-income countries. For sustainability and affordability purposes, LMICs should implement awareness raising and screening interventions in an integrated manner with other non-communicable diseases such as cervical cancer in a phased manner with robust monitoring and evaluation.

CHAPTER

6

"But they that wait upon the Lord shall renew their strength; they shall mount up with wings as eagles; they shall run, and not be weary; and they shall walk, and not faint" Isaiah 40:31

Chapter 6: Cost-Effectiveness of Early Detection, Screening and Breast Cancer Control Interventions in Uganda

Abstract

Objective

Late-stage presentation and delayed treatment are major contributors to poor breast cancer survival rates in low- and middle-income countries (LMICs). Improved early detection interventions for breast cancer can lead to earlier breast cancer detection, lower costs, and improved outcomes. This study aimed to estimate the costs and effectiveness of early detection and treatment interventions for Breast Cancer in Uganda.

Methods

We constructed a dynamic state transition model to estimate the cost-effectiveness of early detection and screening interventions for breast cancer control. Our model is premised on a comprehensive mathematical framework that estimates the stage shifts in early versus late stages of breast cancer diagnosis based on proportional performance rates (Z's) of three early detection and screening interventions (awareness raising, clinical breast examination and mammography) from 2024 to 2060.

Results

By 2060, interventions to raise awareness combined with treatment of all stages, will avert 12,039 incremental deaths, and provide 190,773 incremental Healthy Life Years. Biennial Clinical Breast Examination (CBE) coupled with treatment of all stages will avert 29,121 incremental deaths and provide 417,897 incremental Healthy Life Years. Our analysis found that mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 49,087 incremental deaths and provides 705,879 incremental Healthy Life Years. The Average Cost Effectiveness Ratios (ACERs) range from $87 per death averted for basic awareness raising interventions to $234 per death averted for MMG. The most cost-effective intervention for breast cancer control is awareness raising interventions with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $416 per healthy life year gained. Biennial MMG screening combined with treatment for all stages was not cost effective with an ICER of $3,110 per healthy life year gained.

Conclusion

In conclusion, our results suggest that awareness raising, and biennial CBE are not only crucial for down-staging breast cancer diagnosis, but they are also economically attractive and viable for countries with limited resources such as Uganda. While mammography (MMG) was found to be the most effective intervention, it is very costly and therefore LMICs should only adopt MMG with careful considerations. For sustainability and affordability purposes, LMICs should implement breast cancer awareness raising and screening interventions in an integrated manner with other non-communicable diseases.

6.1 Background

In Uganda, breast cancer is the second most diagnosed female cancer after cervical cancer, with an estimated age-standardized incidence and mortality rate of 21.3/100,000 and 10.3/100,000 respectively [6]. These high mortality rates can be interpreted as almost half of Ugandan women diagnosed with breast cancer die from the disease. This high mortality rate is predominantly attributed to late-stage diagnosis of the disease: up to 89% of the women with breast cancer in Uganda present with stage III or IV [107].

Such late-stage presentation fundamentally permits the breast tumors to advance in stage when prognosis is poor. Other probable reasons for presentation with advanced stage cancers include lack of breast cancer screening services [109], barriers in access to health care [26], lack of awareness [110], and biological tumor factors [111]. As is the case with other black women in developing countries a significant proportion of the Ugandan women who die from breast cancer are 40 years old or younger and the mean age is 45 years [112].

Given the growing burden of breast cancer in Uganda, the country now faces the challenge of effectively detecting and treating a disease that was previously considered too uncommon to merit the allocation of finite health care resources. There is a need to scale up strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor.

While several breast cancer early detection methods and tools exist, they are largely unavailable in many LMICs due to resource constraints[69]. As a result, these scarce health-care resources need to be utilized strategically to allow for timely access to breast health care. To address the too frequent challenge of late-stage presentation, early detection and screening interventions are necessary for shifting breast cancer cases that would have otherwise been diagnosed as “late stage” to an “earlier stage” at diagnosis, and this stage-shift improves prognosis that is associated with lower breast cancer management costs.

To make optimal decisions in a clinical setting, decision makers must compare expected benefits of early detection and treatment interventions for breast cancer against implementation costs. This study developed a model to estimate the projected cost effectiveness of interventions for early detection and treatment of breast cancer in Uganda.

6.2 Methods

We constructed a dynamic state transition model to estimate the cost effectiveness of three breast cancer down-staging interventions in Uganda for a time horizon of 40 years. We used a mixture of empirical estimates, and assumptions from low-income countries to populate parameters in the model. The model imposes normative assumptions about ideal scenarios of three early detection and screening interventions: awareness raising campaigns, clinical breast examination, and mammographic screening and compares these scenarios to the current business-as-usual scenario (the "baseline" scenario). The model philosophy, structure, the population of interest, the model parameters, and the effectiveness of early detection and screening interventions are presented in Chapter 4 of this thesis and will not be repeated in this chapter. Furthermore, the modelled interventions for early detection, screening, treatment, and palliative care are also presented in chapter 4, section 4.2.3 and will not be repeated in this chapter.

6.2.1 Costs

The study considered a provider's perspective i.e., healthcare provider costs only were considered. The study adopted the provider's perspective because the primary focus of the study was to estimate costs borne by the health system, such as those for screening, diagnostics, treatment, and follow-up, which are critical for guiding health policy, budgeting, and resource allocation in Uganda. A normative costing based on the national breast cancer norms, policies and guidelines was done from 2022 for a time horizon of 40 years. An ingredients-based approach to costing was used. The ingredients-based approach entailed three steps: the first was identification of all required resources or inputs, second was to quantify the required resources and last step was the valuation of these resources based on their current replacement value [123].

The cost analysis focused on estimating the recurrent and capital costs separately, which were then summed up to give the total cost. Capital costs were annualized using a discount rate of 3% at the appropriate life years and the unit of analysis was cost per breast cancer case detected and treated. The cost analysis included only the direct medical costs (early detection activities, diagnostic tests, and treatment including surgery, chemotherapy, and radiotherapy), personnel, supplies, equipment, utilities, stationery, and building space. It is important to acknowledge that future unrelated healthcare costs incurred by individuals who live longer because of the early detection and screening interventions but for conditions unrelated to breast cancer were not included in the analysis. The decision to exclude such costs in this analysis was driven by the limited availability of robust data to support their estimation in the Ugandan context. At the program level, the following resources were considered: administrative and managerial costs, media costs, and costs to train healthcare providers. Regarding diagnostic test costs, these were applied to the entire cohort of individuals undergoing testing, inclusive of both true-positive and false-positive cases. In the model, the number of women receiving follow-up diagnostic procedures was derived based on the test performance parameters, specifically, the sensitivity and the underlying age-specific incidence of breast cancer. As a result, the cost estimates for diagnostic services appropriately reflect the diagnostic burden on the system by simulating the actual volume of diagnostic testing generated under each scenario. For all the screening interventions, the cost of diagnostic tests for women who tested negative for all stages of breast cancer were included and a ratio of 16.4:1 was estimated and utilized, consistent with previous similar studies for those that tested negative vs. tested positive [33], [35], [138].

Unit costs of patient services in this study were estimated using a combination of micro-costing principles and available cost data from literature. Where feasible, detailed resource utilization patterns and unit prices were used, based on treatment protocols identified in the literature and contained in the two countries breast cancer policies, cost analyses from comparable low- and middle-income country (LMIC) settings, and consultation with local experts [35], [36], [125]. Cost inputs obtained from the literature were adjusted for inflation using the 2020 Consumer Price Index for Uganda (sourced from Uganda Bureau of Statistics) and converted to 2022 values using exchange rates (1 USD = UGX 3,688) obtained from the OANDA database www.oanda.com).

In instances where local or regional data were unavailable, estimates from the WHO-CHOICE database were employed[141], particularly for standardized medical procedures such as lumpectomy and mastectomy. To estimate total patient costs, these unit costs were multiplied by the projected number of patients requiring each service under each intervention scenario. The total number of patients and their stage-specific treatment requirements were generated from the dynamic model, while the breakdown of services used (e.g., diagnostics, surgery, radiotherapy, systemic therapy) was informed by published treatment protocols and expert consensus.

6.2.2 Estimation of Healthy Life Years (HLYs)

Healthy Life Years (HLYs) were estimated as the primary health outcome metric in this analysis, capturing both the quantity and quality of life gained from the interventions. HLYs were calculated by first estimating the number of life years gained from averted premature deaths due to breast cancer, based on the difference in breast cancer mortality under each intervention scenario compared to the baseline. These life years were then adjusted for disability using stage-specific disability weights obtained from the Global Burden of Disease Study[8]. Specifically, for each averted breast cancer death, the corresponding life expectancy was calculated and weighted by the average health-related quality of life associated with the cancer stage at diagnosis. We summed HLYs across the entire modelled population, which, due to the dynamic demographic simulation over the time horizon, included children born during this period. The model tracked disability weights associated with each health state.

Therefore, HLYs were calculated as: **(1 – Disability Weight) × Life Years** for everyone in each state and summed annually.

All future health benefits were discounted at a 3% annual rate, consistent with standard economic evaluation guidelines.

6.2.3 Cost Effectiveness Analysis

The cost-effectiveness analysis in this thesis adopted a pair-wise comparison of each breast cancer screening and early detection intervention against the current “business-as-usual” scenario. Interventions that were found to be less costly and more effective are called “dominant” interventions.

Incremental Cost Effectiveness Ratios (ICERs) were calculated for each strategy (costs divided by benefits) compared with the baseline scenario [123]. The extended dominance rule of thumb held where interventions with a higher ICER dominated interventions with a previous non-dominated ICER. [124]. To interpret the cost-effectiveness results generated by this study, we carefully considered current best practices and recent methodological developments regarding cost-effectiveness thresholds, particularly for low- and middle-income countries (LMICs). Historically, the World Health Organization (WHO) proposed heuristic thresholds based on multiples of a country's GDP per capita (e.g., an intervention was considered highly cost-effective if the incremental cost-effectiveness ratio [ICER] was less than one times GDP per capita). However, the WHO has formally withdrawn these GDP-based thresholds, recognizing that they may misrepresent local opportunity costs and distort national health priority-setting [147].

For Uganda, we reference the cross-country estimates provided by Woods et al. (2016)[148] and by Pichon-Riviere et al (2023) [149] which suggest that low-income countries (LICs) may have thresholds as low as USD 16 – 537 per DALY averted or as 1% - 54% of GDP per capita. While we acknowledge the uncertainty and limitations of applying general cross-country estimates, these thresholds offer a pragmatic interim benchmark grounded in the opportunity cost-based framework [150].

6.2.4 Sensitivity Analysis

For all the key parameters that influence the results (ICERs), multivariable sensitivity analyses were carried out to assess for robustness of the values used to estimate the ICER. This is particularly important regarding proxies or data extracted from literature. The multivariable sensitivity analysis involved simultaneously varying multiple key input parameters within plausible ranges to assess how combined uncertainties affect model outputs. These parameters were varied across plausible ranges (based on published literature or assumed ±25% uncertainty) to evaluate their joint impact on cost-effectiveness outcomes and the robustness of the study's conclusions. The parameters considered for sensitivity analysis are presented in *Table 22*.

Table 22: Parameters varied through multivariable sensitivity analysis for Uganda

Parameter	Value used in analysis	Lower bound parameter	Upper bound parameter	Source
Sensitivity (MMG)	70%	86.3%	87.60%	A study from Kenya [125]
Sensitivity (CBE)	50%	40%	70%	A study from Kenya [125]
Mean Sojourn time (MMG)++	2 years	1.5 years	2.5 years	Lower and upper bounds were defined as ±25% of the base value
Mean Sojourn time (CBE)	1.5 years	1 year	2 years	Lower and upper bounds were defined as ±25% of the base value
Effect size of awareness raising interventions	10%	7.5	25%	A study from Malaysia [143]
Case fatality rate (early stage)	0.020	0.006	0.063	A study from Ghana [35]
Case fatality rate (late stage)	0.18	0.093	0.300	A study from Ghana [35]

Disability weights (early stage)	0.039	0.035	0.043	Global Burden of Diseases Study [8]
Disability weights rates (late stage)	0.451	0.265	0.527	Global Burden of Diseases Study [8]
Treatment unit costs as estimated by author (early stage) in 2022 USD++	850	828.75	871.25	Lower and upper bounds were defined as ±25% of the base value
Treatment unit costs as estimated by author (late stage) in 2022 USD++	981	959.25	1,001.75	Lower and upper bounds were defined as ±25% of the base value

++ Lower and upper bounds were defined as ±25% of the base value in the absence of empirical confidence intervals for mean sojourn time, treatment costs, and screening costs, Exchange rate (US $1 = UGX 3,688)

Table 23: Unit Costs for Diagnosis, Screening, Treatment and Program Activities per Woman Screened for Uganda Analysis

Activity	Unit Cost per Woman (2022 USD)	Source
Mammography	26.11	[35], [125][10], [33], [36]
Core Biopsy	18.45	[35], [125][10], [33], [36]
Ultrasound	9.85	[35], [125][10], [33], [36]
Clinical Breast Exam – Primary Care Facility	0.90	[80]
Clinical Breast Exam – Secondary level Facility	10.5	[80]
Follow up diagnostic visit	5.01	[35], [125][10], [33], [36]
Treatment Costs (Early Stage)	850	[12]
Treatment Costs (Late Stage)	981	[12]
Palliative care costs	1,132	[12]
Governance and policy	729	[125]
Awareness raising	7,882	[125]
Training	11,273	[125]
M&E and research	2,185	[125]
Screening costs (baseline)	7,010	[125]5

The unit costs presented in *Table 23* were originally sourced from a detailed costing study conducted in Kenya. These figures were adopted due to the absence of granular and disaggregated national-level cost data for breast cancer services in Uganda. To ensure contextual relevance, the Kenyan unit costs were adjusted to 2022 Ugandan Shillings (UGX). Inflation adjustments were made using the Consumer Price Index (CPI), with 2020 used as the base year for deflation, based on official CPI data from Uganda Bureau of Statistics. Currency conversion from Kenyan Shillings to Uganda Shilling was performed using average 2022 exchange rates obtained from the OANDA financial data platform (www.oanda.com) at 1UGX = 34 KSH. No purchasing power parity (PPP) adjustments were applied. The term "cost per woman" refers to the unit cost of service delivery per woman receiving a specific intervention (e.g., awareness intervention, clinical breast examination, or mammography). This does not refer to a unique individual in the entire modelled population, but rather reflects the average cost per service recipient, including those receiving services more than once under the dynamic modeling framework. While cross-country transfer of cost data entails limitations, the Kenyan estimates were deemed a reasonable proxy for Uganda. Table 25 below presents the average utilization of various inputs and unit costs used in the model. The totals for each procedure were derived by summing the costs of all listed procedures for the respective stages.

Table 24: Average utilization of diagnosis and treatment services inputs and unit costs for Uganda

Procedure	Ingredients	Stage 1	Stage 2	Stage 3	Stage 4	Palliative Care	Unit costs per patient (2022 UGX)	Unit Cost per patient (2022 USD)	
Initial diagnosis and evaluation during treatment	No. of health centre visits	1	1	1	1		**6,159.84**	**1.67**	[35], [125][10], [33], [36]
	No. of hospital visits	3	3	3	3		**9,230.98**	**2.50**	[35], [125][10], [33], [36]
	Bilateral mammography	1	1	2	0		**96,311.07**	**26.11**	[35], [125][10], [33], [36]
	Complete blood count	7	7	7	7		**24,937.69**	**6.76**	[35], [125][10], [33], [36]
	FNA or core needle biopsy	1	1	1	1		**68,056.55**	**18.45**	[35], [125][10], [33], [36]
	Liver function tests	8	8	8	8		**10,880.62**	**2.95**	[35], [125][10], [33], [36]
	Ultrasonography	1	1	1	1		**36,309.69**	**9.85**	[35], [125][10], [33], [36]
	Renal function tests	8	8	8	8		**12,302.12**	**3.34**	[35], [125][10], [33], [36]
	Bone scan	0	0	1	1		**192,938.03**	**52.32**	[35], [125][10], [33], [36]
	Chest X-ray	1	1	1	1		**41,995.70**	**11.39**	[35], [125][10], [33], [36]
	ECG	1	1	1	1		**23,621.48**	**6.40**	[35], [125][10], [33], [36]
	Total Initial Diagnosis and Evaluation Costs ($)	179.01	179.01	257.44	205.22	0			
Non-breast cancer evaluation	No. of health centre visits	2	2	2	2		**6,159.84**	**1.67**	[35], [125][10], [33], [36]
	Bilateral mammography	1	1	1	1		**96,311.07**	**26.11**	[35], [125][10], [33], [36]
	Ultrasonography	0.28	0.28	0.28	0.28		**36,309.69**	**9.85**	[35], [125][10], [33], [36]
	FNA or core needle biopsy	0.02	0.02	0.02	0.02		**68,056.55**	**18.45**	[35], [125][10], [33], [36]
	Total Non-breast cancer evaluations ($)	32.57	32.57	32.57	32.57				
Treatment	No. of hospitalization days	2	2	6	6	6	**18,461.96**	**5.01**	[35], [125][10], [33], [36]
	No. of end-of-life hospitalization days				7	4.7	**18,461.96**	**5.01**	[35], [125][10], [33], [36]
	No. of OPD visits radiotherapy	30	30	30	30	1	**9,230.98**	**2.50**	[35], [125][10], [33], [36]
	No. of OPD visit chemotherapy	6	6	6	6	0	**9,230.98**	**2.50**	[35], [125][10], [33], [36]
	% Receiving surgical intervention	Lumpectomy 40%	Lumpectomy 30%	Lumpectomy 10%	Lumpectomy 0%	Lumpectomy 0%	**274,437.41**	**74.41**	[35], [125][10], [33], [36][149]
	% Receiving surgical intervention	Mastectomy 60%	Mastectomy 70%	Mastectomy 90%	Mastectomy 5%	Mastectomy 5%	**1,060,773.08**	**287.63**	[35], [125][10], [33], [36][149]
	% Receiving anesthesia	100%	100%	100%	5%	5%	**240,023.05**	**65.08**	[35], [125][10], [33], [36]
	% Receiving radiotherapy	40%	30%	100%	10%	0	**65,775.13**	**17.83**	[35], [125][10], [33], [36]
	% Receiving endocrine treatment	100%	100%	100%	40%	0	**491.38**	**0.13**	[35], [125][10], [33], [36]
	% Receiving chemotherapy	0	20%	60%	60%	0	**711,996.43**	**193.06**	[35], [125][10], [33], [36]
	% Receiving boost radiotherapy					41%	**65,775.13**	**17.83**	[35], [125][10], [33], [36]
	% Receiving home-based visits					75%	**6,159.84**	**1.67**	[35], [125][10], [33], [36]
	% Receiving morphine					84%	**2,579.76**	**0.70**	[35], [125][10], [33], [36]
	% Receiving laxative					50%	**8,616.75**	**2.34**	[35], [125][10], [33], [36]
	% Receiving ondansetron					36%	**6,159.84**	**1.67**	[35], [125][10], [33], [36]
	% Receiving amitriptyline					41%	**35.10**	**0.01**	[35], [125][10], [33], [36]
	% Receiving zelodronic acid					30%	**190,779.45**	**51.73**	[35], [125][10], [33], [36]
	Total Treatment Costs ($)	801	902	931	1,030	1,132.7			

6.3 Results

We report 40-year cumulative breast cancer costs, effects, and cost-effectiveness projected after implementing early detection and screening interventions in Uganda through three scenarios: (i) awareness raising, (ii) Clinical Breast Examination (CBE) led screening, and (iii) Mammography led screening, among the population of women aged 40 to 75 biennially.

