Incidence patterns, care continuum and impact of treatment on survival among women with breast cancer in Ghana and the United States

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE UNIVERSITY OF MINNESOTA

BY

Eddah Waruiru Mburu

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Advisor: Shalini Kulasingam, PhD, MPH

Co-Advisor: Beth A. Virnig, PhD, MPH

May 2021

ACKNOWLEDGEMENT

I would like to first thank my advisors, Shalini Kulasingam and Beth Virnig. Thank you for always believing in me, reminding me that I belong in academia and I have what it takes to excel. Thank you for challenging me, for the constant encouragement and reminder to take a break and enjoy life.

Thank you to the women in Kumasi, Ghana who participated in the pathways of care study. I would also like to thank the Ghana team for all their support: mentors - John Amuasi, Baffour Awuah, Adwoa Bemah and Ernest Osei-Bonsu; research assistants – Angela, Kwadwo, Joan and Grace; and friends – Tony, Louis, Lady, Leslie, Boham, Abbie and Caleb.

Special thanks my dissertation committee members. Thank you Carolyn Porta for your patience and guidance as I navigated the world of qualitative research. Thank you Jim Hodges for the statistical guidance, encouragement when I would hit analytic walls and the invaluable scientific writing tips and tricks. Thank you Heather Nelson for challenging me to think about the real-world application of my research.

Sincere gratitude to Center for Global Health and Social Responsibility and Fogarty International Center for supporting my research in Ghana. Special thanks to Molly McCoy and Shailey Prasad for their support and advice.

I thank Helen Parsons and Stephanie Jarosek for their countless support with data analysis, encouragement and for creating fun moments in the office.

I thank my colleagues Emily Groene, Anna Stadelman, Naomi Thyden, Collin Calvert, Bridget Griffith and Kimberly Bonner for your feedback and friendship.

Finally, I would like to thank my family: husband Ng'ang'a for leading the way; mom Jane and dad Peter for encouraging me to dream big; sisters Carol, Lilian, Maggie and brother Karani for always reminding me that the Mburu's never quit and always win; grandma Waruiru for showing me that it is possible beat the odds; and my extended family and friends for the prayers and undying support. Grateful to God for making it all possible. It truly took a village to make this dissertation possible.

DEDICATION

This dissertation is dedicated to my grandmother, Waruiru Karani, who was denied education but went on to become a successful business woman, an education champion and invested in her children's, grandchildren's and great-grand children's education.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

- TNBC: Triple negative breast cancer
- US: United States
- ER: Estrogen receptor
- PR: Progesterone receptor
- HER2: Human epidermal growth factor receptor 2
- SSA: Sub-Saharan Africa
- BCS: Breast conserving surgery
- BCT: Breast conserving therapy
- RT: Radiotherapy
- KATH: Komfo Anokye Teaching Hospital
- RA: Research Assistant
- NCCN: National comprehensive cancer network
- OS: Overall survival
- BCSS: Breast cancer specific survival
- SEER: Surveillance Epidemiology and End Results
- NCI: National Cancer Institute
- IPTW: Inverse Probability of Treatment Weighting
- CIF: Cumulative incidence function

CHAPTER 1. INTRODUCTION AND BACKGROUND

1.1 Statement of purpose

This dissertation aims to contribute to the body of knowledge on breast cancer incidence patterns, diagnosis and treatment outcomes in Ghana and the United States (US). The aims of this dissertation research are to:

1. Examine Ghanaian women's pathways from breast cancer-related symptom detection through treatment receipt;
2. Assess factors explaining the younger age at breast cancer diagnosis in Ghana compared to the US;
3. Evaluate whether there is a survival advantage to a more aggressive surgical approach for treating triple negative breast cancer (TNBC).

Findings from this study will help improve breast cancer early detection and treatment interventions in Ghana and the US.

1.2 Specific aims

Breast cancer is the most commonly diagnosed cancer among women worldwide. In 2020, there were approximately 2.3 million new cases of breast cancer and breast cancer accounted for 1 in 6 cancer deaths among women (1). Breast cancer is a heterogeneous disease that is classified into subtypes based on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression patterns. The subtypes include luminal A, luminal B, triple negative (TNBC), and HER2-enriched (2). In the US, TNBC accounts for 12-15% of all invasive breast cancers but has the highest recurrence rate and lowest survival rate compared to the other subtypes (3, 4). Black women in the US and West African countries like Ghana are more

likely to be diagnosed with this aggressive subtype of breast cancer (5). There is an urgent need for research to inform breast cancer early detection and timely treatment strategies among Black women in the US and Ghana.

More than fifty percent of breast cancer patients in Ghana are diagnosed at advanced stages with metastatic disease. Most breast cancer patients in Ghana are diagnosed with advanced metastatic disease due to delays in formal diagnosis (6). No study has traced in detail Ghanaian breast cancer patients' pathways from symptom detection to treatment initiation. An understanding of how Ghanaian women navigate the healthcare system and factors that influence their decisions and ability to seek and access breast cancer care is essential for developing interventions aimed at improving early breast cancer detection, obtaining timely treatment and thus reducing breast cancer related mortality.

Several studies show that Ghanaian breast cancer patients tend to be younger than patients in other parts of the world. For example, the median age at breast cancer diagnosis among women in Ghana is 48 years, compared to 60 years among Black women and 63 years among White women in the US (7, 8). Worldwide, breast cancer in younger patients tends to be more aggressive with rapid progression compared to older women (9). Particularly in an under-resourced healthcare setting, such as Ghana, it is critical to assess factors explaining the younger age at diagnosis in order to inform screening and treatment guidelines. Reasons for younger age at diagnosis are conflicting. Some studies suggest that the young age profile is due to biological differences while others suggest that it is due to differences in population age structures between countries (10, 11). However, these competing hypotheses have not been well explored.

Recommended surgical treatment for TNBC is either mastectomy or breast conserving surgery (BCS). Either surgical option can be followed by radiation therapy (12). Targeted therapies such as trastuzumab cannot be used in the treatment TNBC since it lacks ER, PR and HER2 receptors (13). The poor prognosis of TNBC contributes to the controversy regarding whether mastectomy (the most aggressive surgical approach) is a more appropriate surgical treatment for TNBC than breast conserving surgery (BCS) (14). Given the aggressive nature of TNBC, it is essential to use real world data to examine the most optimal surgical treatment for patients with TNBC.

1.3 Background

1.3.1 Breast cancer subtypes

Breast cancer is grouped into four subtypes based on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression patterns. Immunohistochemistry (IHC) is used to identify ER and/or PR expression while IHC and/or fluorescence in situ hybridization (FISH) is used to identify HER2. The four subtypes are luminal A, luminal B, TNBC and HER2 enriched (2). The different subtypes have different clinical features, which affect treatment responses therefore therapeutic strategies should be tailored by subtype. In the US, luminal A subtype is the most common subtype and has the best prognosis (3). TNBC accounts for 12-15% of all invasive breast cancers but has the worst prognosis (13). For example, the 10-year disease-free survival for Luminal A is approximately 86% while that of TNBC is 71% and the 10 year overall survival for Luminal A is 89% and 75% for TNBC (3).

Table 1: Breast cancer subtypes by estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression patterns and prevalence in the US.

Breast cancer subtype	**ER,PR,HER2 status**	**Prevalence in the US (15, 16)**
Luminal A	ER+, PR+, HER2-	50%-60%
Luminal B	ER+, PR+, HER2+	15%-20%
HER 2 enriched	ER-, PR-, HER2+	15%-20%
Triple Negative (TNBC)	ER-, PR-, HER2-	12%-15%

Breast cancer subtypes in the US vary by race/ethnicity. Luminal A is most common among White women while TNBC is most common among Black women (17)(17).