6.3.1 Intervention Effectiveness

Awareness Raising: Over 40 years' time horizon, interventions to raise awareness combined with treatment of all stages, will avert 12,039 deaths incremental to the baseline scenario, and provide 190,773 Healthy Life Years incremental to the baseline scenario. Awareness raising interventions had minimal effect on down-staging for breast cancer with the number of women diagnosed with early-stage disease increasing by 8% translating into an additional 25,039 women presenting with early stage of breast cancer disease.

Clinical Breast Examination: Over a 40-year period, biennial CBE coupled with treatment of all stages will avert 29,121 deaths incremental to the baseline scenario and provides 417,897 Healthy Life Years incremental to the baseline scenario. CBE had significant effect on down-staging for breast cancer with the number of women diagnosed with early-stage increasing by 21% translating into an additional 59,832 women presenting with early stage of breast cancer disease. When compared with awareness raising, CBE has a stronger down-staging effect by 139%.

Mammography: Our analysis found that mammography coupled with treatment of all stages was the most effective breast cancer control intervention averting 49,087 deaths incremental to the baseline scenario and provides 705,879 Healthy Life Years incremental to the baseline scenario over a 40-year period. Mammography led screening also had very significant effect on down-staging for breast cancer with the number of women diagnosed with early-stage increasing by 36% translating into an additional 100,849 women presenting with early stage of breast cancer disease who would have otherwise presented with late stage of the disease. The results also suggest that mammography has a 68% stronger down-staging effect when compared to CBE and a 303% stronger down-staging effect when compared with awareness raising interventions.

Table 25: Effectiveness of Breast Cancer Control Interventions in Uganda

Intervention Scenarios	Incremental Deaths Averted	Incremental HLYs	Down-staging Effect
Awareness Raising	12,039	190,773	9%
CBE	29,122	417,897	21%
Mammography	49,087	705,879	36%

6.3.2 Costs

Basic awareness interventions coupled with treatment was the cheapest scenario with an annual average cost of $32Million. Biennial CBE coupled with treatment is associated with an annual average cost of $37 Million while MMG led screening coupled with treatment of all stages is the most expensive scenario with an average annual cost of $91 Million. For all the scenarios, the cost driver was treatment costs for late stage of the disease. However, we note a shift in the distribution of the costs once the effectiveness of the screening interventions kicks in from around year 7, where more women are diagnosed early therefore reducing the costs of treatment from late-stage disease by 26%. The costs presented were discounted at 3%.

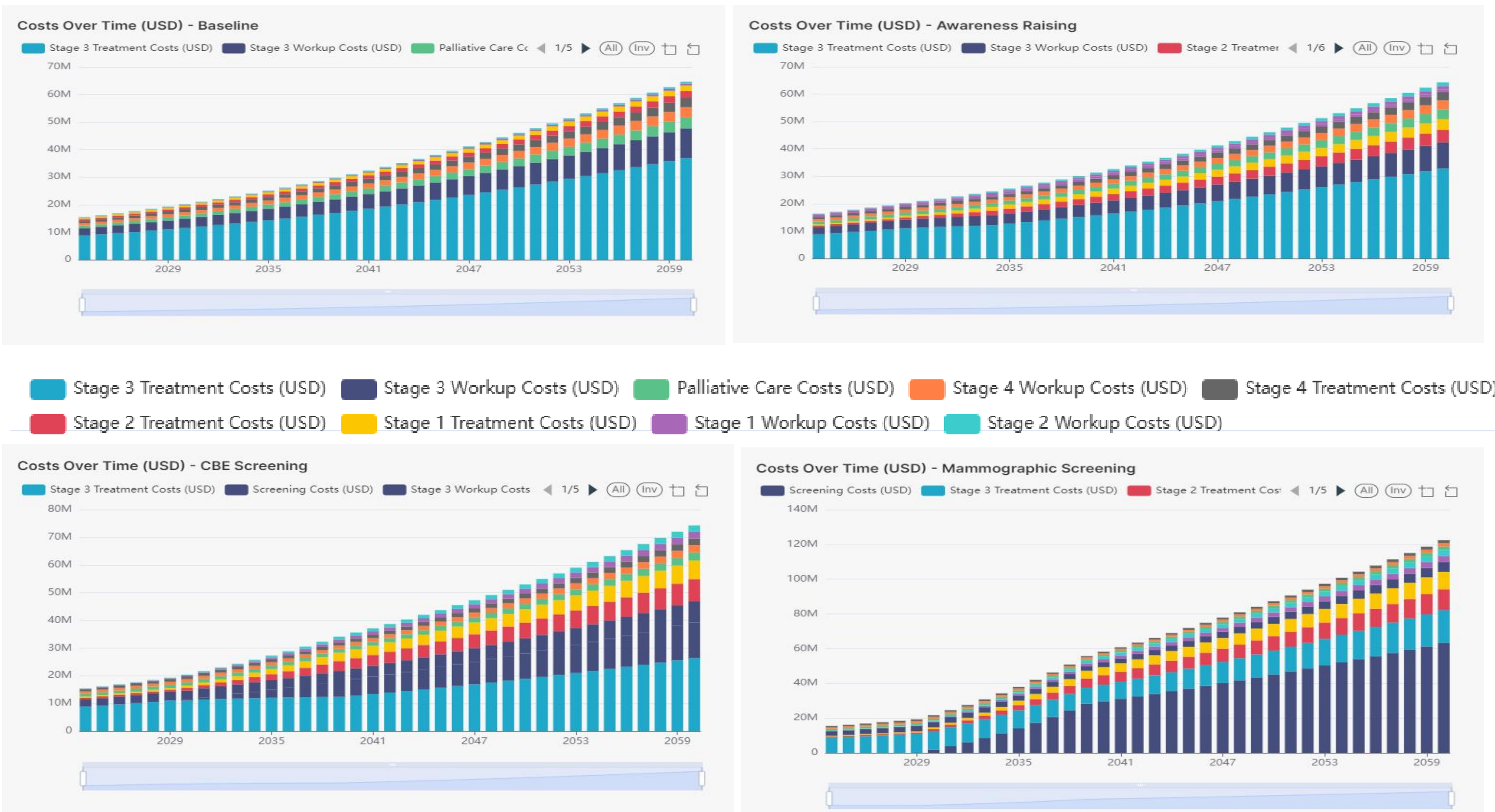
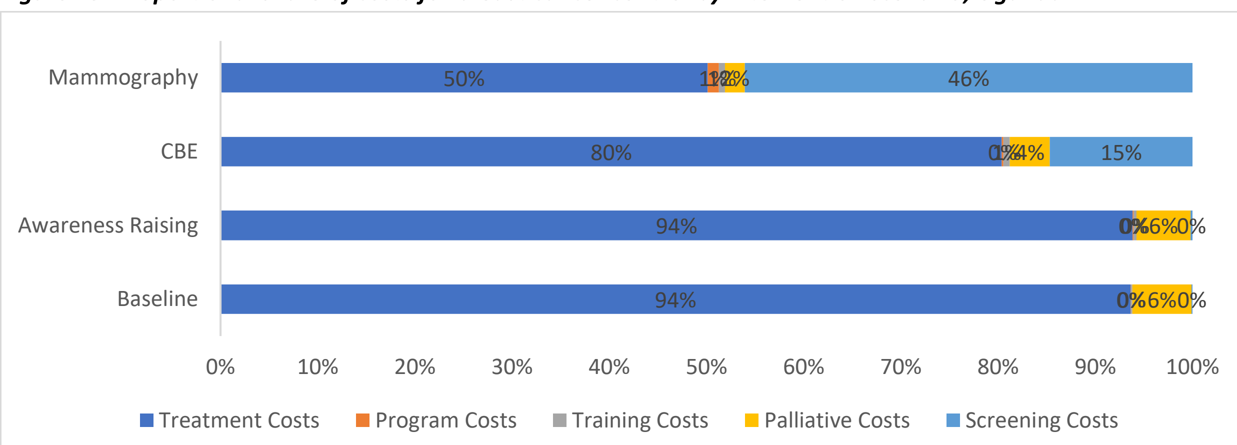


Table 26: Disaggregation of Breast Cancer Control Costs (Discounted) in USD for Uganda

Item	Total Costs (USD)			
	Baseline	**Awareness Raising**	**CBE**	**Mammography**
Treatment Costs	1,251,587,995	1,236,438,712	1,215,305,336	1,190,434,830
Program Costs	455,102	547,821	2,275,510	334,888,211
Training Costs	1,760,840	2,119,580	8,804,200	863,813,012
Palliative Costs	81,453,036	73,323,380	62,020,150	48,698,096
Screening Costs	1,094,925	1,317,997	221,728,464	1,093,631,499
Total Costs	*1,336,351,898*	*1,313,747,490*	*1,510,133,661*	*3,531,465,647*
Annual Average Cost	*33,408,797*	*32,843,687*	*37,753,342*	*88,286,641*
As a % of National Budget	*0.26%*	*0.23%*	*0.28%*	*0.64%*
As a % of Health Budget	*3%*	*3%*	*4%*	*8%*
As a % of GDP	*0.07%*	*0.06%*	*0.08%*	*0.17%*

Except for the mammography led screening scenario, treatment costs account for over 60% of the estimated costs in all scenarios. In the mammography led screening scenario, 31% of the total costs are attributed to screening costs due to the costly mammography resource inputs including equipment, supplies, and the personnel required. Treatment costs and palliative care costs are higher in the baseline and awareness raising scenarios because in these scenarios more patients present with late-stage disease which is more costly to effectively manage.

Figure 13: Proportional share of costs for breast cancer control by intervention scenario, Uganda



6.3.3 Cost Effectiveness Ratios

The Average Cost Effectiveness Ratios (ACERs) range from $87 per death averted for awareness raising interventions to $234 per death averted for Mammography. Using the Woods et al threshold for low-income countries which ranges between USD 16 - USD 537 (51% of GDP per capita for 2024) and Pichon-Riviere threshold for low-income countries and Uganda as 54% of GDP per capita, the most cost-effective intervention for breast cancer control in Uganda is awareness raising interventions with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $416 per healthy life year gained. Mammography screening combined with treatment for all stages is not cost effective with an ICER of $3,110 per healthy life year gained.

Table 27: ICERs for early detection and screening Interventions compared with baseline scenario in Uganda

Intervention Scenarios	Incremental Costs (USD)	Incremental HLYs	Incremental Deaths Averted	ICER/HLYs Gained
Awareness Raising	(22,604,409)	190,773	12,039	(118)
CBE	173,781,762	417,897	29,122	416
Mammography	2,195,113,749	705,879	49,087	3,110

***ICER= (Cost of Intervention – Cost of Baseline Scenario)/ (Health Benefit of Intervention – Health Benefit of Comparator), Costs and HLYs discounted at 3%*

Table 28: ACERs for early detection and screening Interventions compared with baseline scenario in Uganda

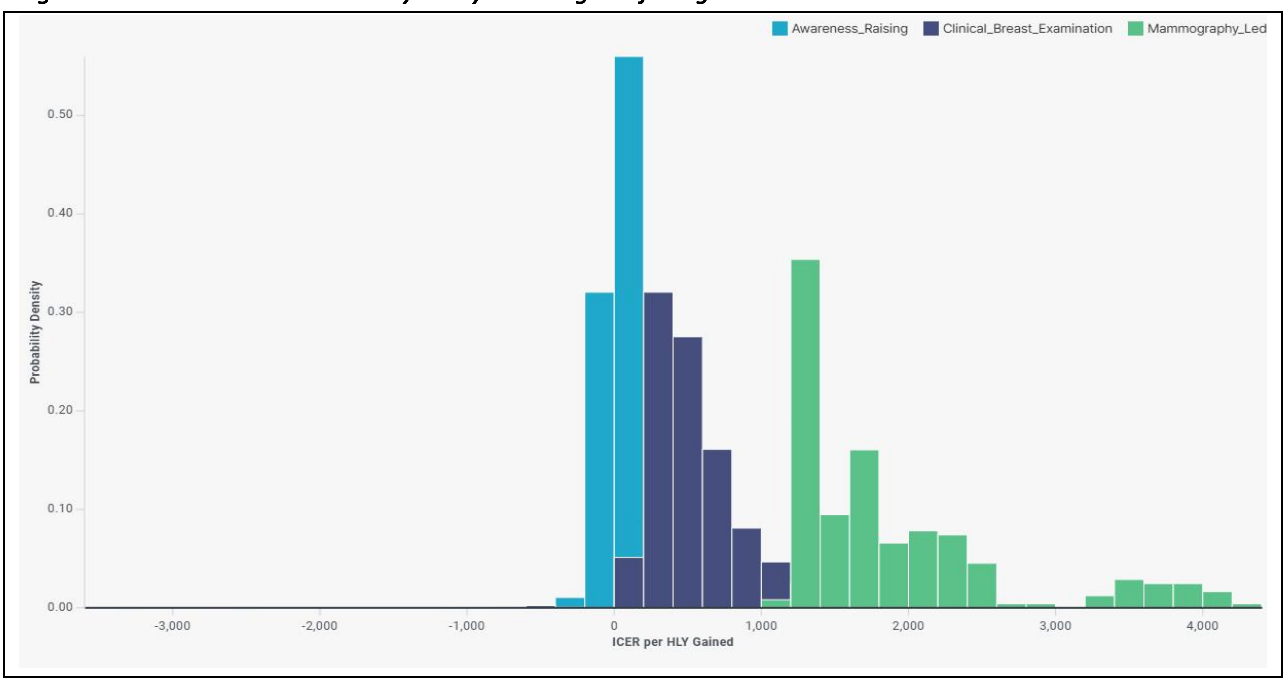
Intervention Scenarios	Total Costs (USD)	Total HLYs	Total Deaths Averted	ACER/HLYs	ACER/Death Averted
Awareness Raising	1,313,747,490	2,975,985,440	15,132,161	0.44	87
CBE	1,510,133,661	2,976,212,564	15,115,079	0.51	100
Mammography	3,531,465,647	2,976,500,546	15,095,113	1.19	234

**ACER=Total Cost of Intervention/Total HLYs or/ Number of Deaths Averted*

6.3.4 Sensitivity analysis

Sensitivity analysis showed that overall, the results were robust to variations in critical parameters. Nonetheless, the sensitivity analysis highlighted that the model was sensitive to alternative assumptions on treatment and screening costs.

Figure 14: Multi-Variable Sensitivity Analysis Histogram for Uganda



The histogram above presents the results of the multivariable sensitivity analysis for Uganda. The x-axis represents cost-effectiveness values (expressed as cost per HLY gained), while the y-axis shows the proportion of simulations falling within each cost-effectiveness range. The distribution for the awareness raising interventions (light blue) is tightly clustered around zero, with a significant proportion of simulations showing cost-saving results (negative or near-zero cost per HLY gained). This indicates that, under a wide range of parameter variations, awareness interventions are highly likely to be either cost-effective or even cost-saving. The CBE interventions (dark blue) shows a broader distribution, primarily between 0 and 1,500 USD per HLY gained, suggesting it doesn't remain cost-effective across most simulations. The mammography-led interventions (green) display a wider and right-shifted distribution, ranging approximately from 1,000 to 4,000 USD per HLY gained. This indicates no cost-effectiveness and greater uncertainty. While mammography may still be considered cost-effective under certain conditions, its performance is more sensitive to changes in input parameters and assumptions, particularly in a resource-limited setting like Uganda. Overall, the results suggest that awareness raising, is more consistently cost-effective across plausible scenarios, while CBE and mammography-led screening, though potentially impactful, may pose greater budgetary and efficiency challenges in the Ugandan context.

6.4 Discussion

We developed a model to estimate the cost effectiveness of early detection and screening interventions on downstaging breast cancer diagnosis in Uganda. Our analysis found that mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 49,087 incremental deaths and provides 705,879 incremental Healthy Life Years. The most cost-effective intervention for breast cancer control is awareness raising interventions with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $ 416 per healthy life year gained. Biennial MMG screening combined with treatment for all stages was not cost effective with an ICER of $3,110 per healthy life year gained.

Our findings are consistent with those from other similar studies, for example, a study from India reported that biennial CBE was a cost-effective intervention with an ICER of $1,341 per life-year gained[84], this aligns with our findings for Uganda, where CBE demonstrated favorable cost-effectiveness compared to mammography. The comparability in results may be attributed to similar health system contexts, both countries are LMICs with constrained resources, relatively low baseline screening coverage, and significant delays in diagnosis, making low-cost, community-based interventions such as CBE highly impactful. Likewise, a study from Ghana reported CBE as the most cost-effective intervention ($1,299 per DALY averted) and found mass media awareness interventions cost effective ($1,364 per DALY averted) [35]. These results echo our own, reinforcing the value of low-intensity, scalable early detection strategies in settings with limited infrastructure. The similarity in findings reflects comparable disease burden profiles and public sector constraints in service delivery, which increase the marginal benefit of low-cost interventions. Further, studies from central America (Mexico and Costa Rica) also found that awareness raising interventions were more cost effective than mammography [34]. Another study from China found that CBE was cost effective when compared with no screening [144]. However, a different study from rural China found that a combination of CBE and ultrasound screening in rural areas was not a cost-effective intervention and the divergent results can be attributed to the fact that this study was set in a rural setting with low breast cancer incidence [145] which reduces the cost-effectiveness of screening due to fewer cases detected. The contrasting findings underscore the importance of contextualizing cost-effectiveness results based on background incidence rates, health system readiness, and the unit costs of service delivery.