1.3.2 Risk factors for breast cancer

Risk factors for breast cancer include reproductive, hormonal and genetic factors. Early age at menarche (18), late onset of natural menopause (18), late age at first childbirth and low parity (19) increase the risk for breast cancer. High body mass index (BMI) (20) and use of hormone replacement therapy (21) are associated with increased risk of breast cancer. In addition, women with high breast density (22) and family history of breast cancer (23) have an increased risk of breast cancer. Lastly, women who have BReast Cancer genes 1 and 2 (*BRACA1 and BRACA2*) are at an increased risk of breast cancer (24). BRACA 1 gene is also associated with increased risk of TNBC (25).

1.3.3 Breast cancer treatment

Mastectomy or breast conserving surgery (BCS) are the two surgical treatment options for early-staged breast cancer. Either surgical option can be followed by radiation therapy (12). The surgical treatment is determined by the nodes involved and tumor size but guidelines do not classify surgical treatment by breast subtype (26). Systemic therapy

which is determined by breast cancer subtype, includes chemotherapy and endocrine therapy. Recommended treatment for early staged TNBC is surgery with or without radiation and chemotherapy. Chemotherapy is the recommended treatment for metastatic TNBC (27).

1.3.4 Breast cancer burden in the US

Breast cancer is the most common cancer and the second leading cause of cancer death among women in the US. The incidence of breast cancer is approximately 127.5 per 100,000 women per year while the mortality is approximately 20.6 per 100,000 women per year (8). Breast cancer incidence has been increasing by about 0.3% per year over the last 10 years while mortality has been decreasing by about 1.8% due to advances in treatment (28). However, there are persistent racial disparities. Compared to White women, Black women have lower incidence of breast cancer (130.5 per 100,000 vs 124 per 100,000 persons respectively) but they have higher mortality rates (20.1 per 100,000 vs 28.1 per 100,000 respectively) (8). These disparities are largely driven by discrimination and racism in accessing breast cancer care. For example, lack or limited health insurance and access to primary care clinics increases the probability of Black women being diagnosed at a late-stage which is associated with lower survival rates (29).

1.3.5 Breast cancer burden in Ghana

The lack of population-based cancer registries in SSA limits the ability to accurately assess the burden and characteristics of cancer cases. Most of the breast cancer studies in Ghana are hospital based and incidence rates are based on the International Association of Cancer Registries (IARC) GLOBOCAN database (30). According to IARC GLOBOCAN database, the age standardized incidence rate of breast cancer in

Ghana is 43.0 per 100,000 and the mortality rate 17.7 per 100,000 (31). In terms of demographic and clinical characteristics, breast cancer patients in Ghana are more likely to be pre-menopausal (32, 33), have had children (6, 32) and are younger (incidence peaks between 40-50 years) (7, 34-36). Further, most patients are diagnosed with advanced metastatic disease (6, 32), are more likely to have TNBC (36, 37) and consequently have low survival rates (36).

CHAPTER 2. MANUSCRIPT 1: PATHWAYS TO BREAST CANCER DIAGNOSIS AND TREATMENT AMONG WOMEN IN GHANA: A QUALITATIVE STUDY.

2.1 Introduction

Breast cancer is the leading cause of cancer death among women worldwide. In sub-Saharan Africa, breast cancer represents 25% of the total cancer burden making it the most common cancer and leading cause of cancer deaths among women (38). Breast cancer is the most common cancer among women in Ghana with an age standardized incidence rate of 43.0 per 100,000 (31).

Most breast cancer patients in Ghana are diagnosed with advanced metastatic disease due to delays in formal diagnosis. Several studies report that time from symptom onset to diagnosis and treatment receipt varies substantially in Ghana. In one study, time between detecting a symptom and reporting to a hospital ranged from one week to 5 years(39) while another study reported an average of 10.8 months between symptom detection and diagnosis (40). Dedey et al. found that the median time between a breast cancer diagnosis and start of definitive treatment was 5 weeks (41). Factors associated with these diagnostic and treatment delays included misdiagnosis in previous medical consultation, financial constraints, lower level of education, older age, not married and lack of adequate information from the healthcare workers (39, 41).

Ghana, like most sub-Saharan African countries, lacks a national breast cancer screening program. Thus most women seek breast cancer care once they identify symptoms (39). The women then have to navigate the healthcare system to get diagnosed and receive treatment. To our knowledge only one study, based in Malawi, has detailed women's

specific pathways to breast cancer diagnosis and treatment in sub-Saharan Africa (42). Three studies set in Ghana have described some aspects of the breast cancer care seeking pathway in Ghana. Two studies described women's symptom recognition, appraisal and intent to seek medical care, while the third described the diagnosis and treatment procedures (40, 43, 44). However, no study has outlined in detail the pathways that women in Ghana navigate from symptom detection through treatment receipt. Understanding this full process and appreciating women's understanding and needs is essential if effective interventions are to be developed.

The objective of this study is to explore Ghanaian women's pathways from breast cancer-related symptom detection to treatment. Our definition of the term 'pathways' is guided by the Model of Pathways to Treatment Framework (45). We define pathways as the sequence of events and processes in a woman's journey from breast cancer-related symptom(s) detection to treatment receipt. According to the Model of Pathways to Treatment Framework, events are the "key time periods" while processes are the "cognitive, emotional, behavioral, organizational or structural actions" in the woman's journey to treatment receipt (45). Based on the findings from the interviews, we present a framework showing specific steps in the pathways and how women transition from one step to another.

2.2 Materials and Methods

2.2.1 Theoretical framework

The Model of Pathways to Treatment framework informed our study development and analysis (45). The model has four intervals: appraisal, help seeking, diagnostic and pre-treatment. The appraisal interval is the time between discovering a symptom and

perceiving reason to seek help from a health care provider. Help-seeking interval is the time-period between perceiving reason to seek help from a healthcare provider to visiting a healthcare provider. In our study we combined the appraisal and help-seeking intervals to form the detection interval. This was based on similar breast cancer studies which have found it challenging to distinguish appraisal and help-seeking intervals (46). The diagnostic interval is the time between seeing a healthcare provider and being diagnosed cancer. The pre-treatment interval is the period between getting diagnosed and starting treatment. We also added the treatment interval in order to have a comprehensive understanding of the care continuum (45).

2.2.2 Study Design and Setting

An empirical phenomenological approach was used to explore the pathways of women diagnosed with breast cancer from the moment they detected symptoms to treatment. Phenomenology is used to describe and understand the lived experiences of a group of individuals grounded in the individuals' description and meaning (47). The aim of our study was to describe the perspectives and experiences of our research participants from breast cancer-related symptom detection through treatment receipt. Given our interest in describing the phenomenon of navigating breast cancer diagnosis and treatment processes and from the perspective of our study participants, a phenomenological approach was the best fit for our study. This study was conducted in Kumasi, Ghana. Participants were recruited from the Komfo Anokye Teaching Hospital (KATH) Oncology Department. KATH is the second largest hospital in Ghana and the main cancer management hospital in the Ashanti region of Ghana.

2.2.3 Study Population, Sampling and Sample Size

Eligible participants were women (18 years and older) with a histopathology confirmed diagnosis of breast cancer, who had started receiving at least one breast cancer treatment (surgery, chemotherapy or radiotherapy), could speak Twi (local language), and were in a stable condition at the time of study. We reviewed the patients' medical records to confirm diagnosis and treatment receipt. We used a purposive sampling technique(48) in order to enroll participants who had experienced the phenomenon under study, were willing to participate and could clearly communicate their breast cancer management experiences. Data saturation was determined from the interviews. We determined we had reached data saturation when data from new interviews tended to be redundant of the data we had already collected (49, 50).

2.2.4 Recruitment

A trained Research Assistant (RA) met the patients at the KATH Oncology department to assess eligibility and invite them to participate in the study. Specifically, the RA read to each potential participant the study information sheet which included the goals of the study, what is required of each participant and a reminder that participation was voluntary. The interviews were carried out between November 2019 and March 2020.

2.2.5 Data collection

A semi-structured interview guide was used for the interview. The guiding questions were based on previous similar publications(42, 46, 51-56) and were adapted for use in the Ghana context. Section 1 of the interview guide (**Appendix A**) was semi-structured, and it was based on the Model of Pathways to Treatment framework. Section 2 (**Appendix A**) included patient demographics and was close-ended. All participants gave

consent by signing or thumb-printing. Interviews were carried out in Twi in a private room within the KATH Oncology department. We pre-tested the interview guide by interviewing three breast cancer patients from the Oncology department and a Ghanaian qualitative researcher with clinical experience in oncology (ABBM) reviewed the guiding questions for socio-cultural appropriateness. Based on the pre-test interviews and advice from ABBM we revised the order of the interview guide questions. The main guiding question was: *Please tell us the story of your journey from when you detected bodily change to when you started receiving breast cancer treatment.* We then used more specific follow up questions to further understand the events in each interval. Interviews lasted 42 minutes on average (range 19 – 84 minutes).

2.2.6 Data Analysis

Data collection and analysis were undertaken concurrently. All interviews were audio-recorded to ensure we captured all the patient's information and to enable transcription for subsequent analysis by independent analysts. At the end of each interview, the interviewer and one of the authors (EWM) reviewed the recording and saved it to a password protected laptop. All interviews were conducted in Twi and translated into English by a professional transcriber who is proficient in Twi and English. One of the authors who is proficient in Twi and English (ABBM) reviewed a random sample of the recordings and transcripts to ensure accuracy in interviewing, transcription and translation. We used NVivo 12plus(57) computer software to facilitate analysis organization.

A deductive coding analytic process was used (58). We had a list of codes ('start list') based on the Model of Pathways to Treatment (45) but we also created codes for

other concepts that emerged from the data and were not part of the start list. Two analysts (EWM and ABBM) independently coded the transcripts in three stages. For the first stage, they independently assigned codes to text sections based on the Model of Pathways to Treatment framework (45). For the second stage, they independently re-reviewed the data to identify emerging codes that were not part of the framework. They then discussed the codes, clarified discrepancies, revised definitions and created new codes. For the third stage the analysts jointly organized the codes into steps and themes guided by the Model of Pathways to Treatment Framework (45). The rest of the authors confirmed the findings. This in-depth analysis process ensured reliability of the results (59).

2.2.7 Trustworthiness and credibility

Credibility was achieved by triangulation(60) and member checking (61). Data source triangulation involved using information from the patient's medical records at KATH to verify the procedures and treatments that the patients received. Analyst triangulation involved two of the authors (ABBM and EWM) comparing and discussing the analyses until consensus was achieved. After each interview, the RA gave a summary of the interview and asked the participant to confirm that the summary reflected their experiences. In addition, five participants independently reviewed their transcripts to affirm that they accurately reflected what they had shared. This was done within one week of transcription. None of the participants had concerns or reservations about the content of the interviews. Field notes, which included the participants' non-verbal cues, concerns, and interviewers' reflections, were recorded after each interview and referred to during the analysis. The two RAs who carried out the interviews are nurses by training,

thus have a clinical understanding of breast cancer. However, none of them work in the KATH Oncology department and had no direct relationship with the participants. Ethical approval was granted by the Institutional Review Boards at KATH (KATH-IRB/AP/001/19) and University of Minnesota (STUDY00006750). In order to protect the patient's identity, we assigned each participant a random number that was used in the transcripts. Audio records and transcripts (without any identifying information) were stored on a password-protected computer. We followed the Standards for Reporting Qualitative Research (62).

2.3 Results

We interviewed thirty-one women who were diagnosed with breast cancer between 2015 and 2019. The mean age of the participants was 51 years. Most of the participants were married/partnered/cohabiting, Christians, had at least primary school education and had no family history of cancer. Of those who had a job (n=14), most of them were self-employed. Thirty of the thirty-one participants had health insurance (**Table 2**).

Table 2: Socio-demographic characteristics of the sample (N=31).

Characteristic	**N (%)**
Age in years, Mean (Range)	51 (28-72)
Marital Status	
Married/Partnered/Cohabiting	22 (71)
Widowed/Divorced/Separated	9 (29)
Highest education level	
Primary School	18 (58)
High School	3 (10)
Technical College diploma	5 (16)
Bachelors degree	2 (6)
Other	3 (10
Religion	
Christian	28 (90)
Muslim	3 (10)

Employed	
Yes	14 (45)
No	17 (55)
Employed Yes	14 (45)
Type of employment	
Government	3 (21)
Self-Employed	10 (71)
Other	1 (7)
Have health insurance	
Yes	30 (97)
No	1 (3)
Family cancer history	
Yes	11 (35)
No	20 (65)

We describe the pathway steps that emerged from each interval. The pathway was not linear and some patients looped back to earlier steps while some skipped some of the steps (**Figure 1**).

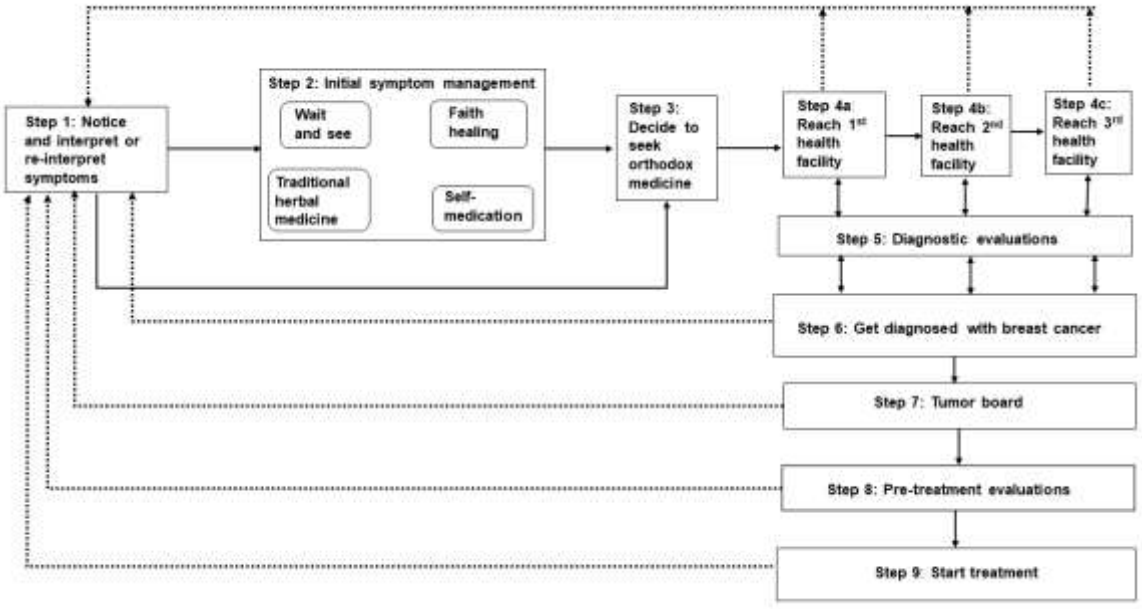


Figure 1: Pathway of care from symptom detection to treatment for breast cancer patients in Kumasi, Ghana. Dotted lines represent patients going back to previous steps. Solid lines represent patients moving forward in the pathway.