Although Mammography has been widely reported as a cost-effective intervention in high income countries, our analysis shows that while mammography is the most effective intervention in terms of health outcomes, it is also associated with very high costs and is therefore not cost-effective for Uganda. Our findings are consistent with those from similar settings, for instance, in Ghana, biennial mammography was not found to be cost effective with an ICER of $12,908 per DALY averted [35]. Similarly, a study from Iran also found mammography not cost-effective ($13,524 - $36,154) when compared to a no-screening scenario [70]. In both Ghana and Iran, as in Uganda, the high infrastructure costs, recurring operational expenses, and limited population coverage dilute the cost-effectiveness of mammography-based programs. These findings point to the broader challenge of transferring technologies from high-income settings into LMICs without adequate adaptation to local cost structures, health system constraints, and population-level coverage.

Our findings have policy implications for breast cancer control in Uganda. Firstly, while our analysis found MMG not to be a cost-effective intervention, we note that Uganda should continue to incrementally make investments for mammographic screening for diagnostic purposes and the scale up of these investments should be gradual and shaped by the improvement in the economic performance of the country especially as it transitions into middle-income status. Secondly, while our results show that awareness raising and CBE are economically attractive interventions, it should be noted that the success of these interventions is greatly hinged on the availability of treatment and on the availability of skilled human resources for health, equipment, and supplies to aid diagnosis [9], [10]. As such, CBE and awareness raising interventions can easily fail if critical socio-cultural factors and other aspects of the health system such as education and information are not considered. Therefore, an enabling environment comprising of the critical socio-cultural and health systems factors should precede the roll out of nation-wide awareness raising and CBE interventions.

Thirdly, while our analysis found that awareness raising and CBE interventions are cost effective, they require significant resources for implementation at scale and this warrants affordability concerns. Implementing the awareness raising interventions annually would require 3% of the total health budget annually while CBE and MMG would require an additional 2% and 3% respectively of the total health budget annually. For purposes of sustainability and affordability, we recommend that these breast cancer control interventions are implemented in an integrated model along with other programs targeted at the same proportion of the demographic such as the cervical cancer program. Resource allocation to the integrated model can happen in a gradual and well sequenced manner over long-term budgetary commitments. Another suggested cost-saving option in the literature is to use risk-based screening approaches which is targeted screening to high-risk groups only, however, the evidence suggests that 100% attendance rate is required for a risk-based screening approach to achieve the standard of cost-effectiveness [145] and this might be challenging to achieve in a complex healthcare setting like Uganda.

As with any other modelling exercises, our study has limitations worth highlighting. Firstly, the cancer registry in Uganda is not fully functional and therefore this analysis relied on secondary data sources and global estimates for critical indicators such as case-fatality which may not be reflective of the reality thus biasing our estimates. Secondly, this study only considered a provider's perspective, excluding the costs to the patients including their productivity loss. We are cognizant of the fact that inclusion of these costs would have provided the complete and more accurate estimate of the resource requirement for breast cancer control in Uganda, especially owing to the high travel costs that have been associated with breast cancer treatment in Uganda. Additionally, the model excludes future unrelated medical costs due to unavailability of robust data to support their estimation in Uganda. Furthermore, our model uses a simplifying assumption that all women diagnosed with breast cancer will receive treatment appropriate to their stage of disease. In Uganda, barriers to breast cancer treatment are quite significant. Scheel et al. (2020) report that the country has limited diagnostic and treatment capacity, concentrated mainly at the Uganda Cancer Institute (UCI), and that fewer than 20% of women diagnosed with breast cancer receive curative treatment [18]. As such, the assumption in the model that all diagnosed patients receive treatment does not reflect current realities but allows for assessment of the full potential impact of scaling up early detection and treatment access. Thirdly, there is limited information on the effectiveness of awareness raising interventions and therefore our estimates for this scenario should be interpreted cautiously. Fourth, our model doesn't account for the harms associated with screening (e.g., false positives, and over-diagnosis). Additionally, the model doesn't predict the direct impact of screening on mortality. Fifth, the degree to which breast cancer early detection and screening interventions are beneficial to Uganda cannot only depend on the estimated cost-effectiveness based on down-staging as quantified by our analysis. Other critical criteria such as affordability (budget impact), value for money, safety, and other political concerns should be considered.

Despite these shortcomings, our study also had several strengths. Firstly, our analysis doesn't include the natural history of the underlying breast cancer disease, but rather, it focuses on the observable events in disease progression, implying fewer inputs, transparency in the model and higher generalizability to other contexts. Secondly, our dynamic state transition model incorporates the compounding effects of intervention scale-up over time and the long-term disease progression, offering a more nuanced projection of health outcomes over a 40-year horizon. Thirdly, to arrive at Ugandan estimates for this study, we relied on a model that showed face validity confirmed by an expert panel. Additionally, despite our study limitations, our results are consistent with the results of studies from comparator countries. Moreover, the above limitations do not greatly hinder the overall objective of this analysis which was to provide an indication of the cost-effectiveness of breast cancer early detection and screening interventions to inform policy decisions rather than to provide very precise estimate for each of the scenarios evaluated.

In summary, our findings indicate that awareness raising interventions (which include training of primary health workers + outreaches by primary health workers to raise breast cancer awareness + enhanced media activities including mass media campaigns), is the most cost- effective breast cancer control intervention for Uganda with a dominant ICER. Our analysis also found CBE to be a cost-effective intervention for Uganda as it facilitates early detection of the disease thereby averting higher treatment and management costs associated with late-stage disease. Our results are consistent with those from other similar settings which have reported that awareness raising, and biennial CBE are not only crucial for down-staging breast cancer diagnosis but that they are also economically attractive and viable for countries with limited resources. While MMG was found to be the most effective intervention, it is very costly and therefore LMICs should only adopt MMG with careful considerations. For sustainability and affordability purposes, LMICs should implement awareness raising and screening interventions in an integrated manner with other non-communicable diseases such as cervical cancer and this should be implemented in a phased manner with robust monitoring and evaluation.

CHAPTER

7

"…The Lord will perfect that which concerns me: your mercy, O Lord, endures forever…" Psalms 138:8

Chapter 7: Universal Public Finance for Early Detection, Screening, and Breast Cancer Control in South Africa: An Extended Cost Effectiveness Analysis

Abstract

Background

Breast Cancer in South Africa exhibits pronounced disparities in breast cancer services across ethnic and socioeconomic lines. Colored and black women present with more aggressive tumors and with more advanced disease presentation. Socio-economic factors greatly contribute to this pattern as they limit access to healthcare services and screening especially in the rural areas. Furthermore, the intersection between breast cancer and HIV/AIDS further exacerbates the challenge especially among the black population.

Methods

We conducted an extended cost effectiveness analysis (ECEA) to quantify the distributional consequences of publicly financing early detection and breast cancer control interventions across socioeconomic strata in South Africa along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through catastrophic health expenditure cases averted.

Results

Our study found that a policy to publicly finance early detection, screening and breast cancer control interventions in South Africa has a pro-rich distribution for health outcomes and a strong pro-poor distribution for financial protection outcomes. Our analysis shows that 44% of the deaths averted are in the wealthiest two quintiles while the poorest two quintiles would account for 34% of the total deaths averted. Concerning healthy life years gained, we report 22% of the healthy life years gained would be concentrated in the wealthiest quintile alone while the poorest quintile would account for 14% of the total healthy life years gained. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $7.89 million over the 40-years, this translates to US $197,254 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the poorest wealth quintile accounting for 76% of the averted catastrophic health expenditure cases, on the other hand, the wealthiest two quintiles account for approximately 1.4% of the catastrophic health expenditure cases averted.

Conclusion

In conclusion our analysis incorporates equity and financial protection considerations into the traditional economic evaluation for breast cancer control interventions in South Africa. The results show that a policy to publicly finance breast cancer interventions in South Africa has the potential to increase health benefits across all wealth quintiles and improve financial protection disproportionately benefiting the poorer wealth quintiles. As South Africa continues to grapple with high breast cancer mortality and late-stage presentation of patients, policy makers should consider public financing of breast cancer control interventions with reinforced pro-poor targeting.

7.1 Background

In 2022, global statistics show that female breast cancer ranked as the second leading cause of global cancer incidence with an estimated 2.3 million cases, and it is the fourth leading cause of mortality worldwide with 665,684 deaths [1].[1][3], [4] [113]In 2020, South Africa reported 15,491 new breast cancer cases and although overall, the age standardized rate (ASR) shows a slight increase, there has been a marked increase in the ASR for South Africans of European decent [95]. [93], [114][115].

The cancer mortality in South Africa is disproportionately greater than the incidence burden in the region and this is mostly attributed to late-stage presentation of the disease[1]. [116], [117]. Moreover, there are ethnic disparities in the late presentation with patients of African/black ancestry more likely to present with advanced-stage disease while patients of European ancestry are more likely to present with early-stage disease[118].

Furthermore, cancer is a high-cost illness that has been a high-ranking cause of catastrophic health expenditures, which can push households into poverty [89], [90], [91]. Moreover, in most LMICs where health insurance is out of reach for many households, cancer healthcare is paid for largely through out-of-pocket payments [92]. Breast Cancer in South Africa exhibits pronounced disparities in breast cancer services across ethnic and socioeconomic lines[93]. Colored and black women present with more aggressive tumors and with more advanced disease presentation [94]. Socio-economic factors greatly contribute to this pattern as they limit access to healthcare services and screening especially in the rural areas [93], [95]. Furthermore, the intersection between breast cancer and HIV/AIDS further exacerbates the challenge especially among the black population[95].

Universal public finance is a financing option which implies that the government finances an intervention irrespective of who delivers or receives the service [88]. The heuristic power of universal public finance lies in its ability to (a) increase coverage and access to the poor population groups, (b) reduce a household’s expenditure on health care and (c) potential positive financial consequences like cost savings resulting from crowding out of private expenditure on the health intervention [96]. This is also in line with the holistic move toward universal health coverage. Despite the importance of considering financial risk protection and equity aspects when conducting economic evaluations, a paucity of research has done so using the ECEA method in low and middle-income countries [96], [102], [103], [104], [105], [106]. This study aims to estimate the extended cost effectiveness analysis of publicly financing early detection and screening interventions for breast cancer control in South Africa.

7.2 Methods

In this analysis, we assume a public financing policy for breast cancer control interventions as a critical tool to move towards universal health coverage. As such, the analysis assumes a shift toward universal public financing as the mechanism for expanding access to breast cancer early detection and screening services. While the analysis does not simulate a specific financing source, it is grounded in the broader health systems context of South Africa, where progressive realization of Universal Health Coverage (UHC) is a stated policy goal. The assumed source of financing is general government revenue, consistent with the dominant health financing mechanisms South Africa. Furthermore, this aligns with the vision of the National Health Insurance (NHI) scheme, which aims to pool funds to provide equitable access to essential services. Additional possibilities include reprioritization of existing health budgets, increased fiscal space through economic growth, and catalytic external funding to support scale-up. These assumptions reflect a normative policy scenario and are consistent with global recommendations on financing priority health services under the WHO's UHC framework.

We conducted an extended cost effectiveness analysis (ECEA) of a policy to publicly finance early detection and breast cancer control interventions in South Africa. The ECEA has been described elsewhere in great details and applied in various low- and middle-income countries [97]. Extended Cost Effectiveness Analysis augments the traditional cost effectiveness analysis method by considering non-health benefits such as financial protection and equity by quantifying: 1) the distribution of health benefits across wealth strata, 2) the cases of catastrophic health expenditure averted by a policy and 3) the financial protection provided by a policy [97].

In this analysis, we quantify the distributional consequences of early detection and breast cancer control interventions across socioeconomic strata in South Africa along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through cases of catastrophic health expenditures averted. In other words, this analysis set out to answer the question, "*Which wealth quintile benefits the most (health gains) and averts the most catastrophic health expenditures due to publicly financing the different early detection and breast cancer control interventions in South Africa? Is it the rich or the poor*?"

Our population of interest were women with breast cancer in South Africa. The annual incidence (women diagnosed with breast cancer) was determined using age specific incidence from 2022, from the IARC Globocan Today database [7]. The operational definitions and intervention packages considered in this analysis have been presented in Chapter 5 of this thesis.

The ECEA model is a direct extension of the analytical model presented in Figure 6 (section 4.2.2), applied separately to each income quintile. Each quintile is parameterized with income-specific values for access, utilization of breast cancer services, and out-of-pocket costs. The no-UPF (status quo) scenario retains observed inequities in access and financial exposure, while the UPF scenario equalizes coverage and eliminates OOP payments. The model then estimates health outcomes (HLYs, deaths averted) and financial outcomes (CHE cases averted) for each quintile, which are aggregated to generate distributional results.

7.2.1 Approach to the Extended Cost Effectiveness Analysis

In this analysis, we assume a public finance policy for early detection, screening, and breast cancer control interventions to be provided to all in need of these services at no cost at the point of care (in other words, no out-of-pocket expenditure). The projection period considered was 40 years consistent with the previous chapters of this thesis and costs are reported in US Dollars. Wealth quintiles were defined at the start of the projection period, and we assumed that an individual's come did not vary through the projection period.

To estimate the distribution of the deaths averted, healthy life years gained, and cases of catastrophic health expenditures averted per wealth quintile data, the following parameters were used: annual income of individuals with y_i and y_h representing the lowest and highest incomes respectively; $f(y)$, the income distribution; c, the cost of breast cancer early detection and management interventions (presented in chapter 5 of this thesis), and s, the down-staging rate corresponding to each early detection and screening interventions for breast cancer (presented in chapter 4 of this thesis). Another assumption is that breast cancer has an annual incidence of probability p. Our analysis also assumed a uniform baseline incidence rate across wealth quintiles, derived from GLOBOCAN 2022 estimates [2], and adjusted for population demographics [132], [133], [137]. This approach was adopted because no empirical data exist for South Africa or Uganda quantifying incidence gradients by socioeconomic status and published global studies do not provide parameterizable estimates that can be applied at country level. Using a uniform baseline avoids embedding unsupported socioeconomic assumptions and prevents potential double-counting of inequities already captured through differences in stage at diagnosis and access to care. To explore how unequal incidence might influence distributional outcomes, we conducted a scenario analysis where we applied relative-risk multipliers to the base-case incidence, representing plausible gradients reported in the broader literature. These scenario analyses are presented in sections 7.2.3, 7.3.4, 8.2.2, and 8.3.4 to illustrate the sensitivity of extended CEA results to socioeconomic variation in disease incidence. Lastly, the underlying assumption is that breast cancer is lethal with a case fatality rate d_0

Before the introduction of universal public finance for breast cancer control, the probability of dying from the disease, conditional on having it, d_a, depends on the probability of getting treatment $u(y)$ (this refers to the pre-existing treatment coverage) and the down-staging rate corresponding to each early detection and screening interventions for breast cancer s. In other words:

$$d_{a(y)=u(y)(1-s)d_0+(1-u(y))d_0} \quad \textit{Equation 1}$$

After the introduction of universal public finance for early detection of breast cancer, every patient receives diagnosis and treatment and therefore the probability of dying from breast cancer, conditional on having it, is given by: d_p is $d_p = (1-s)d_0$. Therefore, the differential of mortality due to breast cancer between ante-universal public finance and post-universal public finance introduction follows as $(d_a - d_p)p$.

The aggregate number of **deaths averted**, $\mathcal{D}$, across the wealth strata was be given by:

$$\mathcal{D} = \Sigma_{y_i}^{y_h}(d_a - d_p)pf(y)dy \quad \textit{Equation 2}$$

The aggregate number of **healthy life years gained**, $\hbar\mathcal{LY}$, across the wealth strata was be given by:

$$\hbar\mathcal{LY} = \Sigma_{y_i}^{y_h}(d_a - d_p)pf(y)dy \quad \textit{Equation 3}$$

For the **catastrophic health expenditures (CHE)**, we defined CHE as the incidence where breast cancer treatment costs exceed a 10% threshold of household disposable income.

Let:

C = treatment cost for breast cancer

y_q = average annual income in quintile q

σ = catastrophic health expenditure threshold (10%)

p_q = proportion of breast cancer patients in quintile q

N_q = number of women diagnosed with breast cancer in quintile q

Then:

$$\mathbb{C}\mathcal{HE}_q = \begin{cases} 1, & if \frac{C}{y_q} \geq \sigma \\ 0, & Otherwise \end{cases} \quad \textit{Equation 4}$$

And the total number of cases of catastrophic expenditure averted under universal public financing is:

$$Total\ CHE\ Averted = \sum_{q=1}^{5} N_q\ x\ \mathbb{C}\mathcal{HE}_q\ x\ p_q \quad \textit{Equation 5}$$

Equations 1–5 represent the analytical steps through which the ECEA model derives health and financial protection outcomes for each income quintile. These expressions are directly derived from the analytical model presented in Figure 6.

Description of the Baseline Vs universal public financing scenario

Breast Cancer in South Africa exhibits pronounced disparities in breast cancer services across ethnic and socioeconomic lines[93]. Colored and black women present with more aggressive tumors and with more advanced disease presentation [94]. Socio-economic factors greatly contribute to this pattern as they limit access to healthcare services and screening especially in the rural areas [93], [95]. Additionally, the intersection between breast cancer and HIV/AIDS further exacerbates the challenge especially among the black population[95]. In South Africa there is low screening uptake (baseline coverage for MMG is 20%, CBE is 20% and awareness raising is 10%) and many face financial barriers as they seek breast cancer services with catastrophic health expenditure as high as 30% in the poorest wealth quintile. In South Africa's baseline, higher-income quintiles have greater access to mammography (though overall low) and better access to timely treatment, whereas lower-income quintiles have very low screening uptake and face financial barriers to treatment. The baseline utilization coverage for breast cancer services is 14% in the poorest wealth quintile versus 22% in the wealthiest income quintile. We utilized a uniform baseline across all quintiles of 32.87 per 100,000, however, some evidence suggests that wealthier quintiles have higher incidence [155], [156], [157], [158], and this limitation was accounted for through performing a sensitivity analysis described in section 7.2.3.

Under universal public financing (UPF) scenario, we assume these disparities are eliminated: the policy finances screening and treatment for all, so effectively all quintiles get equal coverage of screening (we modeled 100% of target women screened across all quintiles) and equal access to treatment (assumed 100% across quintiles). However, given the assumption that the wealthier quintiles have more access and higher incidence of breast cancer, they are likely to have more absolute health gains.