2.3.1 Detection interval

The average time between symptom detection and seeking orthodox medicine was 11 months.

Step 1: Initial symptom recognition and appraisal

Type of symptom and way of discovery

All the women detected initial symptoms themselves. The most common initial symptom was lump (n=23). Other initial symptoms included swollen breast (n=3), fluid oozing from the breast nipple (n=2), burning sensation (n=1), rashes on the breast (n=1) and pain (n=1). Two of the women recognized the initial symptom while doing a self-breast exam, while the other twenty nine discovered them accidentally.

> *"I was there one day and I examined my breast and I realized that there is a lump at the top." (P21)*
>
> *"When I woke up in the morning, I wore a white nightie the previous night and I realized there was blood where my breast touched the fabric." (P19).*

Initial symptom interpretation

Only two women thought the initial symptom was due to breast cancer. Both of these women had aunts who died of breast cancer and one of them was a nurse, thus they were aware of breast cancer.

> *"In my mind, I thought maybe I have been afflicted with breast cancer… because my mother's sister had it." (P3)*
>
> *"I felt the lump so I kept touching it. My mind went there….. [assuming it was due to breast cancer]." (P8)*

The other twenty-nine women did not think the initial symptom was serious. Most of them thought it was a boil while others associated the symptoms to the menstrual cycle, insect bite, food they had eaten, or breast-feeding.

> *"It was like Oh this is just like a lump…. I did not anticipate that it was serious or going to be breast cancer." (P6).*
>
> *"Whenever I am about to have my menses, my breasts will swell up and become bigger… When I observed this change… I reasoned that it could be related to my menses. I did not perceive it serious." (P11).*

Symptom disclosure

The women disclosed their symptoms to individuals they trusted which included relatives, friends who were in the healthcare field, and work colleagues. Most of the people advised the women to go to the hospital for a checkup, others advised them to wait and monitor the symptoms while some advised them to see a traditional healer.

> *"And when I saw it [blood oozing from nipple], I informed a sister living in the same house. She advised going for herbal medicine." (P19)*
>
> *"I showed it to three of my sisters…. It looked as if the breast was tilted…One of my sisters advised me to take it straight to [a district hospital] in the morning if I have insurance." (P12)*
>
> *"There was a nurse in our house and…when I told her, she told me to wait for a while because it could be the result of the 'sure' [deodorant] I am using, so I should stop using it." (P18)*

Step 2: Initial symptom management before seeking orthodox care

Only two patients sought orthodox medicine right after discovering the symptoms (i.e. Step 1 to Step 3) while the rest used alternative strategies to manage the symptoms (i.e. Step 1 to Step 2).

Traditional herbal medicine

Six women, most of whom thought the symptom was a boil, visited traditional healers for herbal medicine which they applied on the breast hoping the lump would disappear.

"When it [lump] initially started, I bought some herbal medication...and… smear it on the place… I thought it was a boil and when I take the drugs, it will eliminate it." (P12)

"I considered the lump as one of the usual breast problems. So, I started treating it with herbal medications." (P9)

Self- medication

Two women whose initial symptom was breast pain used over the counter medication to reduce the breast pain and stop the spread of the infection.

"It was Ampiclox and Paracetamol that were helping me. So whenever I took these, then the pains would reduce a little…and stop the infection." (P22)

"My children…bought me some medication from the chemist to stop the breast pains." (P32)

Faith healing

Two women who associated the symptoms to spiritual causes sought faith healing to manage the initial symptoms.

"A friend introduced me to a prayer group and so I joined…I put [prayer group anointed] oil on it." (P32)

"I initially thought the breast heaviness was due to evil witches bedeviling me. So I went to my personal priest…and resorted to prayers." (P26)

Wait and see

Nineteen women decided to monitor the symptoms since they were not disrupting their daily activities and they did not consider them serious enough to seek care.

"So when I observed the lump, I decided to wait awhile…because it wasn't causing me any pain. I could carry on my normal activities." (P25).

"I found the lump in August, I thought it was just an ordinary lump…. Hence I waited until around October but monitored the symptom alongside." (P6)

Step 3: Decision to seek orthodox medicine

Eventually all the women decided to seek orthodox medicine (i.e. either Step 1 to Step 2 or Step 2 to Step 3) due to a combination of the following factors

Additional symptoms

Ten women decided to seek allopathic medicine only when additional symptoms disrupted their daily activities. These additional symptoms included pain, lump enlargement, wound, increased breast swelling and liquid oozing from the breast.

"The lump was tiny but later on, it was getting bigger and that was the reason that prompted me to come to [hospital]." (P27)

"Since it started being painful I had to do away with the herbal treatment and report to the [hospital]." (P24)

Alternative therapy failure

Some women decided to seek orthodox medicine when there was no improvement from the use of alternative therapy.

> *"Later, I realized the lump was getting bigger and when I touch the breast, it was more painful… I couldn't groom regularly…that was when I realized that I have to go to the hospital." (P22).*
>
> *"When the lump appeared, we started treating it with herbal medications and it went down a bit and it reappeared a little worse…When the herbal medication did not work we brought it to [hospital]." (P9)*

Advice and pressure from social network

Other patients sought orthodox medicine due to advice from their social network. The advice could have been immediately after the patient saw the initial symptom, after failed alternative therapy or after they had additional symptoms.

> *"So when I told my husband, he said you are saying you have observed a lump…take it to the hospital". (P18).*
>
> *"The moment I told them [friends about symptoms], they said 'be quick and take it to the hospital because you don't play around with diseases affecting the breast….' And I rushed to the hospital." (P7)*

2.3.2 Diagnostic interval

The average time between reaching the first health facility and getting a breast cancer diagnosis was 6 months.

Step 4a: Reach first health facility

The healthcare system in Ghana includes both private and public hospitals. The public healthcare structure comprises three main levels: health centers and district hospitals that provide basic health care, regional hospitals that provide secondary health care and teaching hospitals that provide tertiary care (63). The two major factors that influenced which initial health facility women sought care at were recommendation from social network and familiarity with the specific healthcare providers. Familiarity with specific healthcare providers could be due to information the women had heard from the media or where they sought regular medical care. Most women first sought medical care at health centers and district hospitals. Only eight women initially sought care at teaching hospitals. Three women initially sought care at one of the private hospitals. Once at the first healthcare facility, the women were examined and either a) referred for diagnostic evaluations (i.e. Step 4a to Step 5); or b) referred to a higher level facility that had breast cancer specialists (i.e. Step 4a to Step 4b); or c) misdiagnosed and went back home (i.e. Step 4a to Step 1).

> *I felt the burning sensation and to [health center] who declared there was nothing wrong…I went back home (Patient 3).*
>
> *"And when we went there [district hospital] the doctor declared it to be a lump so we should go and take a scan and he will take it (the lump) out for me." (Patient 17)*
>
> *"I went to see the doctor [district hospital] and he told me that those who used to work on these kind of cases are no longer working at the hospital. So he called*

another doctor at [tertiary hospital] and informed him that he is sending a patient to him…I started coming here [tertiary hospital]." (P30)

Step 4b: Reach second health facility

Once the women reached the second health facility, women were either a) referred for diagnostic evaluations (i.e. Step 4b to Step 5), or b) others went back home due to misdiagnosis (i.e. Step 4b to Step 1), or c) referred to a third higher level facility for diagnosis (i.e. Step 4b to Step 4c).

"[At district hospital], they made me take a scan… And then later on, I was told...they wouldn't be able to take care of me so I should come to [tertiary hospital]." (P12).