For South Africa, we divided the total population into five wealth quintiles based on the population projections by UNDP [127]. For each wealth quintile, we obtained the quintile specific breast cancer service coverage from published literature [56].

7.2.2 Estimation of Outcomes

The projections for health outcomes (deaths averted and healthy life years gained) of breast cancer control interventions were provided by the dynamic state transition model for South Africa described in detail in Chapter 5 of this thesis. To estimate the cases of catastrophic health expenditures averted, we used the total costs estimated by the dynamic model for South Africa (Chapter 5) and multiplied these costs by the current out-of-pocket expenditure ratio (6.71%) in South Africa [151]. We defined catastrophic health expenditure as private expenditure on health that exceeded 10% of the household's income after subsistence needs have been met [152]. We then quantified the total private expenditures on breast cancer control that could lead to catastrophic health expenditures that exceed the 10% threshold. Basing on the 10% income threshold (Th), a case of catastrophic health expenditure is realized when the cost, c, of breast cancer control interventions is greater than the income threshold. In other words:

$$c > y * Th \quad \textit{Equation 6}$$

Therefore, the financial risk protection afforded by publicly financing breast cancer control interventions will correspond to the total catastrophic health expenditures averted owing to a reduction in the incidence of private expenditures. This corresponds to a direct comparison of the number of cases of catastrophic health costs averted due to the decision to publicly finance breast cancer control interventions, with a numerical integration along the income distribution of the targeted population.

In this analysis, both *wealth* and *income* stratifications were used to examine disparities in breast cancer service access and financial protection. While recognizing that these are distinct constructs, the use of both metrics was driven by the availability of stratified data across different sources, for example, access to breast cancer services in South Africa was assessed based on wealth quintiles as reported by Mapanga et al (2023) [56], while financial risk protection metrics relied on income-based stratification as reported in the National Income Dynamics Study (NIDS). While this approach is imperfect, it aligns with the guidance in the literature on the need to pragmatically use the best available data in equity analyses[160].

Furthermore, we assumed that differential treatment access by income quintile observed in the current system would be eliminated under universal public financing. That is, while ante-universal public finance scenario incorporated income-based treatment probabilities and corresponding mortality risks, the post-universal public finance scenario applied equal treatment probabilities across all income groups, simulating the removal of financial access barriers. Consequently, mortality differentials by income were only retained in the ante-universal public finance scenario. This assumption simplifies reality, as structural access barriers beyond cost (e.g., geography, health system capacity) may still differentially affect outcomes. However, this approach aligns with the aim of evaluating the equity-promoting potential of public financing reforms under ideal conditions. It reflects assumptions commonly used in extended cost-effectiveness analyses of UHC interventions [124], and was necessary to quantify the reduction in financial hardship attributable solely to changes in financing policy.

Description of Parameters Used for the ECEA

Table 29 provides a list of the all the parameters that were considered for the extended cost effectiveness analysis for South Africa. Parameters held constant across quintiles include disease incidence, age-specific mortality, disability weights, and treatment efficacy. Parameters that vary by income and thus drive the distributional outcomes include:

- **Breast cancer service utilization coverage:** ranges from very low in the poorest quintile to moderate in the richest under the no-UPF scenario, equalized to 100 % under UPF.
- **Out-of-pocket expenditure (OOP):** highest among poorer quintiles and zero under UPF.
- **Average individual income:** defines the denominator for calculating catastrophic health expenditure (CHE) incidence.

These parameters feed into the conceptual model as follows: incidence determines case load; coverage and stage distribution affect early detection; treatment access and OOP define mortality and financial protection outcomes; and household income calibrates the CHE threshold.

Table 29: Parameters for Extended Cost Effectiveness Analysis for South Africa

Parameter	Symbol / Value (Q1–Q5)	Units / Notes	Source / Reference
Individual income (average per quintile)	Q1: ZAR 21 000 Q2: ZAR 43 000 Q3: ZAR 74 000 Q4: ZAR 128 000 Q5: ZAR 295 000	Annual household income	[153]
Income distribution *f(y)*	Modeled using quintile means above	Function fitted to quintile means	[153]
Income threshold (Th) for CHE	10 % of annual household income	CHE defined as OOP > 10 % of income	[152]
Baseline breast-cancer incidence	32.87 per 100 000 women	Uniform across quintiles (base case)	GLOBOCAN 2022
Relative-risk multiplier (scenario analysis)	1.00, 1.10, 1.20, 1.30, 1.30	Used in SES-gradient scenario only	Assumed (Refs 152–155)

Total program and treatment costs (c)	From Table 20 (Chapter 5)	Includes early detection, screening, treatment, palliative care	Thesis data
Deaths averted (D)	From Table 22 (Chapter 5)	Model output per scenario	Thesis data
Healthy life-years gained (hLY)	From Table 22 (Chapter 5)	Model output per scenario	Thesis data
Breast-cancer service utilization / coverage *u(y)*	14 %, 19 %, 22 %, 22 %, 22 % (Q1–Q5)	Reflects differential uptake by income quintile	[56]
Baseline coverage – CBE	20 %	All quintiles (base case)	[56]
Baseline coverage – awareness raising	10 %	All quintiles (base case)	[56]
Baseline coverage – MMG	20 %	All quintiles (base case)	[56]
Catastrophic health expenditure (CHE) rate by quintile	30 %, 8 %, 4 %, 1 %, 0 % (Q1–Q5)	Baseline proportion facing CHE	Table 32, Ch. 7
OOP share of total cost (baseline)	70 %, 40 %, 30 %, 20 %, 10 % (Q1–Q5)	Applied to compute financial burden	Derived based on Table 32
OOP share under UPF	0 % (all quintiles)	Reflects full public financing	Assumed (policy scenario)

It is important to note that unlike Chapters 4 to 6, which modelled idealized implementation scenarios assuming 100% screening coverage and 100% treatment uptake for all diagnosed cases, the analysis in this chapter incorporates income-based variation in access and utilization of breast cancer services. This was done to better reflect real-world inequities in care access and to quantify the potential health and financial protection gains of universal public financing. For the analysis presented in this chapter, we model the distributional consequences of publicly financing breast cancer interventions, and as such, incorporates variation in access and utilization of breast cancer services by income quintile. This approach relaxes the 100% treatment assumption used in earlier chapters, particularly for the ante universal public financing scenario, where utilization of breast cancer services varies by socioeconomic status. The universal public financing scenario, on the other hand, assumes equal access to treatment was assumed across all income groups, reflecting an equity-oriented financing reform.

7.2.3 Sensitivity Analysis

To address the limitation of utilizing uniform baseline incidence rate across wealth quintiles, we performed a scenario analysis on income-stratified breast cancer incidence by varying the assumed incidence rates by income group (using Equation 7) to test how sensitive the distributional outcomes are:

$$i_q = i_{base} \; x \; RR_q \quad \textit{Equation 7}$$[1]

Where:

- i_q: Incidence rate (per 100,000 women) for wealth quintile q (Q1–Q5, poorest to richest).
- i_{base}: Baseline incidence, 20 per 100,000 women (GLOBOCAN 2022).
- RR_q: Relative risk multiplier, set at 1.0, 1.05, 1.10, 1.15, 1.15 for Q1–Q5, with PSA ranges [1.0–1.0], [1.0–1.07], [1.05–1.12], [1.10–1.18], [1.12–1.20], based on higher incidence in wealthier quintiles [155], [156], [157], [158].

It is important to note that the parameters involved in the scenario analysis were essentially the relative risk multipliers for incidence in each quintile (Q1–Q5) and their ranges, which were used to simulate 1,000 runs (e.g., Relative Risk = 1.0 in Q1 up to 1.15 in Q5, with ranges as given in Equation 7, and no other model parameters were stochastically varied.

[1] Equation 7 and 9 define how the income-specific incidence rates were calculated for each simulation (they show incidence for quintile *q* as a baseline rate times a relative risk factor). In other words, Equation 7 and 14 were used to introduce a differential incidence by income in the uncertainty analysis, *not* to imply a full PSA on all parameters.

7.3 Results

7.3.1 Distribution of Deaths Averted

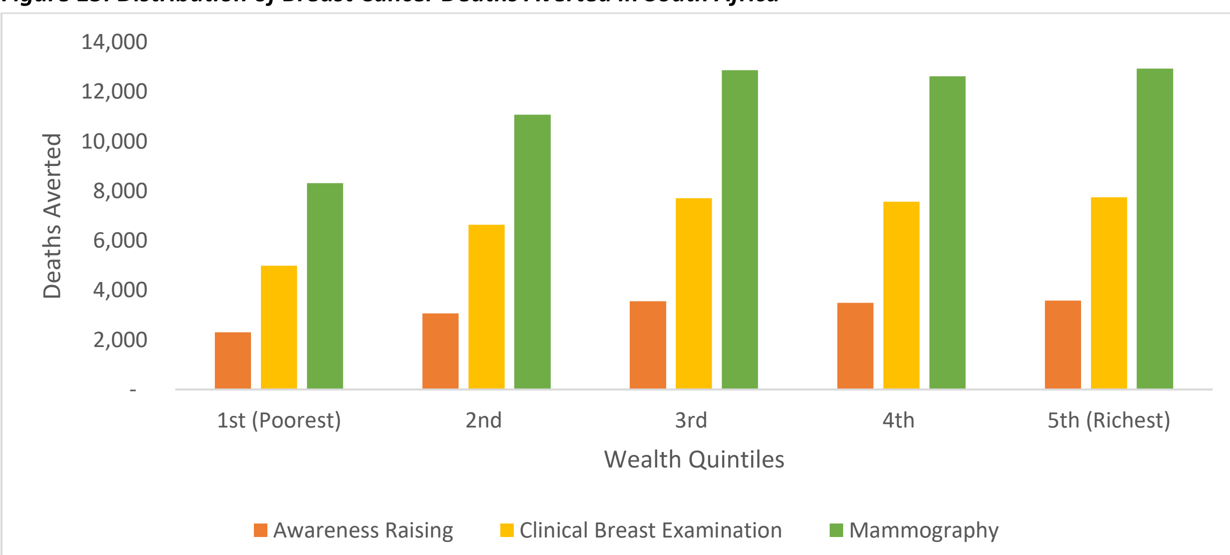
Our analysis shows that the distribution of breast cancer deaths averted over the 40-year period is pro-rich thus benefiting the richer population, with 44% of the deaths averted in the wealthiest two quintiles while the poorest two quintiles account for 34% of the total deaths averted.

Overall, the distribution of deaths averted across the different early detection and screening interventions is pro-rich with the deaths averted in the wealthiest quintile being higher than those in the poorest quintile by 1.5 times.

Table 30: Distribution of Breast Cancer Deaths Averted in South Africa

	Number of Deaths Averted					
	Quintiles					
	1st (Poorest)	2nd	3rd	4th	5th (Richest)	Total (National)
Awareness Raising	2,301	3,068	3,563	3,494	3,580	16,006
Clinical Breast Examination	4,983	6,645	7,715	7,568	7,752	34,663
Mammography	8,313	11,084	12,870	12,623	12,931	57,821
Total	15,598	20,797	24,147	23,685	24,263	108,490

Figure 15: Distribution of Breast Cancer Deaths Averted in South Africa



Across all wealth quintiles, Mammography services would avert the greatest number of deaths, accounting for 53% of all deaths averted and 66% of these averted deaths are concentrated among the wealthiest three quintiles. Clinical Breast Examination averts 32% of the total deaths with the three top wealth quintiles benefiting the most. Awareness raising interventions account for 15% of all the total deaths averted and this also follows a pro-rich distribution.

7.3.2 Distribution of Healthy Life Years Gained

We observe a similar pro-rich trend distribution for the healthy life years gained over the 40-year period benefiting the richer population, with 22% of the healthy life years gained concentrated among the wealthiest quintile while the poorest quintile accounts for 14% of the total healthy life years gained.

Table 31: Distribution of Breast Cancer Healthy Life Years Gained in South Africa

	Healthy Life-Years Gained					
	Quintiles					
	1st (Poorest)	2nd	3rd	4th	5th (Richest)	Total (National)
Awareness Raising	38,478	51,304	59,569	58,429	59,854	267,635
Clinical Breast Examination	77,322	103,096	119,706	117,415	120,278	537,816
Mammography	129,314	172,419	200,197	196,366	201,155	899,450
Total	245,114	326,818	379,472	372,209	381,288	1,704,901

As is the case with deaths averted, mammography offers the highest number of healthy life years gained across all the wealth quintiles followed by Clinical Breast Examination and awareness raising interventions offer the least healthy life years gained across all quintiles.

Figure 16: Distribution of Healthy Life Years Gained in South Africa

7.3.3 Catastrophic Health Expenditure Cases and Incidence by Wealth Quintile

Our analysis shows that breast cancer control interventions could avert approximately US$7.86 million over the 40-years, this translates to US$197,254 total patient costs annually. Furthermore, the comparison between scenarios with and without universal public financing (UPF) for breast cancer services highlights a substantial reduction in cases of catastrophic health expenditure (CHE), particularly among the poorest households. Without universal public financing, an estimated 19,760 CHE cases occur, with over half (51%) concentrated among the poorest quintiles. Following the implementation of universal public financing, approximately 7,863 CHE cases are averted, representing a 40% reduction. Notably, the poorest quintile accounts for 76% of these averted CHE cases, underscoring the pro-poor impact of public financing in reducing financial hardship. In contrast, the richest quintile sees a minimal reduction in CHE, contributing only 1.4% of the total averted cases. Without universal public financing, approximately 10 % of households with a breast cancer case experienced catastrophic health expenditure, concentrated more in the poorest quintiles. Implementation of UPF reduced this incidence to about 1 %.

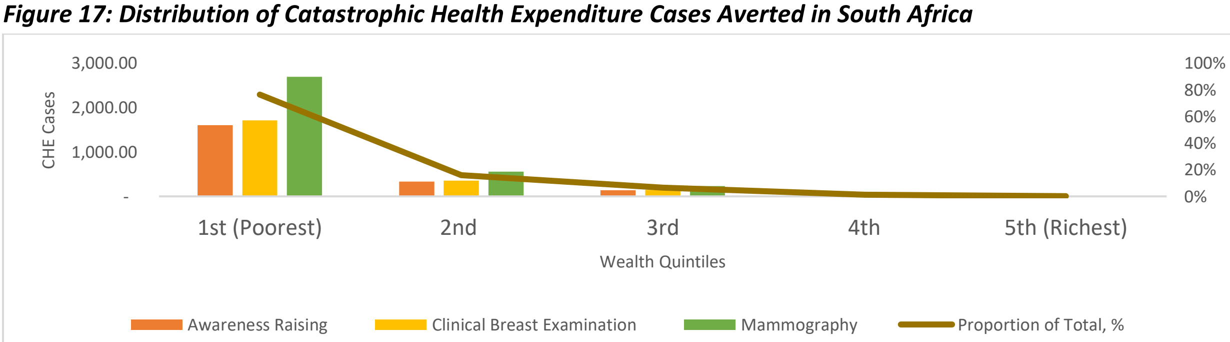
Table 32: Catastrophic Health Expenditure Cases and Incidence by Wealth Quintiles in South Africa

Wealth Quintile	Awareness Raising	CBE	MMG	Total CHE Cases (no UPF)	Proportion of Total (%)	CHE Incidence (no UPF)	CHE Cases Averted (after UPF)	CHE Incidence (after UPF)	Total CHE Expenditure Averted (USD)
1st (Poorest)	1,790	2,040	6,280	10,110	51.0	30 %	6,004.79	5.0 %	6,025,314
2nd	840	2,340	3,600	6,780	34.0	8 %	1,244.41	1.0 %	1,248,667
3rd	350	910	1,250	2,510	12.7	4 %	510.35	0.5 %	512,099
4th	35	80	170	285	1.4	1 %	91.05	0.2 %	91,366
5th (Richest)	15	20	30	75	0.4	0 %	12.70	0.0 %	12,742
Total	3,030	5,390	11,330	19,760	100.0	~9.9 % overall	7,863.31	~1.0 % overall	7,890,187

***CHE incidence** refers to the proportion of households incurring catastrophic health expenditure (>10 % of annual income) due to breast cancer care*

The analysis further shows that publicly investing in mammography led screening interventions would avert 57% of the catastrophic health expenditure with a strong pro-poor distribution as 76% of the averted expenditures would be concentrated in the poorest wealth quintile alone. Awareness raising, and clinical breast examination interventions would avert 20% and 23% of the catastrophic health expenditures respectively, similarly following a pro-poor distribution.

Figure 17: Distribution of Catastrophic Health Expenditure Cases Averted in South Africa



7.3.4 Sensitivity Analysis Results

The sensitivity analysis reveals a substantial impact of changing breast cancer incidence across wealth quintiles on the estimated number of catastrophic health expenditure (CHE) cases averted. At baseline, the interventions prevent approximately 7,863 cases of CHE. However, when quintile-specific incidence rates are applied, the estimated number of cases averted rises to 9,298, representing an 18.3% increase. The 95% uncertainty interval ranges from 9,003 to 9,617 cases, suggesting that even modest variations in incidence can significantly affect the magnitude of financial protection benefits. Importantly, while the poorest quintile still accounts for the majority of CHE cases averted, higher relative increases are observed among richer quintiles as incidence assumptions rise with wealth.

Table 33: Cases of CHE averted with varying Breast Cancer Incidecne by Wealth Quintile in South Africa

Quintile	Baseline of CHE Cases Averted (with UPF)	UI Range	Lower Bound	Upper Bound
Q1	6,004.79	7.8–8.2	5,854.65	6,155.90
Q2	1,244.41	8.4–9.2	1,306.62	1,432.31
Q3	510.35	9.2–10.0	586.65	637.94
Q4	91.05	9.9–10.9	112.62	123.25
Q5	12.70	10.0–11.1	15.88	17.89
Total	7,863.31		9,003.42	9,617.29

7.4 Discussion

We assessed the extended cost-effectiveness of three early detection and screening interventions for breast cancer control in South Africa. Our study found that a policy to publicly finance early detection, screening and breast cancer control interventions in South Africa has a pro-rich distribution for health outcomes and a strong pro-poor distribution for financial protection outcomes. Our analysis shows that 44% of the deaths averted are in the wealthiest two quintiles while the poorest two quintiles would account for 34% of the total deaths averted. Concerning healthy life years gained, we report a pro-rich distribution as we found that 22% of the healthy life years gained would be concentrated in the wealthiest quintile alone while the poorest quintile would account for 14% of the total healthy life years gained. The plausible explanation for the pro-rich distribution of the health outcomes is due to the pronounced disparities in breast cancer services across ethnic and socioeconomic lines [93]. The observed pro-rich distribution of health gains largely reflects underlying structural and demographic differences across income quintiles. In the model, wealthier groups not only have higher life expectancy, which amplifies the number of healthy life years (HLYs) gained per death averted, but also better baseline access to diagnosis and treatment services, leading to greater absolute improvements when early detection interventions are scaled up. Consequently, the pro-rich pattern of HLY gains should be interpreted not as inequitable program impact, but as a reflection of pre-existing disparities in longevity and healthcare access, reinforcing the need for targeted strategies to improve reach and effective service use among lower-income quintiles.

Regarding financial protection, our analysis found that publicly financing breast cancer control interventions could avert approximately US $7.89 million over the 40-years, translating to US $197,254 annually. The distribution of the cases of catastrophic health expenditures averted is pro-poor, with the poorest wealth quintile accounting for 76% of the averted catastrophic health expenditure cases, on the other hand, the wealthiest two quintiles account for approximately 1.4% of the catastrophic health expenditures averted. Our analysis demonstrates that if government invested more public resources for breast cancer control interventions, the poorer households would benefit disproportionately for the financial protection gained. This is largely because the poorer households currently bear the biggest burden of catastrophic expenses for health and the main determinant of catastrophic health expenditure has been found to be poverty with the odds being 13.9 times higher among the households in the poorest wealth quintile [154]. On the other hand, spending on health insurance (by the wealthier quintiles) provided a protective safety net against catastrophic health expenditures[154]. Furthermore, previous South African evidence suggests that government grants to the poorer households did not show a positive association to reducing catastrophic health expenditures due to the nature of the grants as they are not dedicated to support health care services solely[154]. The implementation of South Africa's National Health Insurance (NHI) scheme has the potential to substantially strengthen publicly funded breast cancer control interventions by enhancing financial protection, expanding access to early detection and treatment services, and promoting equity across population groups [163]. The NHI could improve the availability and quality of early detection interventions particularly in underserved areas. However, the effectiveness of these interventions under the NHI framework will depend on the adequacy of resource allocation, timely implementation, and the capacity of the health system to absorb increased demand.

Overall, the results from our analysis are consistent with findings from other extended cost-effectiveness analyses (ECEA) that examine the distributional impact of publicly financed health interventions. For instance, a study from Vietnam found a pro-rich distribution of health benefits for cataract surgery reflecting higher baseline access among wealthier individuals and a pro-poor distribution for the catastrophic health expenditures averted as the intervention shielded poorer populations from out-of-pocket expenditures [155]. This mirrors our findings, where publicly financed early detection and screening for breast cancer delivered financial protection gains that disproportionately benefitted lower-income quintiles. The similarity suggests that even when health gains are more evenly distributed or slightly skewed toward higher-income groups (due to higher health-seeking behaviors), the financial risk protection dimension of universal public financing interventions can have equity-enhancing effects. Verguet et al. 2017 found that in South Africa and India, improvements in treatment for drug-sensitive and multidrug resistant tuberculosis could reduce catastrophic costs by 5-20% albeit these gains would only set in after 5-10 years [104]. This temporal dimension is particularly relevant to our analysis, which also projects long-term reductions in financial hardship as screening programs improve early detection and reduce treatment intensity and costs. The lagged equity gains noted by Verguet et al. underscore the importance of policy commitment and sustained financing for early detection strategies, as the benefits particularly for poorer households' compound over time. Further, a study from South Africa on the distributional impact of taxing sugar-sweetened beverages on diabetes reported a pro-rich distribution for health outcomes[105] consistent with our study findings. Another study found that publicly financing interventions for maternal child health in Nigeria had a pro-poor distribution for health and financial benefits [103]. Other studies from

Ethiopia and India also found that public financing for rotavirus vaccine [102] and tuberculosis treatment [96]would provide financial protection especially for the poorer wealth quintiles. These results collectively reinforce the case that publicly financing high-burden health services not only improves health outcomes but also enhances equity by alleviating catastrophic expenditures among the most vulnerable.

Our findings have some policy implications for breast cancer control in South Africa. Our analysis has demonstrated the need to publicly finance early detection and screening interventions for breast cancer to alleviate a considerable proportion of breast cancer burden and catastrophic health expenditures benefiting the poorest wealth quintiles. Therefore, to improve financial protection among the poorer wealth quintiles, the government should considerably expand existing social protection schemes for the poorest wealth quintiles as they are most susceptible to health and financial risks of seeking breast cancer control services. Additionally, while investing in breast cancer control will go a long way in reducing catastrophic health expenditures, it will not be sufficient to eliminate catastrophic expenditures due to the indirect costs associated with breast cancer. Future research therefore should estimate the distributional impact of government covering the full societal cost of breast cancer in South Africa and assess other social protection strategies required to substantially reduce catastrophic health expenditures.

Our study has limitations worth noting. Firstly, our study assigned wealth quintiles at the start of the projection period, and we assumed that an individual’s income did not vary through the projection period of 40 years, and this might not be the case as the economic status of a household might change overtime. However, given that we utilized a relative rather than absolute measures of socioeconomic measures, we controlled for the assumption that as absolute factors change, for instance salaries for some households, relative conditions would averagely remain the same. Additionally, we did not vary incidence and other critical parameters, such as non–breast cancer mortality by income quintile, and we acknowledge the importance of incorporating these differences into the model. However, due to data constraints, these variations were not included in the current analysis. Future work should aim to integrate more comprehensive data to capture the full spectrum of socioeconomic disparities in health outcomes. Secondly, our analysis focused on the South Africa setting and therefore our findings might not be generalizable to other contexts with different demographic, epidemiological, and economic characteristics. Thirdly, the analysis did not utilize patient-level data, as such, the analysis relied heavily on aggregated datasets, secondary sources, and model-based assumptions and these assumptions may not fully reflect intra-group variation or the nuanced realities for South Africa. Although national and regional data were employed to stratify outcomes by income quintile, the absence of individual-level information constrained the ability to precisely estimate health and financial protection outcomes across different socioeconomic strata. This limitation highlights the importance of future studies incorporating patient-level data to strengthen model accuracy, allow for more refined subgroup analyses, and reduce uncertainty particularly in low- and middle-income countries, where equity considerations are paramount. Additionally, we acknowledge that publicly financing breast cancer interventions from the providers perspective might not automatically warrant an increase in actual service use due to high non-medical costs associated with long term illnesses such as cancer [89], [90]. Furthermore, our model did not vary the direct medical costs by wealth quintile due to limited disaggregated data and their omission likely underestimates the total financial burden especially for the lower wealth quintiles. Future research should stratify costs by income quintiles and include both direct and indirect costs. Fourth, we have only estimated financial protection using catastrophic health expenditure metric leaving out other financial protection metrices such as impoverishment due to out-of-pocket expenditure. We considered catastrophic expenditure due to its widespread use for similar analyses [96], [103], [104]. Furthermore, due to lack of disaggregated empirical data, we used general out-of-pocket expenditure indicators that were not breast cancer specific. Fifth, due to the nature of available data sources, this analysis draws on studies and national surveys that use either wealth or income measures. As a result, in some instances, the terms were used interchangeably without fully preserving this distinction. This may introduce interpretive limitations, particularly when assessing gradients in access or protection across socioeconomic strata. We therefore urge caution in interpreting cross-study comparisons or stratified outcomes. Where feasible, future work should prioritize harmonizing socioeconomic metrics or explicitly modeling both dimensions to capture their unique contributions to health inequities.

Despite these limitations, our study has notable strengths, firstly, this analysis contributes to the very limited evidence base on the distributional impact of breast cancer interventions for the sub-Saharan African region. To the best of our knowledge, this is the first study to assess the distributional health and financial impact of publicly financing breast cancer control interventions in South Africa using the extended cost-effectiveness analysis approach. Complementary analyses such as this to assess equity and financial protection aspects of policies improves evidence driven priority setting for decision makers. Secondly, to arrive at the South Africa estimates for this study, we relied on a dynamic model that showed face validity confirmed by an expert panel.

In conclusion our analysis incorporates equity and financial protection considerations into the traditional economic evaluation for breast cancer control interventions in South Africa. The results show that a policy to publicly finance breast cancer interventions in South Africa has the potential to increase health benefits across all wealth quintiles and improve financial protection disproportionately benefiting the poorer wealth quintiles. As South Africa continues to grapple with high breast cancer mortality and late-stage presentation of patients, policy makers should consider public financing of breast cancer control interventions with reinforced pro-poor targeting using existing policies and structures such as the National Health Insurance. Future research should estimate the distributional impact of government covering the full societal cost of breast cancer in South Africa and assess other social protection strategies required to substantially reduce catastrophic health expenditures.

CHAPTER

8

"Not that I have already attained, or am already perfected; but I press on, that I may lay hold of that for which Christ Jesus has also laid hold of me" Philippians 3:12

Chapter 8: Universal Public Finance for Early Detection, Screening, and Breast Cancer Control Interventions in Uganda: An Extended Cost Effectiveness Analysis

Background
The 2022 Uganda Demographic Health Survey reveals a significant disparity in service access, with women in the wealthiest quintile three times more likely to receive breast cancer services than those in the poorest quintile. If such unfair distribution of service utilization is not addressed, health inequalities will be further perpetuated and entrenched leaving the poorer households behind in accessing breast cancer services and in the attainment of Universal Health Coverage. A potential solution to address these disparities and improve financial risk protection is through enhanced and expanded universal public finance for breast cancer services.

Methods
We conducted an extended cost effectiveness analysis (ECEA) to quantify the distributional consequences of publicly financing early detection and breast cancer control interventions across socioeconomic strata in Uganda along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through catastrophic health expenditure cases averted.

Results
Our study found that a policy to publicly finance early detection, screening and breast cancer control interventions in Uganda has a pro-rich distribution for health outcomes and a pro-poor distribution for financial protection outcomes. Our analysis shows that 55% of the deaths averted are concentrated in the wealthiest two quintiles while the poorest two quintiles would account for 26% of the total deaths averted. Concerning healthy life years gained, we report 33% of the healthy life years gained would be concentrated among the wealthiest quintile while the poorest quintile would account for 11% of the total healthy life years gained. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $29.2 million over the 40-years, this translates to US$729,098 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the lowest three wealth quintiles accounting for 63% of the catastrophic cases averted while the richest two quintiles account for 37% of the cases of catastrophic expenditures averted.

Conclusion
Our analysis shows that a policy to publicly finance breast cancer interventions in Uganda has the potential to increase health benefits and improve financial protection to Ugandan households. This would contribute to reducing socioeconomic inequalities given that the financial protection benefits would accrue preferentially to the poorest wealth quintiles in Uganda. As the country continues to grapple with high breast cancer mortality and late-stage presentation of patients, policy makers should consider public financing of breast cancer control interventions with specific targeting to the poorer households.

8.1 Background

In Uganda, breast cancer is the second most diagnosed female cancer after cervical cancer, with an estimated age-standardized incidence and mortality rate of 21.3/100,000 and 10.3/100,000 respectively [6]. These high mortality rates can be interpreted as almost half of Ugandan women diagnosed with breast cancer die from the disease. This high mortality rate is predominantly attributed to late-stage diagnosis of the disease: up to 89% of the women with breast cancer in Uganda present with stage III or IV [107].

Breast cancer is a high-cost illness that has been a high-ranking cause of catastrophic health expenditures, which can push households into poverty [89], [90], [91]. Moreover, in most LMICs such as Uganda where health insurance is out of reach for many households, cancer healthcare is paid for largely through out-of-pocket payments [92]. Despite the removal of user fees over two decades ago, the latest National Health Accounts shows that out-of-pocket expenditures are still very prevalent accounting for 28% of total health expenditure for 2020/21 [156]. As a result, the incidence of catastrophic health expenditures defined as 10% of household expenditure on health care was 11.9% in 2019/20, and this translates to approximately 1.06 million households [157]. Furthermore, large socioeconomic inequalities exist in utilization of breast cancer services in Uganda. The 2022 Uganda Demographic Health Survey reveals a significant disparity in service access, with women in the wealthiest quintile three times more likely to receive breast cancer services than those in the poorest quintile [158]. If such unfair distribution of service utilization is not addressed, health inequalities will be further perpetuated and entrenched leaving the poorer households behind in accessing breast cancer services and in the attainment of Universal Health Coverage.

A potential solution to address these disparities and improve financial risk protection is through enhanced and expanded universal public finance for breast cancer services. Universal Public Financing is a financing option which implies that the government finances an intervention irrespective of who delivers or receives the services [88]. The heuristic power of universal public finance lies in its ability to (a) increase coverage and access to the poor population groups thus increasing health gains, (b) reduce a household's expenditure on health care and this provides some form of insurance to cover households against financial ruin or impoverishment and (c) potential positive financial consequences like cost savings resulting from crowding out of private expenditure on the health intervention [96]. This is also in line with the holistic move toward universal health coverage.

The extended cost-effectiveness analysis (ECEA) method can be used to evaluate equity and financial protection consequences of publicly financing a health intervention [97]. Despite the importance of considering financial risk protection and equity aspects when conducting economic evaluations, a paucity of research has done so using the ECEA method in low and middle-income countries [96], [102], [103], [104], [105], [106]. This study aims to estimate the extended cost effectiveness analysis of publicly financing early detection and screening interventions for breast cancer control in Uganda.

8.2 Methods

In this analysis, we assume a public financing policy for breast cancer control interventions as a critical tool to move towards universal health coverage. We conducted an extended cost effectiveness analysis (ECEA) of a policy to publicly finance early detection and breast cancer control interventions in Uganda. The ECEA has been described elsewhere in great details and applied in various low- and middle-income countries [97]. Extended Cost Effectiveness Analysis augments the traditional cost effectiveness analysis method by considering non-health benefits such as financial protection and equity by quantifying: 1) the distribution of health benefits across wealth strata, 2) the cases of catastrophic health expenditure averted by a policy and 3) the financial protection provided by a policy[97]. In this analysis, we quantify the distributional consequences of early detection and breast cancer control interventions across socioeconomic strata in Uganda along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through catastrophic health expenditures averted. In other words, this analysis set out to answer the question, "*Which wealth quintile benefits the most (health gains) and averts the most catastrophic health expenditures due to publicly financing the different early detection and breast cancer control interventions in Uganda? Is it the rich or the poor*?"

Our population of interest were women with breast cancer in Uganda. The annual incidence (women diagnosed with breast cancer) was determined using age specific incidence from 2022, from the IARC Globocan Today database [7]. The operational definitions and intervention packages considered in this analysis have been presented in Chapters 6 of this thesis. The approach to the extended cost effectiveness analysis used in this chapter has been described in Chapter 7 above.

Description of the Baseline Vs universal public financing scenario

large socioeconomic inequalities exist in utilization of breast cancer services in Uganda. The 2022 Uganda Demographic Health Survey reveals a significant disparity in service access, with women in the wealthiest quintile three times more likely to receive breast cancer services than those in the poorest quintile [158]. In Uganda there is low screening uptake (baseline coverage for MMG is 0.02%, CBE is 10% and awareness raising is 10%) and many face financial barriers as they seek breast cancer services with catastrophic health expenditure estimated at 7% in the poorest wealth quintile and 16% in the richest wealth quintile. The baseline utilization coverage for breast cancer services is 11% in the poorest wealth quintile versus 33% in the wealthiest income quintile. We utilized a uniform baseline across all quintiles of 20 per 100,000, however, some evidence suggests that wealthier quintiles have higher incidence [155], [156], [157], [158], and this limitation was accounted for through performing a sensitivity analysis described in section 8.2.2.

Under universal public financing (UPF) scenario, we assume these disparities are eliminated: the policy finances screening and treatment for all, so effectively all quintiles get equal coverage of screening (we modeled 100% of target women screened across all quintiles) and equal access to treatment (assumed 100% across quintiles). However, given the assumption that the wealthier quintiles have higher access and higher incidence of breast cancer, they are likely to have more absolute health gains.

8.2.1 Estimation of Outcomes

The projections for health outcomes (deaths averted and healthy life years gained) of breast cancer control interventions were provided by the dynamic state transition model for Uganda described in detail in Chapter 6 of this thesis. To estimate the cases of catastrophic health expenditures averted, we used the total costs estimated by the dynamic model for Uganda (Chapter 6) and multiplied these costs by the current out-of-pocket expenditure ratio (28%) in Uganda [156]. We defined catastrophic health expenditure as private expenditure on health that exceeded 10% of the household's income after subsistence needs have been met [152]. We then quantified the total expenditures on breast cancer control that could lead to catastrophic health expenditures that exceed the 10% threshold. Basing on the 10% income threshold (Th), a case of catastrophic health expenditure is realized when the cost, c, of breast cancer control interventions is greater than the income threshold. In other words:

$$c > y * Th \quad \text{Equation 8}$$

Therefore, the financial risk protection afforded by publicly financing breast cancer control interventions corresponded to the total catastrophic health expenditures averted owing to a reduction in the incidence of private expenditures on breast cancer disease. This corresponds to a direct comparison of the number of cases of catastrophic health costs averted due to the decision to publicly finance breast cancer control interventions.

Description of Parameters Used for the ECEA

Table 34 provides a list of the all the parameters that were considered for the extended cost effectiveness analysis for Uganda. As with the South Africa model, parameters held constant across quintiles include disease incidence, age-specific mortality, disability weights, and treatment efficacy. Parameters that vary by income and thus drive the distributional outcomes include:

- **Breast cancer service utilization coverage:** ranges from very low in the poorest quintile to moderate in the richest under the no-UPF scenario, equalized to 100 % under UPF.
- **Out-of-pocket expenditure (OOP):** highest among poorer quintiles and zero under UPF.
- **Average individual income:** defines the denominator for calculating catastrophic health expenditure (CHE) incidence.

These parameters feed into the conceptual model as follows: incidence determines case load; coverage and stage distribution affect early detection; treatment access and OOP define mortality and financial protection outcomes; and household income calibrates the CHE threshold.