"I went to the hospital [regional facility], and they told me 'No, it is not anything' so I should go home…Three weeks' time, I went to [another facility] … for review. And when they checked, they said the thing [lump] was no longer there. And me too, I just relaxed and stayed at home." (Patient 16).

Step 4c: Reach third health facility

One woman was referred to multiple facilities before she was diagnosed (i.e. Step 4a to 4b to 5 to 4c).

"I went back to the nurses [in a health center] who advised going to see the doctor [at district hospital]. He [doctor] said I should go to [private lab] and take a scan and bring it back to him. When I brought it back…the doctor recommended being transferred because of how advanced my situation was. He directed me to [regional hospital]. However, we didn't go but came here instead [tertiary hospital]." (P4)

Step 5: Diagnostic evaluations

None of the hospitals, including the tertiary hospitals, had all the necessary diagnostic services available. Patients had to be referred to private laboratories for diagnostic procedures such as mammogram. This process involved the women going back and forth from the referring hospital to the diagnostic labs for sample collection and back to the hospital to present the results.

> *"The staff of [tertiary hospital) required me to do a lot of labs… I was made to place my breast in a machine [mammogram] in [private lab] and I brought all the results back to them." (P13)*

> *"Well, when I came to [tertiary hospital] he [doctor] gave us some tests and we took a very big picture [scans]. He also requested another test at [private lab]. I have even been to that place two times. And all the documents associated with these are there. And I can't even count the numerous other tests I've done over here" (P5).*

> *"He [doctor] took a sample of the breast…then he asked that I take a scan of the breast. He also asked me to go to [private lab] where they put the breast in a machine (mammogram]" (P11).*

Step 6: Get diagnosed with breast cancer

Eventually all women were diagnosed with breast cancer. Twenty women were diagnosed at tertiary hospitals, three women were diagnosed at private hospitals while the

rest were diagnosed at regional and district hospitals. At the diagnosing facility, the women were examined and if the provider was suspicious of breast cancer, they would order diagnostic evaluations for her. These evaluations included mammogram, CT scan and biopsy.

> *"I did the mammogram and then the ultra sound… then biopsy. It was the biopsy that proved it that it was cancerous cells." (P6)*
>
> *"I did the breast scan mammogram and the tissue biopsy...and I went for the results and it they told me it was cancer" (P8)*

Of the women who had stage information, six had stage III disease, two had stage IV and two had stage II. Of the women who had breast subtype information, two had HER2 enriched subtype, two had luminal A, and four had triple negative subtype. The women stated their initial reactions to the diagnosis included shock, fear of mastectomy and death, crying, and financial worry. However, others said they were not scared or worried as they leaned on their religious faith and encouragement from the doctor who delivered the diagnosis. Some patients continued to Step 7 while others went back to Step 1.

2.3.3 Pre-treatment interval

The average time between breast cancer diagnosis and starting treatment was 5 months.

Step 7: Discussion at tumor board

Komfo Anokye Teaching Hospital (KATH) tumor board group consists of surgeons, pathologists, oncologists, radiologists, and nurses. After diagnosis, all patients are discussed by the tumor board to determine the treatment course. Patients are encouraged to be present when their cases are being discussed if at all possible.

"The doctor scheduled me for a meeting [tumor board]. The nurse brought me to this meeting. So after they [tumor board members] had asked me a few questions, they discussed it and started me on the chemo." (P28)

"Following the diagnosis, we were scheduled for a meeting [tumor board] in two weeks. The doctor explained that everyone involved [at the tumor board] will bring their opinion …it is important for me to sit in during deliberations… However, the same doctor later told us not to come for the meeting due to my long distance, so he will represent me." (P4)

Step 8: Evaluations prior to starting treatment

After breast cancer diagnosis, the women typically needed more laboratory testing before they started treatment.

"I had to finish my labs; the full blood count, the kidney function test and everything before they started the treatment." (P8)

"He requested I go for a lab test… they examined a lot of tissues They examine your blood; they check the blood to know if you can take the thing [chemotherapy]" (P23)

2.3.4 Treatment interval

Step 9: Start treatment

The most common treatment course was neoadjuvant chemotherapy, followed by surgery followed by adjuvant chemotherapy and radiotherapy and hormone therapy.

"I was given six injections of chemotherapy… then they took me to cut off the breast [mastectomy]. After the operation I was put on a machine [radiotherapy],

and after the machine, I was given a prescription for medication that I was buying [hormone therapy].” (P29)

“I did four chemotherapy cycles before I was operated on. Then another four after operation.” (P12)

2.4 Discussion

This study describes Ghanaian women’s paths from the moment they detect breast cancer-related symptoms through receipt of breast cancer treatment. To our knowledge, this is the first study to trace the breast cancer care pathway from Ghanaian women’s perspectives. Similar to Kohler at al.(42) study we found that the breast cancer pathway in Ghana is not linear. The Model of Pathways to Treatment framework(45) which we used to guide our data collection is built on an assumption that women only use orthodox medicine to manage their breast cancer. However, in our study we found that women frequently moved among different management approaches. We propose a modified framework (**Figure 1**) which is grounded in findings from our interviews with Ghanaian women with breast cancer.

All the women discovered the symptoms themselves but only two women initially associated their symptoms with breast cancer. The rest thought their symptoms were not serious or could be easily managed by alternative therapies. This contributed to the substantially long average time of 11 months between detection symptoms and seeking orthodox medicine. The women in our study used different strategies to manage their breast cancer symptoms: traditional herbal medicine, over the counter medication, faith healing and wait and see if the symptoms went away. Wait and see was the most common

management strategy and involved the women monitoring their symptoms at home until they progressed to where the symptoms disrupted their ability to carry out daily activities. The main reasons for a wait and see approach were no pain associated with the symptom and interpretation that the symptoms were not serious and would resolve with time. This is consistent with previous research which has shown that women who have symptoms that are not associated with pain and who interpret symptoms as not serious are less likely to seek care immediately (54).

The second most common symptom management strategy was seeking care from traditional herbalists and faith healers (alternative therapy providers). In our study, the women who sought alternative therapies assumed their symptoms were due to common ailments such as a boil or were caused by evil powers. Alternative therapy providers are more accessible thus are more often consulted for common ailments. They are also more trusted, compared to orthodox medicine providers, to treat diseases whose cause is associated with spiritual powers (64). Alternative therapy is commonly used in Ghana and other sub-Saharan African countries for cancer management (65). However, the literature typically describes alternative therapy as a barrier to early detection and timely orthodox medicine receipt (39, 42). In order to improve breast cancer management in this community, it is essential to acknowledge the critical role of alternative therapy in the breast cancer diagnosis and care pathways and develop approaches that integrate them into breast cancer diagnosis and management. In 2011, a plan for integrating alternative therapy and orthodox medicine for all diseases was launched in Ghana. However, there were no clear guidelines on what integration meant and how to go about it. For example, a study in one of the pilot hospitals for the integration found that patients who were

seeking care at the hospital were not even aware that herbal services were also being provided. In addition, the orthodox medicine providers at the pilot hospital perceived both systems to be parallel instead of integrated (66).

There is potential for successful integration of alternative therapy providers in breast cancer management in Ghana. Faith healers and traditional herbal medicine providers in Ghana have expressed interest in working collaboratively with orthodox medicine providers (67, 68). Alternative therapy providers have previously been successfully integrated in HIV/AIDS and mental health care prevention and delivery (69, 70). For the integration to be successful, there needs to be trust between orthodox and alternative therapy providers and an acknowledgement that both providers are complimentary (71). In an integrated system, alternative therapy providers can play two major roles: triage and offering psychosocial care and support. This may reduce the time between symptom detection and seeking orthodox medicine. In the triage role, alternative therapy providers would immediately refer women with breast cancer related symptoms to orthodox medicine. The psychosocial role of alternative therapy providers was also clear from our study where some women consulted with faith healers for emotional support after the diagnosis.