Table 34: Parameters for Extended Cost Effectiveness Analysis for Uganda

Parameter	Symbol / Value (Q1–Q5)	Units / Notes	Source / Reference
Income parameters			
Individual income (average per quintile)	Q1: UGX 350 000 Q2: UGX 720 000 Q3: UGX 1 300 000 Q4: UGX 2 400 000 Q5: UGX 5 100 000	Annual household income (≈ USD 95–1 400)	[153]
Income distribution *f(y)*	Fitted to quintile means above	Continuous income function used in CHE calculation	[153]

Income threshold (Th) for CHE	10 % of annual household income	CHE defined as OOP > 10 % of income	[152]
Disease and program parameters			
Baseline breast-cancer incidence	31.14 per 100 000 women	Uniform across quintiles (base case)	GLOBOCAN 2022
Relative-risk multiplier (scenario analysis)	1.00, 1.10, 1.20, 1.30, 1.30	Applied only in SES-gradient scenario	Assumed (Refs 152–155)
Total program and treatment costs (c)	From Table 24 (Chapter 8)	Includes early detection, screening, treatment, palliative care costs	Thesis data
Deaths averted (D)	From Table 26 (Chapter 8)	Model output per scenario	Thesis data
Healthy life years gained (hLY)	From Table 26 (Chapter 8)	Model output per scenario	Thesis data
Access, coverage and utilization parameters			
Breast-cancer service utilization / coverage *u(y)*	5 %, 8 %, 12 %, 15 %, 20 % (Q1–Q5)	Reflects differential uptake by income quintile	[56] and national survey estimates
Baseline coverage – CBE	10 %	Low organized coverage across all quintiles (base case)	[56]
Baseline coverage – awareness raising	5 %	Reflects sporadic campaigns in urban areas	[56]
Baseline coverage – MMG	5 %	Limited availability in urban tertiary facilities	[56]
Financial protection parameters			
Catastrophic health expenditure (CHE) rate by quintile	55 %, 38 %, 25 %, 12 %, 5 % (Q1–Q5)	Baseline proportion of households facing CHE	Table 35, Ch. 8
OOP share of total cost (baseline)	85 %, 70 %, 60 %, 45 %, 30 % (Q1–Q5)	Estimated share of health cost borne out-of-pocket	Derived from Table 35
OOP share under UPF	0 % (all quintiles)	Reflects universal public financing scenario	Assumed (policy scenario)

It is important to note that unlike Chapters 4 to 6, which modelled idealized implementation scenarios assuming 100% screening coverage and 100% treatment uptake for all diagnosed cases, the analysis in this chapter incorporates income-based variation in access and utilization of breast cancer services. This was done to better reflect real-world inequities in care access and to quantify the potential health and financial protection gains of universal public financing. For the analysis presented in this chapter, we model the distributional consequences of publicly financing breast cancer interventions, and as such, incorporates variation in access and utilization of breast cancer services by income quintile. This approach relaxes the 100% treatment assumption used in earlier chapters, particularly for the ante universal public financing scenario, where utilization of breast cancer services varies by socioeconomic status. The universal public financing scenario, on the other hand, assumed equal access to treatment across all income groups, reflecting an equity-oriented financing reform.

8.2.2 Sensitivity Analysis

To address the limitation of utilizing uniform baseline incidence rate across wealth quintiles, we performed a scenario analysis on income-stratified breast cancer incidence by varying the assumed incidence rates by income group (using Equation 14) to test how sensitive the distributional outcomes are:

$$i_q = i_{base}\ x\ RR\_q \quad \textit{Equation 9}$$

Where:

- i_q: Incidence rate (per 100,000 women) for wealth quintile q (Q1–Q5, poorest to richest).
- i_{base}: Baseline incidence, 20 per 100,000 women (GLOBOCAN 2022).
- RR_q: Relative risk multiplier, set at 1.0, 1.05, 1.10, 1.15, 1.15 for Q1–Q5, with PSA ranges [1.0–1.0], [1.0–1.07], [1.05–1.12], [1.10–1.18], [1.12–1.20], based on higher incidence in wealthier quintiles [155], [156], [157], [158].

It is important to note that the parameters involved in the scenario analysis were essentially the relative risk multipliers for incidence in each quintile (Q1–Q5) and their ranges, which were used to simulate 1,000 runs (e.g., Relative Risk = 1.0 in Q1 up to 1.15 in Q5, with ranges as given in Equation 7, and no other model parameters were stochastically varied.

8.3 Results

8.3.1 Distribution of Deaths Averted

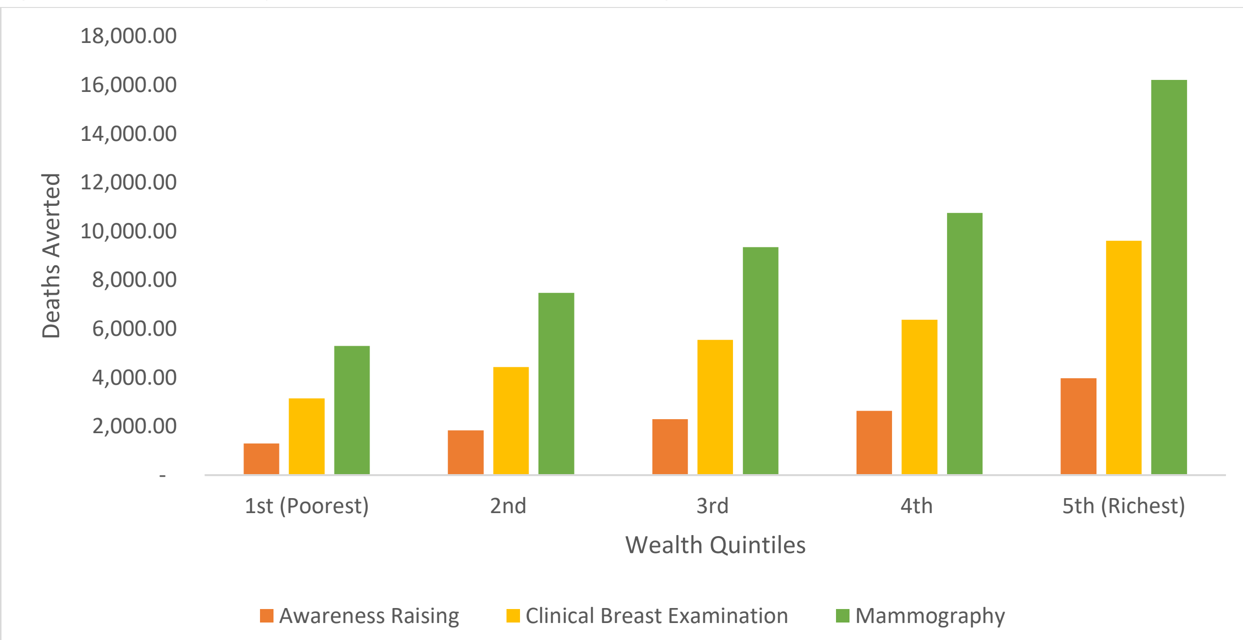
From our analysis, we note that the distribution of breast cancer deaths averted over the 40-year period is pro-rich benefiting the richer population, with 55% of the deaths averted in the wealthiest two quintiles while the poorest two quintiles would account for 26% of the total deaths averted.

Overall, the distribution of deaths averted across the different early detection and screening interventions is pro-rich with the deaths averted in the wealthiest quintile being higher than those in the poorest quintile by three (3) times.

Table 35: Distribution of Breast Cancer Deaths Averted in Uganda

	Number of Deaths Averted					
	Quintiles					
	1st (Poorest)	2nd	3rd	4th	5th (Richest)	Total (National)
Awareness Raising	1,299	1,834	2,293	2,637	3,974	12,039
Clinical Breast Examination	3,143	4,437	5,547	6,379	9,614	29,122
Mammography	5,298	7,479	9,349	10,752	16,206	49,087
Total	9,741	13,752	17,190	19,768	29,796	90,248

Figure 18: Distribution of Breast Cancer Deaths Averted in Uganda



Across all wealth quintiles, Mammography services would avert the greatest number of deaths, accounting for 54% of all deaths averted and 33% of these averted deaths are concentrated among the richest wealth quintile alone. Clinical Breast Examination averts 32% of the total deaths with the three top wealth quintiles benefiting the most. Awareness raising interventions account for 13% of all the total deaths averted and this also follows a pro-rich distribution.

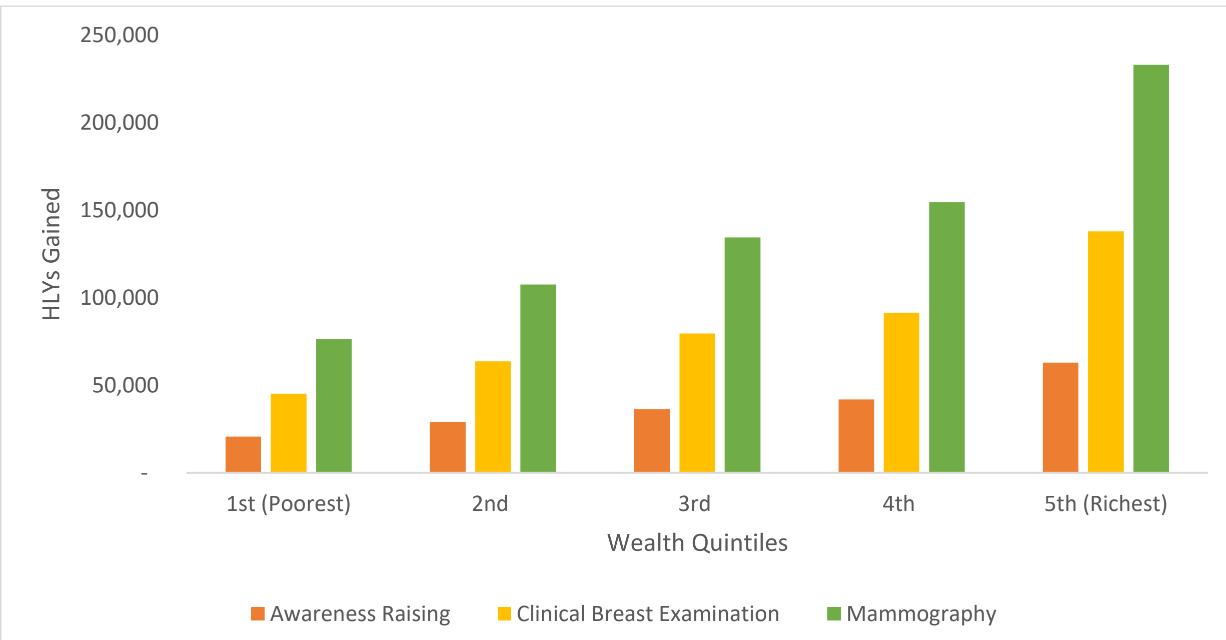
8.3.2 Distribution of Healthy Life Years Gained

Our analysis shows that the distribution of healthy life years gained also follows a pro-rich trend over the 40-year period benefiting the richer population, with 33% of the healthy life years gained concentrated among the wealthiest quintile while the poorest quintile accounts for 11% of the total healthy life years gained.

Table 36: Distribution of Breast Cancer Healthy Life Years Gained in Uganda

	Healthy Life-Years Gained					
	Quintiles					
	1st (Poorest)	2nd	3rd	4th	5th (Richest)	Total (National)
Awareness Raising	20,591	29,070	36,338	41,788	62,985	190,773
Clinical Breast Examination	45,106	63,680	79,599	91,539	137,972	417,897
Mammography	76,190	107,563	134,453	154,621	233,052	705,879
Total	141,888	200,312	250,390	287,949	434,010	1,314,549

Figure 19: Distribution of Healthy Life Years Gained in Uganda



As is the case with deaths averted, mammography offers the highest number of healthy life years gained across all the wealth quintiles followed by Clinical Breast Examination and awareness raising interventions offer the least healthy life years gained across all quintiles.

8.3.3 Catastrophic Health Expenditure Cases and Incidence by Wealth Quintile

Our analysis shows that breast cancer control interventions could avert approximately US $29.2 million over the 40-years, this translates to US $729,098 annually. The analysis comparing catastrophic health expenditure (CHE) before and after the implementation of universal public financing (UPF) reveals a significant overall reduction in financial hardship across all wealth quintiles. Prior to UPF, an estimated 24,510 CHE cases were recorded, with the burden distributed across both poor and wealthy households most notably within the bottom three quintiles, which together accounted for over 63% of all the CHE cases. Following the introduction of UPF, approximately 15,779 CHE cases were averted, reflecting a 64% reduction. Unlike the South African scenario, where the benefits were heavily pro-poor, the financial protection gains for Uganda were more evenly distributed, with each of the bottom four quintiles contributing between 19% and 22% of total averted CHE cases. Regarding CHE incidence, our analysis shows that in Uganda, approximately 28 % of households with a breast cancer case faced catastrophic health expenditures under the status quo, compared to less than 4 % under UPF.

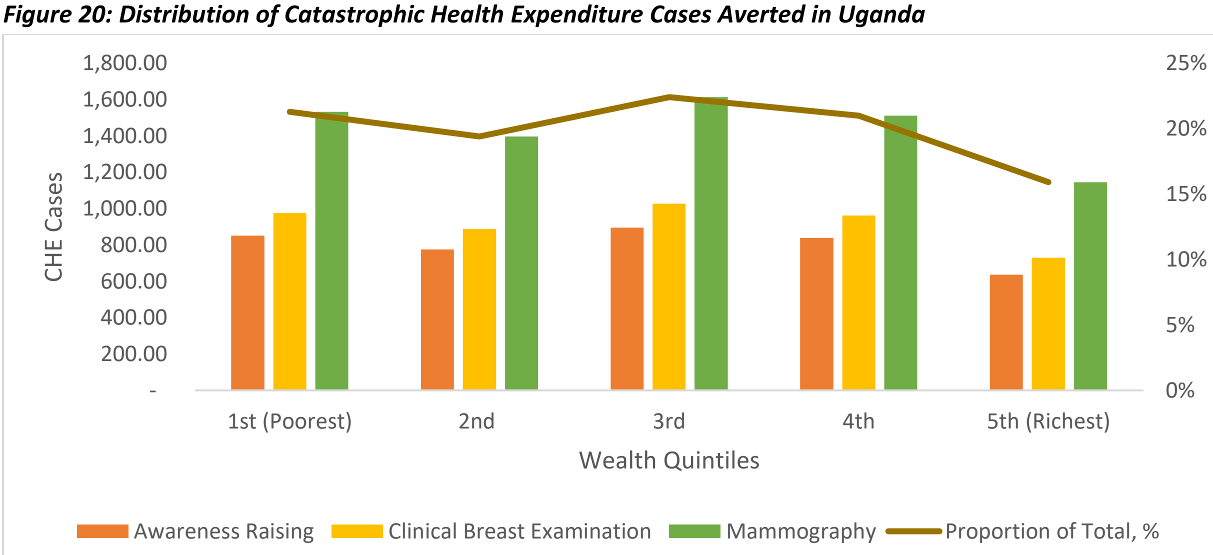
Table 37: Catastrophic Health Expenditure Cases and Incidence by Wealth Quintiles in Uganda

Wealth Quintile	Awareness Raising	Clinical Breast Examination (CBE)	MMG	Total CHE Cases (no UPF)	Proportion of Total (%)	CHE Incidence (no UPF)	CHE Cases Averted (after UPF)	CHE Incidence (after UPF)	Total CHE Expenditure Averted (USD)
1st (Poorest)	1,380	2,020	2,940	6,340	25.8	55 %	3,360.29	10 %	6,210,574
2nd	1,260	2,030	2,840	6,130	25.0	38 %	3,060.26	6 %	5,656,059
3rd	890	2,050	2,540	5,480	22.4	25 %	3,536.30	4 %	6,535,890
4th	910	1,150	1,780	3,840	15.7	12 %	3,311.59	2 %	6,120,566
5th (Richest)	650	810	1,260	2,720	11.1	5 %	2,510.98	1 %	4,640,869
Total	5,090	8,060	11,360	24,510	100.0	~27.8 % overall	15,779.43	~4 % overall	29,163,958

***CHE incidence** refers to the proportion of households incurring catastrophic health expenditure (>10 % of annual income) due to breast cancer care*

The analysis further shows that publicly investing in mammography led screening interventions would avert 58% of the catastrophic health expenditure. Awareness raising, and clinical breast examination interventions would avert 18% and 24% of the catastrophic health expenditures respectively.

Figure 20: Distribution of Catastrophic Health Expenditure Cases Averted in Uganda



8.3.4 Sensitivity Analysis Results

The sensitivity analysis demonstrates that the estimated number of cases of catastrophic health expenditure (CHE) averted by breast cancer interventions is moderately sensitive to variations in baseline breast cancer incidence across wealth quintiles. Under the base case scenario, approximately 15,779 cases of CHE are averted. When applying incidence-based sensitivity adjustments, this figure increases to 16,817 cases. The uncertainty interval analysis suggests that the number of CHE cases averted could range between 15,873 and 17,608. Notably, the impact of rising incidence is more pronounced among higher wealth quintiles (Q4 and Q5), indicating that if incidence increases disproportionately in wealthier populations, the absolute number of CHEs averted could increase substantially.

Table 38: Cases of CHE averted with varying Breast Cancer Incidecne by Wealth Quintile in Uganda

Quintile	Baseline Incidence (20 per 100,000)	Sensitivity Analysis (Mean)	Sensitivity Analysis (95% UI)	Baseline of CHE averted (with UPF)	Range of CHE Cases Averted
Q1 (Poorest)	5.0	5.0	4.9–5.2	3,360.29	3,289.08 – 3,494.70
Q2	5.0	5.2	4.8–5.4	3,060.26	2,939.05 – 3,306.68
Q3	5.0	5.4	5.0–5.6	3,536.30	3,536.30 – 3,951.46
Q4	5.0	5.5	5.2–5.8	3,311.59	3,446.28 – 3,841.65
Q5 (Richest)	5.0	5.6	5.3–6.0	2,510.98	2,662.37 – 3,013.18
Total	25.0	26.2	25.2–27.0	15,779.43	15,873.08 – 17,607.67

UI = Uncertainty Interval

8.4 Discussion

We assessed the extended cost-effectiveness of three early detection and screening interventions for breast cancer control in Uganda. Our study found that a policy to publicly finance early detection, screening and breast cancer control interventions in Uganda has a pro-rich distribution for health outcomes and a pro-poor distribution for financial protection outcomes. Our analysis shows that 55% of the deaths averted in the wealthiest two quintiles while the poorest two quintiles would account for 26% of the total deaths averted. Concerning healthy life years gained, we report 33% of the healthy life years gained would be concentrated among the wealthiest quintile while the poorest quintile would account for 11% of the total healthy life years gained. While our finding for a pro-rich distribution for the health outcomes is counter intuitive to the expectation that publicly financing an intervention should primarily benefit the poorer wealth quintiles, our findings are consistent with the evidence in Uganda, where large socioeconomic inequalities exist in utilization of breast cancer services. The 2022 Uganda Demographic Health Survey shows a disproportionately pro-rich distribution in the number of women who received breast services in the wealthiest quintile as three (3) times higher than the women in the poorest wealth quintile [158]. A benefit incidence analysis also showed that the distribution of total health sector service benefits follows a pro-rich distribution, with the rich accounting for a higher share of benefits relative to their need [160], [161]. As such, it is logical to attribute the pro-rich distribution reported by our analysis, at least in part, to higher consumption among richer households, with potentially demand suppression by the poor, who generally have higher health needs but with very limited ability to pay. It is important to note that while our analysis indicates a pro-rich distribution, it possibly points to unmet need and demand suppression among the poorer wealth quintiles.

Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $29.2 million of health expenditures over the 40-years, this translates to US$729,098 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the lowest three wealth quintiles accounting for 63% of the catastrophic cases averted while the richest two quintiles account for 37% of the cases of catastrophic expenditures averted.

Our results are corroborated by findings from other evaluations suggesting that publicly financed health interventions can play a pivotal role in enhancing equity and advancing the goals of universal health coverage. For instance, a study from Vietnam evaluating cataract surgery found a greater concentration of health benefits among the wealthier segments of the population, whereas financial protection gains were more substantial among poorer households [155]. This duality reflects the pattern observed in our own study, where public financing of breast cancer screening led to wider financial protection for the most economically vulnerable, even in the context of persistent inequities in health system utilization. Another study from South Africa on the distributional impact of taxing sugar-sweetened beverages on diabetes reported a pro-rich distribution for health outcomes underscoring how intervention type and behavioral factors can influence distributional outcomes [105]. Verguet et al. 2017 further showed that scaled-up tuberculosis treatment in South Africa and India could meaningfully reduce catastrophic expenditures over time, particularly for poorer households, albeit with delayed benefits emerging over a 5–10-year horizon[104]. Furthermore, the equity benefits of publicly financed vaccination programs have been observed in multiple LMIC contexts. In Malaysia, a study found that public financing for vaccination against rotavirus would provide financial protection across all quintiles [106]. Additionally, consistent with our findings, several studies have reported a pro-poor distribution for financial protection due to publicly financing public health interventions for maternal and child health interventions in Nigeria [103], for rotavirus vaccination in Ethiopia [102] and tuberculosis treatment in India[96] where ECEAs of rotavirus and tuberculosis interventions found that removing out-of-pocket payments significantly reduced the economic burden on poorer households.

Our findings have some policy implications for breast cancer control in Uganda. Our study shows that publicly financing early detection and screening interventions is vital for reducing poor health outcomes and financial burden favoring the poorer wealth quintiles therefore having the potential to improve financial protection among the poor and vulnerable. As such, the government should consider expanding universal public financing for breast cancer with a targeting mechanism to address the unmet need and underuse of services among the poorer wealth quintiles. Targeting would maximize the financial protection benefits among the poorest wealth quintiles who stand to benefit the most. Additionally, the health and financial protection indicators would have a stronger pro-poor distribution. In practice, the targeting mechanism could be implemented geographically prioritizing the poorer households in the rural areas. However, for such geographical targeting to be successful, the previous challenges that have plagued free access to health services at the point of care must first be addressed.

Furthermore, the country needs to track and assess service utilization patterns on a regular basis to identify and address underlying drivers of underuse or overuse of prioritized services such that disparities are not inadvertently further reinforced. Additionally, while investing in breast cancer control will go a long way in reducing catastrophic health expenditures, it will not be sufficient to eliminate catastrophic expenditures due to the indirect costs associated with breast cancer services. Future research should estimate the distributional impact of government covering the full societal cost of breast cancer in Uganda and assess other social protection strategies required to substantially reduce catastrophic health expenditures. Further, we report a pro-rich distribution for health outcomes and a pro-poor distribution for financial protection outcomes, and this points to a trade-off associated with interventions designed to improve financial protection without initially putting in place mechanisms to address barriers to access. Future research should assess this trade-off further and devise plans to maximize health and financial protection benefits for the vulnerable population.

Our study has limitations worth noting. Firstly, our study assigned wealth quintiles at the start of the projection period, and we assumed that an individual's income did not vary through the projection period of 40 years, and this might not be the case as the economic status of a household might change overtime. However, given that we utilized a relative rather than absolute measures of socioeconomic measures, we controlled for the assumption that as absolute factors change, for instance salaries for some households, relative conditions would averagely remain the same. Furthermore, we did not vary incidence and other critical parameters, such as non–breast cancer mortality by income quintile, and we acknowledge the importance of incorporating these differences into the model. However, due to data constraints, these variations were not included in the current analysis. A sensitivity analysis was performed to assess for robustness in the results with varying incidence by wealth quintiles. Future work should aim to integrate more comprehensive data to capture the full spectrum of socioeconomic disparities in health outcomes. Secondly, our analysis focused on the Ugandan setting and therefore our findings might not be generalizable to other contexts with different demographic, epidemiological, and economic characteristics. Thirdly, the analysis did not utilize patient-level data, as such, the analysis relied heavily on aggregated datasets, secondary sources, and model-based assumptions and these assumptions may not fully reflect intra-group variation or the nuanced realities for Uganda. Although national and regional data were employed to stratify outcomes by income quintile, the absence of individual-level information constrained the ability to precisely estimate health and financial protection outcomes across different socioeconomic strata. This limitation highlights the importance of future studies incorporating patient-level data to strengthen model accuracy, allow for more refined subgroup analyses, and reduce uncertainty particularly in low- and middle-income countries, where equity considerations are paramount. Furthermore, we acknowledge that publicly financing breast cancer interventions from the providers perspective might not automatically warrant an increase in actual service use due to high non-medical costs associated with long term terminal illnesses such as cancer. Additionally, our model did not vary the direct medical costs by wealth quintile due to limited disaggregated data and their omission likely underestimates the total financial burden especially for the lower wealth quintiles. Future research should stratify costs by income quintiles and include both direct and indirect costs. Fourth, we have only estimated financial protection using catastrophic health expenditure metric leaving out other financial protection metrices such as impoverishment due to out-of-pocket expenditure. We considered catastrophic expenditure due to its widespread use for similar analyses. [96], [103], [104]. Furthermore, due to lack of disaggregated empirical data, we used general out-of-pocket expenditure indicators that were not breast cancer specific.

Despite these limitations, our study has notable strengths, firstly, this analysis contributes to the anecdotal literature on the economics of breast cancer control for the sub-Saharan African region. To the best of our knowledge, this is the first study to assess the distributional health and financial impact of publicly financing breast cancer control interventions in Uganda using the extended cost-effectiveness analysis approach. Secondly, to arrive at Ugandan estimates for this study, we relied on a dynamic model that showed face validity confirmed by an expert panel.

In summary, our analysis incorporates equity and financial protection considerations into the traditional economic evaluation for breast cancer control interventions in Uganda. Our analysis shows that a policy to publicly finance breast cancer interventions in Uganda has the potential to increase health benefits and improve financial protection to Ugandan households. This would contribute to reducing socioeconomic inequalities given that the financial protection benefits would accrue preferentially to the poorest wealth quintiles in Uganda. As the country continues to grapple with high breast cancer mortality and late-stage presentation of patients, policy makers should consider public financing of breast cancer control interventions with specific targeting to the poorer households. Future research should estimate the distributional impact of government covering the full societal cost of breast cancer in Uganda and assess other social protection strategies required to substantially reduce catastrophic health expenditures.

CHAPTER 9

"Until the spirit is poured upon us from on high, and the wilderness becomes a fruitful filed, and the fruitful field is counted as a forest" Isaiah 32:15

Chapter 9: Discussion and Conclusion

9.1 Synthesis of Thesis Findings

Given the growing burden of breast cancer in Low- and Middle-Income Countries (LMICs), these countries now face the challenge of effectively detecting and treating a disease that was previously considered too uncommon to merit the allocation of finite health care resources. Early detection of breast cancer pertains to early diagnosis of breast cancer in symptomatic patients[20]. Key prerequisites for early detection are ensuring that women are supported in seeking care and that they have access to appropriate, affordable diagnostic tests, and treatment[50].

As such, in LMICs there is a need for early detection and screening strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor. While several breast cancer early detection methods and tools exist, they are largely unavailable in many LMICs due to resource constraints[15]. Furthermore, due to constrained fiscal space for health in LMICs, the quantification of potential down-staging for breast cancer diagnosis has implications for policy and pragmatic planning. Now more than ever, there is a need to optimally utilize available resources to benefit the largest proportion of the population.

It is therefore critical to understand the costs, effectiveness, and distributional impact of using public resources for early detection, screening methods, and subsequent treatment of breast cancer in LMICs. This study focused on the economics of breast cancer detection, screening, and treatment in one low-income country (Uganda) and one middle-income country (South Africa).

9.1.1 Aims of the Research

Chapter 1 of this thesis provided an overview of the aims and objectives of this thesis based on the approved protocol for this doctoral research. The overarching aim of this study was to assess the cost effectiveness and distributional impact of publicly financing interventions for early detection, screening, and breast cancer control on the health system in Uganda and South Africa.

9.1.2 Specific Objectives

The specific objectives of this thesis were to:

5. To estimate the downstaging effect of early detection and screening interventions for breast cancer.
6. To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in South Africa.
7. To estimate the cost effectiveness of early detection, screening, and breast cancer control interventions in Uganda.
8. To quantify the financial and health distributional impacts of publicly financing early detection, screening, and breast cancer control interventions in South Africa and Uganda.

Each of the study objectives builds on the previous, for instance to quantify the distributional consequences of publicly financing breast cancer control interventions, we had to firstly estimate the downstaging effecting and secondly estimate the cost-effectiveness of the breast cancer early detection, screening and control interventions in South Africa and Uganda. Therefore, if each study objective is achieved, then the overarching aim of the study would be achieved.

We accomplished the study aim and objectives by constructing a dynamic state transition model to estimate and predict down-staging of breast cancer associated with early detection and screening strategies. Our model assessed the performance of three early detection and screening interventions (awareness raising campaigns, clinical breast examination, and mammography) and quantified their ability to shift breast cancer cases that would have otherwise been diagnosed as "late stage" to an "earlier stage" at the time of diagnosis. The dynamic model was also used to estimate the costs and effectiveness of the three early detection and screening interventions. Furthermore, we performed an extended cost effectiveness analysis to quantify the distributional consequences of publicly financing early detection and breast cancer control interventions across socioeconomic strata in Uganda and South Africa along three dimensions: (a) number of deaths averted, (b) number of life years gained and (c) financial protection benefits provided through catastrophic health expenditure cases averted.

9.1.3 Summary of Chapter Contents

Detailed discussion and conclusions relevant to each study objective are presented in the five results chapters (4 to 8). The cumulative summary of this thesis is presented in turn:

Predicting down-staging of breast cancer due to early detection and screening strategies
Chapter Four includes a manuscript that has been prepared for submission later in 2025. We constructed a dynamic state transition model to estimate and predict down-staging of breast cancer as result of early detection and screening strategies for breast cancer control. For Uganda, we estimate that the three early detection and screening interventions are associated with a 66% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease for over the period of 40 years. For South Africa, we report a 32% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease over the 40-year period. Awareness raising interventions have similar downstaging effect in both countries (9% in Uganda and 8% in South Africa) while Clinical Breast Examination (CBE) has a stronger effect in Uganda (21%) than in South Africa (9%). In both countries, mammography led screening is reported to have the strongest down-staging effect of 36% in Uganda and 15% in South Africa. Our analysis indicates that early detection and screening interventions have nearly twice the impact in contexts with a high prevalence of late-stage breast cancer presentation, such as Uganda, compared to settings like South Africa, where moderate late-stage presentation.

Cost effectiveness of early detection, screening, and breast cancer control interventions in South Africa
Chapter Five includes a manuscript that has been prepared for submission later in 2025 which presents the results of a cost effectiveness analysis for breast cancer control interventions in South Africa. Over a 40-year time horizon, interventions to raise awareness combined with treatment of all stages, will avert 16,006 deaths incremental to the baseline scenario, and provide 267,635 Healthy Life Years incremental to the baseline scenario. Awareness raising interventions have an 8% down- staging effect translating into an additional 73,719 women presenting with early stage of breast cancer disease. Biennial Clinical

Breast Examination (CBE) coupled with treatment of all stages will avert 34,663 deaths incremental to the baseline scenario and provides 537,816 Healthy Life Years incremental to the baseline scenario. CBE down-staged breast cancer diagnosis by 8% translating into an additional 78,167 women presenting with early stage of breast cancer disease. Our analysis found that mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 57,821 deaths incremental to the baseline scenario and provides 899,450 Healthy Life Years incremental to the baseline scenario over a 40-year time horizon. Mammography led screening down-staged breast cancer diagnosis by 15% translating into an additional 130,487 women presenting with early stage of breast cancer disease. The Average Cost Effectiveness Ratios (ACERs) range from $377 per death averted for awareness raising interventions to $634 per death averted for Mammography. Furthermore, our analysis shows that Biennial CBE coupled with treatment interventions for all stages is cost-effective for South Africa with an ICER of $2,782 per healthy life year gained. Awareness raising interventions were also found to be cost effective with an ICER of 3,204 per health life year gained. Mammography screening combined with treatment for all stages was not found to be a cost-effective intervention for South Africa with an ICER of $8,492 per healthy life year gained.

Cost effectiveness of early detection, screening, and breast cancer control interventions in Uganda
Chapter Six includes a manuscript that has been prepared for submission later in 2025 which presents the results of a cost effectiveness analysis for breast cancer control interventions in Uganda. Over a 40-year time horizon, interventions to raise awareness combined with treatment of all stages, will avert 12,039 incremental deaths, and provide 190,773 incremental Healthy Life Years. Awareness raising interventions have an 8% down-staging staging effect translating into an additional 25,039 women presenting with early stage of breast cancer disease. Biennial Clinical Breast Examination (CBE) coupled with treatment of all stages will avert 29,121 incremental deaths and provide 417,897 incremental Healthy Life Years. CBE down-staged breast cancer diagnosis by 21% translating into an additional 59,832 women presenting with early stage of breast cancer disease. Our analysis found that mammography (MMG) coupled with treatment of all stages was the most effective breast cancer control intervention averting 49,087 incremental deaths and provides 705,879 incremental Healthy Life Years. Mammography led screening down-staged breast cancer diagnosis by 36% translating into an additional 100,849 women presenting with early stage of breast cancer disease. The Average Cost Effectiveness Ratios (ACERs) range from $87 per death averted for basic awareness raising interventions to $234 per death averted for MMG. The most cost-effective intervention for breast cancer control is awareness raising interventions with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $ 416 per healthy life year gained. Biennial MMG screening combined with treatment for all stages was not cost effective with an ICER of $3,110 per healthy life year gained.

Distributional consequences of publicly financing breast cancer control interventions in South Africa
Chapter 7 presents results from an extended cost effectiveness analysis on universal public financing for early detection, screening, and breast cancer control interventions in South Africa. Our results found that a policy to publicly finance early detection, screening and breast cancer control interventions in South Africa has a pro-rich distribution for health outcomes and a strong pro-poor distribution for

financial protection outcomes. Our analysis shows that 44% of the deaths averted are in the wealthiest two quintiles while the poorest two quintiles would account for 34% of the total deaths averted. Concerning healthy life years gained, we report 22% of the healthy life years gained would be concentrated in the wealthiest quintile alone while the poorest quintile would account for 14% of the total healthy life years gained. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $7.89 million over the 40-years, this translates to US $197,254 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the poorest wealth quintile accounting for 76% of the averted catastrophic health expenditure cases, on the other hand, the wealthiest two quintiles account for approximately 1.4% of the catastrophic health expenditure cases averted. These findings demonstrate that universal public finance not only reduces the overall incidence of CHE but also promotes equity by offering greater financial protection to the most vulnerable populations.

Distributional consequences of publicly financing breast cancer control interventions in Uganda

Chapter 8 presents results from an extended cost effectiveness on universal public financing for early detection, screening, and breast cancer control interventions in Uganda. Consistent with the South Africa results, our analysis found that a policy to publicly finance early detection, screening, and breast cancer control interventions in Uganda has a pro-rich distribution for health outcomes and a pro-poor distribution for financial protection outcomes. Our analysis shows that 55% of the deaths averted are concentrated in the wealthiest two quintiles while the poorest two quintiles would account for 26% of the total deaths averted. Concerning healthy life years gained, we report 33% of the healthy life years gained would be concentrated among the wealthiest quintile while the poorest quintile would account for 11% of the total healthy life years gained. Regarding financial protection, our analysis shows that publicly financing breast cancer control interventions could avert approximately US $29.2 million over the 40-years, this translates to US$729,098 annually. The distribution of catastrophic health expenditures averted is pro-poor, with the lowest three wealth quintiles accounting for 63% of the catastrophic cases averted while the richest two quintiles account for 37% of the cases of catastrophic expenditures averted. In contrast to the South African scenario, where the financial protection benefits were strongly pro-poor, Uganda’s financial protection gains are more broadly distributed, with each of the lowest four wealth quintiles accounting for between 19% and 22% of the total catastrophic health expenditure cases averted.

9.2 Generalizability

Broadly, the results from this thesis are generalizable to other low-and-middle-income countries with similarities to South Africa and Uganda to inform pragmatic planning for Breast Cancer control. As described in Chapter 4, the dynamic model constructed for this thesis doesn’t follow the natural history of the underlying breast cancer disease, but rather, it focuses on the observable events in disease progression. This implies that the model can easily be adapted and generalized for use by other countries and contexts given that our model requires fewer inputs and is highly transparent.

The findings from this dissertation are directly applicable and generalizable to the two countries assessed (Uganda and South Africa) as our model and analyses utilized country-specific parameters to the degree possible.

In the absence of empirical investigations such as randomized controlled trials, we believe that the easy-to-use model developed by this thesis can be very useful in generating robust evidence to identify resource-appropriate breast cancer control interventions and to guide the allocation of scare resource in other low-and-middle-income countries.

9.3 Study Limitations

As with any other modelling exercises, this dissertation has limitations worth highlighting. Firstly, our model is not a dynamic simulation of individual patients but is rather based on cohort age-specific parameters. As such, we were not able to model very advanced nuanced scenarios. Nevertheless, it is well established that more advanced individual simulation models require advanced information that is not readily available in most LMICs at the expense of their usefulness for decision makers.

Secondly, our model doesn't account for the harms associated with breast cancer screening (e.g., false positives, and over-diagnosis). Furthermore, it is important to note that an increase in early-stage presentation should be accompanied by appropriate treatment otherwise, the indirect impact of early detection and screening on breast cancer mortality is diminished.