All the women in our study detected the symptoms themselves. This is expected given Ghana does not have a national breast cancer screening program thus screening is ad hoc (39). However, there are non-governmental organizations (NGOs) in Ghana that organize clinical breast examinations (CBE). CBE is the physical examination by a healthcare provider to check for breast abnormalities (72). CBE has been shown to lead to significant breast cancer down staging (73). However, the CBE programs organized by

the NGOs in Ghana are sporadic which reduces their effectiveness. For example, one of the women in our study noticed the breast cancer related symptoms in August. However, she was not aware of any hospitals that carried out breast cancer screening so she decided to wait for the annual October community breast cancer screening. For these programs to be effective, they need to be consistently available and women need to be aware of their locations.

Given the challenges of implementing national screening programs, a more cost effective method to increase early diagnosis might be breast cancer awareness programs. Four women in our study sought medical care faster since they had learnt about breast cancer through the media and church events. In addition, a study in Ghana found that a community based breast cancer awareness program significantly improved women's breast cancer knowledge and uptake of breast self-exam (74). Studies found that 60% of women in Ghana got health information from radio and television(75) and that mass media awareness is a cost effective intervention for increasing participation in breast cancer screening Ghana (76).

Our study has several limitations. There is potential for selection bias. All our study participants were receiving breast cancer care thus we missed the experiences of women who never made it to the end of the breast cancer care pathway. Women who are not engaged in the cancer pathway may have had different experiences that we did not capture. However, we believe that the experiences of women who successfully navigated the various health care systems have insights that apply to those who were not successful. We asked women to remember all the steps that they took since symptom detection. Some of the women admitted they did not recall some of the events. Recall bias could

also impact our study. For example, women may not have mentioned that they sought alternative therapies at some point in their pathway due to stigma. Strengths of our study include examining the pathway from the women's perspective and use of medical records to confirm procedures and treatment.

2.5 Conclusions

Our study highlights that women go through approximately nine steps from symptom detection to receiving allopathic breast cancer treatment in Ghana. Some women skipped some of the steps while others looped back to earlier steps. At each step in the pathway, there are opportunities to intervene in order to increase the rate at which women are diagnosed and start receiving treatment. These interventions include integration of alternative therapy providers and allopathic medicine and consistent breast cancer awareness and clinical breast exam programs. Lastly, this breast cancer care pathway framework may be applicable to other cancers and other sub-Saharan African countries.

CHAPTER 3. MANUSCRIPT 2: BREAST CANCER IN GHANA: WHY THE YOUNGER AGE AT DIAGNOSIS?

3.1 Introduction

Breast cancer is the most common cancer and leading cause of cancer deaths among women in sub-Saharan Africa (SSA). In 2020, breast cancer incidence rates in SSA ranged from 33 per 100,000 to 50 per 100,000 while mortality rates ranged from 18 per 100,000 to 22 per 100,000 (1). Breast cancer patients in SSA tend to be younger (incidence peaks between 40-50 years)(7, 32, 77) than patients in other parts of the world such as the United States (US), where incidence peaks at approximately 62 years (8). Breast cancer among younger women (<40 years) tends to be more aggressive (higher

grade and larger tumor sizes) and have higher mortality rates compared to breast cancer among older women (≥40 years) (78, 79). It is therefore essential to identify factors that can explain the younger age at diagnosis in SSA.

Several studies suggest that the younger age profile in SSA compared to Europe and North America reflects differences in population age structures between countries (10, 11). For example, in Ghana, 35% of the population is between 25 and 59 years and only 4.7% of the population is above 65 years(80), while in the US 16% of the population is above 65 years (81). Therefore, breast cancer cases in Ghana are more likely to occur among younger age groups because a larger proportion of their at-risk population is in younger age groups. Bidoli and colleagues used data from 24 cancer registries in Eastern Mediterranean and Africa to explore the association between the median age at breast cancer diagnosis and the median age of the corresponding population (82). They found that the age at breast cancer diagnosis is associated with the age of the underlying population where a one year increase in population age was associated with 0.26 increase in median age at breast cancer onset. However, this study provided the association between median age at breast cancer diagnosis and median age of the population at the continental level where data from Africa and Eastern Mediterranean cancer registries were grouped together and did not adjust in detail for the age structure of any one country. Also, the study only included information from 24 cancer registries in the Eastern Mediterranean and Africa. Given the variation in cancer incidence rates between SSA countries, there is a need to understand factors contributing to country-specific breast cancer patterns (30).

Breast cancer screening may also impact a country's average age at breast cancer diagnosis. Introduction of mammographic screening in the US is associated with an increase in breast cancer incidence rates among women 50 years and older and subsequent increase in median age at diagnosis (83). While most SSA countries, including Ghana, do not have a national breast cancer screening program, screening in the US is widespread (32, 84).

Research has also shown that breast cancer incidence rates are on average lower in SSA compared to North America and Europe (5). However, estimating cancer incidence rates in SSA is a challenge due to limited population-based cancer registries. In Ghana, only two studies have used population-based cancer registry data to assess the breast cancer incidence rates which were estimated at 7.9 per 100,000 in 2012 and 16.1 per 100,000 in 2015 (7, 85). There is a need to better understand the breast cancer incidence patterns in Ghana.

This study examines the impact of population age structure and breast cancer screening on the mean age at breast cancer diagnosis in Ghana and the US. We also examine the breast cancer incidence patterns in Ghana and the US between 2012 and 2016. To achieve these aims we analyzed breast cancer data from the Kumasi Cancer Registry, the only population-based cancer registry in Ghana, and compare it to the US Surveillance, Epidemiology and End Results (SEER) data.

3.2 Methods

3.2.1 Data sources

We obtained data on incident breast cancer cases in Ghana from the Kumasi Cancer Registry (KCR) and for the United States (US) from the Surveillance, Epidemiology and End Results (SEER) program. The KCR was established in 2004 as a hospital-based registry and was converted to a population-based registry in 2012 (7). The catchment area for the KCR is Kumasi which is the second largest city in Ghana and has a population of 2,035,064 (80). The cancer information in the registry is based on patients' medical records from six laboratories and five hospitals in Kumasi. One of the hospitals is the Komfo Anokye Teaching Hospital (KATH), which is the largest hospital in Kumasi and the second largest in Ghana (67). Information abstracted from medical records is reviewed and verified by a clinician and data quality monitored by the Registry Manager. A combination of date of birth, patient age, National Health Insurance number, and Hospital ID are used to create patient unique identifiers (7).

SEER is a US database that includes cancer cases from population-based cancer registries that presently covers 34% of the US population and is representative of different racial/ethnic groups in the US (86). SEER collects information on incident cancer cases, key information about the tumors including stage at diagnosis, first course of treatment and survival (87). The SEER registries are grouped into three overlapping categories based on the years of data that the registries contribute: SEER 9, SEER 13 and SEER 18. SEER 9 includes cases diagnosed from 1975 to 2017 from nine cancer registries, SEER 13 includes cases diagnosed from 1992 to 2017 from the original nine registries plus four registries and, SEER 18 includes cases diagnosed from 2000 to 2017 from an additional five cancer registries (88).

We obtained US population estimates stratified by race (White and Black), age (5-year age groups) and sex from the National Cancer Institute (89). The Kumasi population estimates stratified by age (5-year age groups) and sex were obtained from the Ghana Statistical Services (90).