Thirdly, the degree to which breast cancer early detection and screening interventions are beneficial to Uganda and South Africa cannot merely depend on estimated stage-shifting as quantified by our model. Other critical criteria such as affordability (budget impact), value for money, safety, and other political economy concerns should be considered.

Fourthly, for the extended cost effectiveness analysis, assigned wealth quintiles at the start of the projection period, and we assumed that an individual's income did not vary through the projection period of 40 years, and this might not be the case as the economic status of a household might change overtime.

Fifthly, parametrization of the model relied on secondary data sources and global estimates for critical indicators such as case-fatality which may not be reflective of the reality in the two countries studied thus biasing our estimates. Additionally, there is limited information on the effectiveness of awareness raising interventions and therefore our estimates for this scenario should be interpreted cautiously.

Lastly, this thesis considered a provider's perspective, excluding the costs to the patients including their productivity loss. Furthermore, for the extended cost effectiveness analysis, our study did not include non-medical societal costs bore by households such as transportation, which may vary by wealth quintile. We also acknowledge that publicly financing breast cancer interventions from the providers perspective might not automatically warrant an increase in actual service use due to high non-medical costs associated with long term terminal illnesses such as cancer.

9.4 Summary of Thesis Contributions

The overarching objective of this thesis was to assess the cost effectiveness and distributional impact of publicly financing interventions for early detection, screening, and breast cancer control in Uganda and South Africa. To meet this study objective, this thesis answered two distinct research questions:

1) What is the cost-effectiveness of early detection, screening, and breast cancer control interventions in Uganda and South Africa?

2) Which wealth quintile benefit the most (health gains) and averts the most cases of catastrophic health expenditures due to publicly financing the different early detection and breast cancer control interventions in South Africa and Uganda? Is it the rich or the poor?"

To answer these research questions, this thesis first undertook a comprehensive review (chapter two) investigating the literature on the cost-effectiveness of breast cancer control interventions in low- and middle-income countries. The literature review concluded that that early detection and treatment of breast cancer in LMICs was a cost-effective strategy. However, there is a paucity of good quality evidence on the same in the LMICs. Moreover, not a single full economic evaluation comparing various early detection and screening interventions for breast cancer control had been conducted in the Eastern or Southern African countries.

Furthermore, no study (both in the developing and developed countries) has investigated equity and financial protection aspects associated with publicly financing interventions for early detection, screening, and treatment of breast cancer. Thus, this literature review concluded that the overall aim of this thesis remained unanswered. The literature review heighted the following areas as the main priorities for future economic analyses for breast cancer research in LMICs.

- Development of dynamic simulation models to predict shifts in stage distribution of Breast Cancer as a result of implementing early detection and treatment interventions for breast cancer in LMICs.
- Cost analyses for various early detection methods in LMICs and especially in Sub Saharan Africa.
- Full economic evaluations for early detection interventions for breast cancer in LMICs especially in Sub Saharan Africa. These can include cost effectiveness analyses, cost benefit analyses or cost utility analyses.
- Considering the move towards UHC -- investigate the distributional impact on equity and financial protection of publicly financing early detection methods for breast cancer in LMICs.

The study presented in this thesis extends the growing body of evidence on economic models for breast cancer management. The analysis presented in this thesis distinguishes itself by borrowing aspects from the Zelle model[140] by using proportional performance rates and futher aligns with the Birnbaum model [68](by not developing a predictive natural disease model), but unlike Birnbaum who used individual level micro-simulation that requires more granular individual-level data, our model simulated a cohort level population over a 40-year horizon. These methodological strengths better account for demographic transitions, screening coverage trajectories and require less granular data needed by microsimulations. The economic evidence generated by this thesis will go a long way in bridging the gaps highlighted in the evidence by our comprehensive review. In turn is a summary of the contributions made by the 5 result chapters of this thesis to the evidence base on the economics of breast cancer control in LMICs.

Predicting down-staging of breast cancer due to early detection and screening strategies

Chapter 4 of this thesis primarily contributed to the evidence base on the down-staging impact of early detection and screening interventions for breast cancer to shift cases that would have been detected later to an earlier stage at diagnosis, resulting in better prognosis. Two other studies have developed breast cancer downstaging models for LMICs specifically for Ghana[35], Peru[36], and another study focused on Colombia and the East Africa Region [69]. Our model differs from that of Zelle et al. that was developed for Ghana and Peru in that our model doesn't include the natural history of breast cancer progression which requires specification of parameters that are often unknown [69]. While the Birnbaum et al model for Colombia and the East African region is aligned to our model as it also doesn't include the natural history of the underlying disease, the modelling framework assesses health outcomes only leaving out costs, which our dynamic model included. Moreover, the Birnbaum et al study did not consider composite health outcomes measures such as quality-adjusted and disability-adjusted life-years [69], which the model we developed addressed by including healthy life years gained as one of the health outcome indicators. Additionally, their model doesn't consider the full continuum of breast cancer control interventions such as palliative care, which our model included. Furthermore, the Birnbaum et al model did not evaluate mammography screening led interventions for the East African context [69]. Our analysis contributed to this gap in the evidence by evaluating mammography screening led interventions for both South Africa and Uganda.

From our analysis on the impact of early detection and screening interventions on down-staging of breast cancer, we note that early detection and screening interventions have almost double the impact in settings where late-stage presentation of breast cancer disease is very prevalent (Uganda) as compared with settings where late-stage presentation of the diseases is not as prevalent (South Africa). For Uganda, we estimate that the three early detection and screening interventions are associated with a 66% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease for over the period of 40 years. For South Africa, we report a 32% cumulative stage-shift of breast cancer patients from late-stage to early-stage of the disease over the 40-year period.

Cost effectiveness of early detection, screening, and breast cancer control interventions in LMICs

Considering that only two other studies from LMICs have conducted full cost-effectiveness analysis on interventions for breast cancer control in Ghana [35] and Peru [36], the evidence from this dissertation will meaningfully contribute to reducing gap in the evidence base. This dissertation found that biennial CBE (ages 40-75) and awareness raising interventions are not only crucial for down-staging breast cancer diagnosis, but they are also economically attractive and viable for options for both Uganda and South

Africa. While mammography (MMG) was found to be the most effective intervention, it is very costly and therefore LMICs should only adopt MMG with careful considerations.

Biennial CBE coupled with treatment interventions for all stages is very cost-effective for South Africa with an ICER of $2,782 per healthy life year gained. Awareness raising interventions were also found to be very cost effective with an ICER of 3,204 per health life year gained. Mammography screening combined with treatment for all stages was not found to be a cost-effective intervention for South Africa with an ICER of $8,492 per healthy life year gained.

For Uganda, we found that the most cost-effective intervention for breast cancer control is awareness raising interventions with a dominant ICER of $-118 per healthy life year gained. Biennial CBE for women aged 40-74 combined with treatment for all stages was also cost effective with an ICER of $416 per healthy life year gained. Biennial MMG screening combined with treatment for all stages was not cost effective with an ICER of $3,110 per healthy life year gained.

Distributional consequences of publicly financing breast cancer control interventions in LMICs
To ably guide policymakers in LMICs on priority setting for breast cancer control interventions, chapters 7&8 of this thesis incorporated equity and financial protection considerations into the traditional economic evaluation using the extended cost effectiveness analysis framework. To the best of our knowledge, apart from this thesis, no other study has investigated the distributional impact of publicly financing breast cancer control interventions on equity and financial protection in both developing and developed countries. For both South Africa and Uganda, our analysis found that a policy to publicly finance breast cancer interventions has the potential to increase health benefits across all wealth quintiles and improve financial protection disproportionately benefiting the poorer wealth quintiles.

9.5 Key messages for Policy Makers

Findings from this thesis have implications for policymakers as articulated in the result chapters 4 to 8. Below is a high-level summary of the cumulative policy implications of this dissertation:

This thesis predicts significant down-staging associated with early detection and screening interventions for breast cancer in Uganda and South Africa. In countries where late-stage presentation of breast cancer patients is very prevalent like Uganda, early detection and screening interventions have nearly a double impact as compared with settings where late-stage presentation of the diseases is not as prevalent like in the case of South Africa. LMICs should therefore consider improving and enhancing investments in early detection and screening interventions as they can yield substantial down-staging for breast cancer. While our findings confirm a strong downstaging effect associated with early detection and screening interventions, we recommend careful and well-thought-out planning to precede the full roll out and expansion of early detection and screening interventions. This is because early detection and screening interventions will cause a surge in the number of women seeking breast cancer services, and if this surge is not met with the expected diagnostic and effective treatment capacity, the benefits of early detection will be negated. Furthermore, this can increase mistrust in the public health system and result in an increase in health care costs through the private sector [9].

This dissertation found that biennial CBE (ages 40-75) and awareness raising interventions are not only crucial for down-staging breast cancer diagnosis, but they are also economically attractive and viable for options for both Uganda and South Africa. These interventions have lower resource implications and are less complex to implement. For South Africa, we recommend a combination of nation-wide scale up of biennial CBE for women aged 40-75 and awareness raising interventions to facilitate timely diagnosis, referral, and treatment.

While our results show that awareness raising and CBE are economically attractive interventions, it should be noted that the success of these interventions is greatly hinged on the availability of treatment and on the availability of skilled human resources for health, equipment, and supplies to aid diagnosis. As such, CBE and awareness raising interventions can easily fail if critical socio-cultural factors and other aspects of the health system such as education and information are not considered. Therefore, an enabling environment comprising of the critical socio-cultural and health systems factors should precede the roll out of nation-wide awareness raising and CBE interventions.

Our analysis highlights that while mammography (MMG) was found to be the most effective intervention, it is very costly and therefore LMICs should only adopt MMG with careful considerations. We recommend that LMICs should incrementally make investments for mammographic screening for diagnostic purposes and the scale up of these investments should be gradual and shaped by the improvement in the economic performance of the countries.

While awareness raising and CBE interventions were found to be cost effective in both countries, they require significant resources for implementation at scale and this warrants affordability concerns. For purposes of sustainability and affordability, we recommend that these breast cancer control interventions are implemented in an integrated model along with other programs targeted at the same proportion of the demographic such as the cervical cancer program. Resource allocation to the integrated model can happen in a gradual and well sequenced manner over long-term budgetary commitments.

This thesis demonstrated the need to publicly finance early detection and screening interventions in LMICs for breast cancer to alleviate a considerable proportion of breast cancer burden and catastrophic health expenditures benefiting the poorest wealth quintiles. Therefore, to improve financial protection among the poorer wealth quintiles, the LMICs should considerably expand existing social protection schemes for the poorest wealth quintiles as they are most susceptible to health and financial risks of seeking breast cancer control services.

Furthermore, in both countries, we reported a pro-rich distribution in the health outcomes associated with breast cancer control interventions and this is due to the higher utilization of breast cancer services by the wealthier quintiles. As such, we recommend to LMICs targeting mechanisms aimed at addressing unmet need and underuse of services among the poorer wealth quintiles.

9.6 Future Direction

Due to constrained fiscal space for health in LMICs, now more than ever, there is a need to optimally utilize available resources to benefit the largest proportion of the population. Easy to use models like the one we have developed will be very useful in generating robust evidence to identify resource-appropriate interventions and to guide the allocation of scare resource in LMICs. The findings from this thesis have provided evidence on the cost effectiveness and distributional impact of publicly financing interventions for down-staging breast cancer in Uganda and South Africa and these findings can inform priority setting in other contexts with similar epidemiologic, demographic, and socio-economic characteristics.

While this thesis in Chapter 4 predicts significant down-staging associated with early detection and screening interventions for breast cancer in LMICs, we note that the success of these interventions depends on the quality of the interventions as well as other logistical, socio-cultural, political, and health system factors. Future research should assess what bearing such factors have on the success or failure of breast cancer control interventions.

Furthermore, the recommendations for breast cancer control in LMICs should not only depend on the estimated cost-effectiveness based on down-staging as quantified by our analysis. We recommend that future assessments consider other multi-decision criteria to assess issues of affordability (budget impact), value for money, safety, and other political economy concerns that can constrain full uptake and scalability of breast cancer control interventions.

In chapter 5 & 6 of this dissertation, we considered a provider's perspective, excluding the costs to the patients including their productivity loss. We acknowledge that inclusion of these costs would have provided the complete and more accurate estimate of the resource requirement for breast cancer control in LMICs, especially owing to the high non-medical costs associated with long term illnesses like cancer. Furthermore, our model did not vary the direct medical costs by wealth quintile due to limited disaggregated data and their omission likely underestimates the total financial burden especially for the lower wealth quintiles. Additionally, we acknowledge that publicly financing breast cancer interventions from the providers perspective (as reported in chapters 7&8) might not automatically warrant an increase in actual service use due to high non-medical costs. Therefore, future cost effectiveness and the extended cost effectiveness analyses for breast cancer should consider a societal perspective and should stratify costs by income quintiles for both direct and indirect costs.

In Chapter 7&8 of this thesis, we represented financial protection in terms of cases averted for catastrophic health expenditures but the main drawback with this metric is the inadvertent exclusion of households owing to the choice of threshold used (in this thesis 10% of disposable income). Future research should consider other possible measures such as cases of poverty averted pr cases of borrowing (or other coping mechanisms) avoided but to publicly financing breast cancer control interventions. Furthermore, our analysis did not vary incidence and other critical parameters, such as non–breast cancer mortality by income quintile, and we acknowledge the importance of incorporating these differences into the model. Future work should aim to integrate more comprehensive data to capture the full spectrum of socioeconomic disparities in health outcomes.

Furthermore, in chapters 7&8, we report a pro-rich distribution for health outcomes and a pro-poor distribution for financial protection outcomes, and this points to a trade-off associated with interventions designed to improve financial protection without initially putting in place mechanisms to address barriers to access. Future research needs to assess this trade-off further and devise plans to maximize health and financial protection benefits for the vulnerable population. There is need to evaluate other social protection strategies required to substantially reduce catastrophic health expenditures associated with cancer.

9.7 Conclusion

In conclusion, the findings from this thesis are notable for breast cancer policy in low-and-middle-income countries as the analysis demonstrated significant down-staging associated with early detection and screening interventions for breast cancer. The findings from this thesis suggest that biennial clinical breast examination (ages 40-75) and awareness raising interventions are not only crucial for down-staging breast cancer diagnosis, but they are also economically attractive and viable for options for LMICs. Implementation of these breast cancer control interventions will require substantial additional financial investments, but our analysis shows that the health benefits will broadly outweigh these additional resource requirements. This dissertation propagates the notion that cost-effectiveness analysis should be extended by additional analyses or multiple criteria to ably guide decision makers on priority setting and allocation of scare resources. As such, this thesis incorporated equity and financial protection considerations into the traditional economic evaluation using the extended cost effectiveness analysis (ECEA) framework. From the ECEA, this thesis demonstrated that publicly financing early detection and screening interventions in LMICs for breast cancer can alleviate a considerable proportion of breast cancer burden and catastrophic health expenditures benefiting the poorest wealth quintiles.

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Appendices

Appendix 1: UCT PhD Ethical Approval and Renewal (HREC 257/2018)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2026
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	21/1/2025

Note: Please note that incomplete submissions will not be reviewed.
Our website address: https://health.uct.ac.za/home/human-research-ethics

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

HUMAN RESEARCH ETHICS COMMITTEE
21 JAN 2025
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	20th January 2025		
HREC REF Number	257/2018	Current Ethics Approval was granted until	30th May 2024
Protocol title	Extended Cost Effectiveness Analysis of Interventions for Early Detection and Treatment of Breast Cancer: A Case Study of South Africa and Uganda		
Principal Investigator	Prof Edina Sinanovic		
Department and email address	Public Health/Health Economics edina.sinanovic@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
✓	Publication or thesis submitted and final completion?
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	91	
Total number of records or specimens collected, reviewed or stored since last progress report	0	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ Yes	☐ No
Please complete the Closure form (FHS019) if the study is completed within the approval period		

2 April 2024 Page 1 of 2 FHS017

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

4. Signature

Signature of PI		Date	20/01/2025

Appendix 2: Uganda Ethical Approval TASO REC/010/19-UG-REC-009

The AIDS Support Organisation (TASO) Uganda Ltd.

TASO Headquarters
Mulago Hospital Complex
P.O. Box 10443, Kampala-Uganda
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Fax: +256 414 541 288
Email:
Website:

27/10/2023

27 OCT 2024

To: Christabel Abewe

World Health Organization
+256771456662

Type: Annual Renewal

Re: Extended Cost Effectiveness Analysis of Interventions for Early Detection and Treatment of Breast Cancer: A Case Study of South Africa and Uganda

I am pleased to inform you that at the **112th** convened meeting on **27/10/2023**, the **The AIDS Support Organization (TASO) REC** reviewed the progress report to the above study reference number **TASOREC/010/19-UG-REC-009** and found it satisfactory. In this respect, annual renewal of the study is granted. The study was initially approved on **31/05/2019** and expired on **31/05/2020**.

The Approval of the research is for the period of **27/10/2023** to **27/10/2024.**

As Principal Investigator of the research, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the protocol or the consent form must be submitted to the REC for re-review and approval **prior** to the activation of the changes.
3. Reports of unanticipated problems involving risks to participants or any new information which could change the risk benefit: ratio must be submitted to the REC.
4. Only approved consent forms are to be used in the enrollment of participants. All consent forms signed by participants and/or witnesses should be retained on file. The REC may conduct audits of all study records, and consent documentation may be part of such audits.
5. Continuing review application must be submitted to the REC eight weeks prior to the expiration date of **27/10/2024** in order to continue the study beyond the approved period. Failure to submit a continuing review application in a timely fashion may result in suspension or termination of the study.
6. The REC application number assigned to the research should be cited in any correspondence with the REC of record.
7. You are required to notify the Uganda National Council for Science and Technology (UNCST) for final clearance to undertake the study in Uganda.
8. **All approved study documents should be stamped by the REC before commencement of data collection.**

The following is the list of all documents reviewed in this application by **The AIDS Support Organization (TASO) REC:**

No.	Document Title	Version	Date
1	Approved Protocol (part 2)		2023-07-20
2	Approved Protocol		2023-07-20
3	Continuing Review Application		2023-07-20
4	Payment		2023-07-20

Yours Sincerely

27 OCT 2024

Dr. Adrian Jjuuko
For: The AIDS Support Organization (TASO) REC

"… the end of a thing is better than it's beginning…" Ecclesiastes 7:8