3.2.2 Breast cancer cases

We included US and Ghanaian women diagnosed with invasive and in situ breast cancer with known age at diagnosis. For Ghana, we restricted to women diagnosed between 2012 and 2016 since these were the years that the KCR was population-based and had complete and accurate data. For the US, we included women diagnosed between 2012 and 2016 to match the Ghana cohort and women diagnosed between 1975 and 1979 to account for the effect of screening (more detail below). SEER 9 registries are the only ones that include cases diagnosed between 1975 and 1979 therefore we were limited to using the SEER 9 registries only. To ensure consistency, we also limited our US 2012-2016 cancer diagnosis to those from the SEER 9 registries.

3.2.3 Statistical Analysis

Effect of population age structure on the differences in mean age at diagnosis between Ghana and the US

We examined whether differences between Ghana and the US in mean age at breast cancer diagnosis persisted after accounting for differences between the two countries' population age structures. First, we calculated the crude mean age at diagnosis for Ghanaian and US female breast cancer patients diagnosed between 2012 and 2016. Research has shown that in the US, Black women are diagnosed with breast cancer at a younger age than White women, therefore we also calculated the crude mean age at

diagnosis by race (White vs Black) for the US population (91). Crude mean age was calculated as $\frac{\Sigma y}{\Sigma N}$ where *y* is the age at diagnosis and *N* is the number of people with breast cancer. Second, to examine the effect of differences in population age structure between Ghana and the US, we calculated the adjusted mean age at diagnosis. We used the World Health Organization (WHO) world standard population as the standard population since it reflects the average age structure of the world's population and facilitates comparisons with findings published from other countries (92). In the adjusted analysis, the weight was the proportion of people in the corresponding age group of the WHO world standard population. Overall adjusted mean age at diagnosis was calculated as $\frac{\Sigma(y*w_i)}{\Sigma w_i}$ where y_i is the age at diagnosis and w_i is the proportion of people in WHO standard world population for age y_i. The adjusted mean age at diagnosis represents what the mean age at diagnosis would be if Ghana and the US had the same age population distribution. Third, age differences were calculated by subtracting the mean age at diagnosis among the US cases from the mean age at diagnosis among Ghanaian cases. Negative differences showed a lower mean age at diagnosis among cases in Ghana. We used a t-test to test whether the crude and adjusted mean ages between the two countries differ significantly.

Effect of breast cancer screening on the differences in mean age at diagnosis between Ghana and the US

We examined whether differences between Ghanaian and US women in mean age at breast cancer diagnosis persisted after accounting for breast cancer screening. SEER does not include screening information. Screening mammography was not nationally

adopted in the US until the 1980s, so we used data for US women diagnosed with breast cancer between 1975 and 1979 to adjust for the effect of screening mammography on the cancer incidence in the US (93). Specifically, we calculated crude mean age at diagnosis and adjusted mean age at diagnosis using the US SEER 9 1975-1979 breast cancer data. We then compared these values to the crude and adjusted mean age at diagnosis for Ghanaian women diagnosed with breast cancer between 2012 and 2016.

Sensitivity analyses – impact of the standard population on the adjusted mean age at diagnosis

We conducted a sensitivity analysis to assess the influence of using the WHO standard population on our estimates and conclusions. We calculated the adjusted mean age at diagnosis in the US and Ghana (as described above) using two standard populations: the US standard population and the European standard population. We then compared the estimates to those we had calculated using the WHO world standard population.

Breast cancer incidence rates in Ghana and the US 2012 - 2016

Lastly, we calculated and compared three breast cancer incidence rates in 2012-2016 in Ghana and the US: crude, 5-year age-specific and age standardized incidence rates. The crude incidence rate is the number of new breast cancer cases for the period of interest as a proportion of the total population for the specific period. The 5-year age-specific incidence rate is calculated as the new breast cancer cases in the 5-year age group as a proportion of the total population in the 5-year age group. The age standardized rates represent the incidence rate that would have been observed if Ghana and the US had the same age structure as the WHO world standard population.

All analyses used SAS (PC SAS 9.4, SAS Institute, Inc., Cary, NC). Ethical approval was granted by the Institutional Review Boards at KATH and University of Minnesota.

3.3 Results

Our dataset included 542 women from Ghana and 114,100 women from the US diagnosed with breast cancer between 2012 and 2016. Women were diagnosed at older ages in the US than in Ghana (**Figure 2a, Figure 2b**). Twenty-three percent of the women with breast cancer in Ghana were <40 years of age at diagnosis compared to four percent in the US. In the US, six percent of the Black women with breast cancer were <40 years of age at diagnosis compared to four percent White women. Only ten percent of the cases in Ghana were older than 70 years compared to twenty-eight percent of cases in the US, twenty-two percent of cases among Black women and thirty percent of cases among White women.

Figure 2a: Age distribution for Ghanaian and US women diagnosed with breast cancer 2012-2016

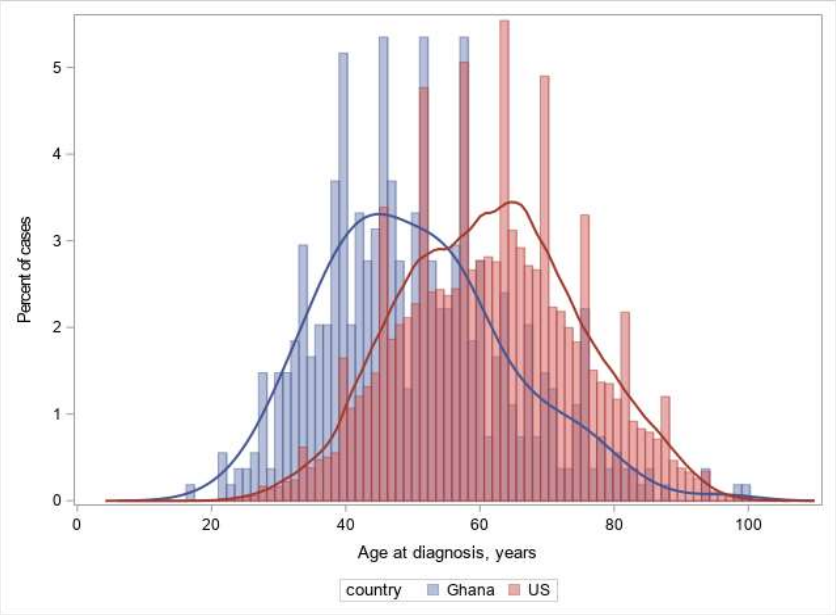
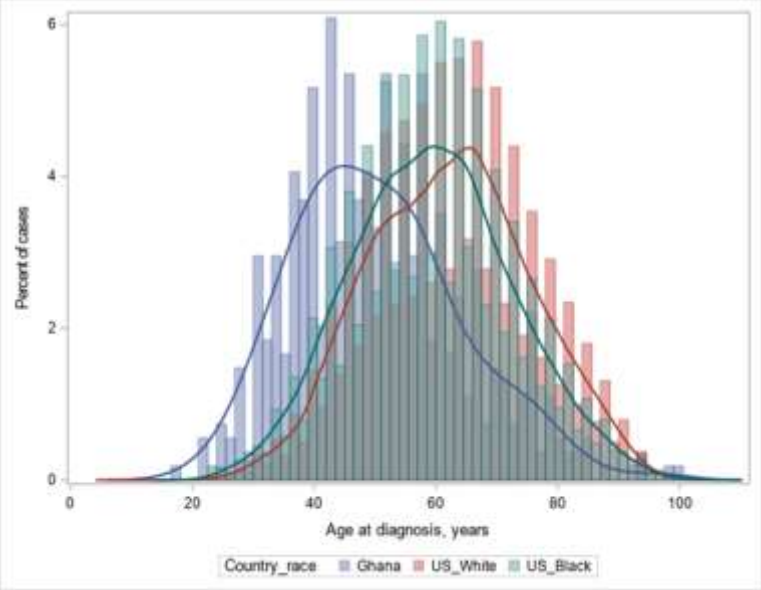


Figure 2b: Age distribution for Ghanaian women and US Black and White women diagnosed with breast cancer 2012-2016



Effect of population age structure on the differences in mean age at diagnosis between Ghana and the US

Prior to adjustment, the mean age at diagnosis in Ghana was 50.3 years compared with 61.6 years among the US cases (crude difference of 11.3 years), which was significantly different ($p<0.0001$). After adjusting for population age structure, the mean

age at diagnosis remained significantly different between the two countries where the adjusted mean age in Ghana was 45.6 years and 55.1 years in the US (adjusted difference of 9.6 years, p <0.0001) (**Table 3**).

After adjusting for population age structure, women diagnosed with breast cancer in Ghana were on average 8 years younger than Black women and 10.2 years younger than White women diagnosed with breast cancer in the US (**Table 3**).

Effect of breast cancer screening on the differences in mean age at diagnosis between Ghana and the US

To examine the combined impact of breast cancer screening and population age structure on the differences in mean age at breast cancer diagnosis between Ghana and the US, we compared 1975-1979 US breast cancer cases (before widespread breast cancer screening) to 2012-2016 Ghanaian breast cancer cases. Similar to the findings above, US women diagnosed with breast cancer between 1975 and 1979 were on average older than women in Ghana diagnosed with breast cancer between 2012 and 2016 (**Figures 3a and 3b, Table 4).** However, the adjusted difference in mean age between 2012-2016 Ghanaian and the 1975-1979 US breast cancer cases was smaller compared to the adjusted difference between 2012-2016 Ghanaian and the 2012-2016 US breast cancer cases (-8.0 years vs -9.6 years respectively). Even after accounting for screening and population age structure, a difference of -8 years remains between Ghana and the US (**Tables 3 and 4**).

There was a similar trend when considering US White and Black cases separately. The adjusted difference in mean age between 2012-2016 Ghanaian cases and 1975-979 US White cases was -8.5 years compared to -10.2 years when using 2012-2016 US White

cases. When we restricted to the US Black cases, the adjusted difference in mean age between 2012-2016 Ghanaian cases and 1975-1979 US Black cases decreased substantially from -8 years to -4.6 years(**Tables 3 and 4**).

Figure 3a: Population age distribution for Ghanaian women diagnosed with breast cancer 2012-2016 and US women diagnosed with breast cancer 1975-1979

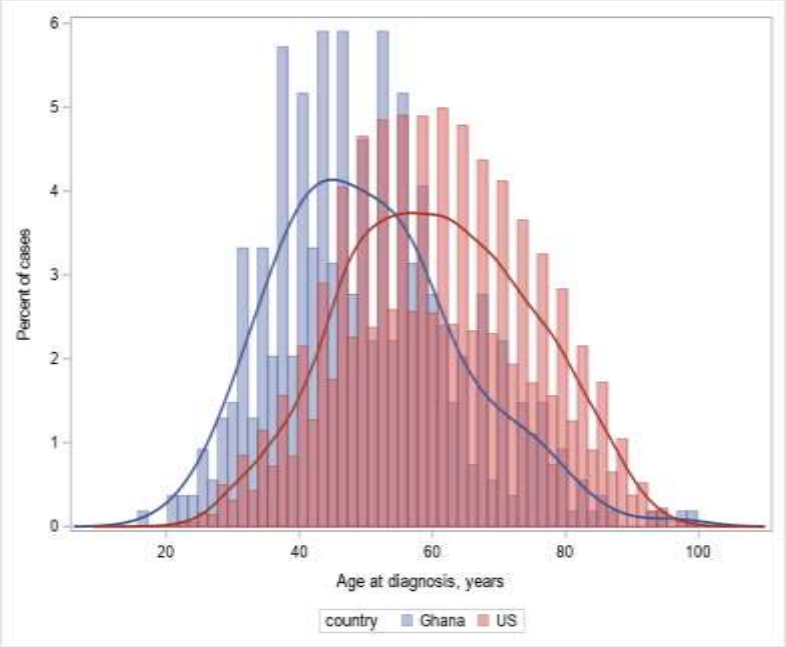


Figure 3b: Age distribution for Ghanaian women diagnosed with breast cancer 2012-2016 and US Black and White women diagnosed with breast cancer 1975-1979

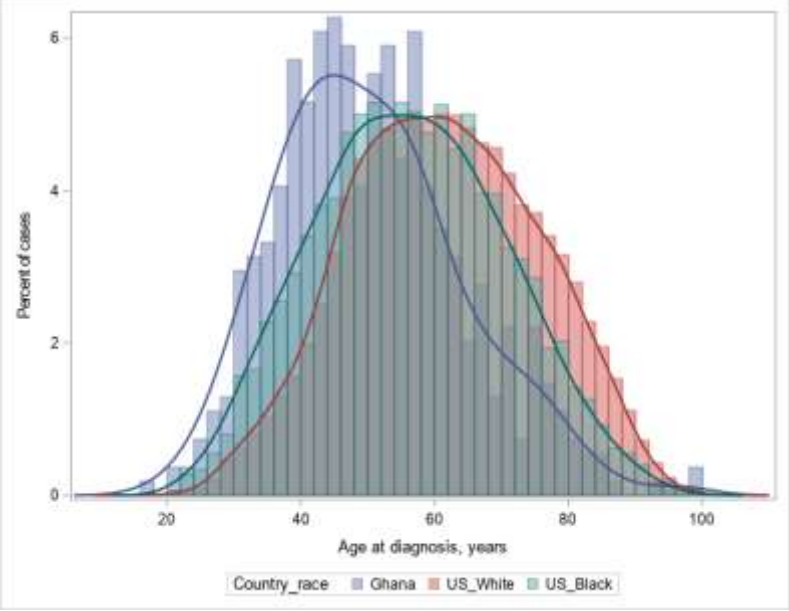


Table 3: Mean age at diagnosis (crude and adjusted) for women diagnosed with breast cancer in Ghana and the US 2012-2016

	Cases, N (%)		**Crude mean age (years) at diagnosis**		**P value (T-test)**	**Adjusted mean age (years) at diagnosis**		**P value (T-test)**	**Difference in mean (Ghana – US)**	
Year	**Ghana**	**US**	**Ghana**	**US**		**Ghana**	**US**		**Crude**	**Adjusted**
2012-2016 Ghana and US all races	542	144100	50.3	61.6	<0.0001	45.6	55.1	<0.0001	-11.3	-9.6
2012-2016 Ghana and US White women	542	110174	50.3	62.3	<0.0001	45.6	55.8	<0.0001	-12.0	-10.2
2012-2016 Ghana and US Black women	542	16241	50.3	59.4	<0.0001	45.6	53.6	<0.0001	-9.1	-8.0

Table 4: Mean age at diagnosis (crude and adjusted) for breast cancer cases diagnosed in Ghana in 2012-2016 and the US 1975-1979

	Cases, N (%)		**Crude mean age (years) at diagnosis**		**P value (T-test)**	**Adjusted mean age (years) at diagnosis**		**P value (T-test)**	**Difference in mean (Ghana – US)**	
	Ghana	**US**	**Ghana**	**US**		**Ghana**	**US**		**Crude**	**Adjusted**
2012-2016 Ghana and 1975-1979 US all races	542	50496	50.3	60.6	<0.0001	45.6	53.6	<0.0001	-10.3	-8.0
2012-2016 Ghana and 1975-1979 US White women	542	45537	50.3	61.2	<0.0001	45.6	54.1	<0.0001	-10.9	-8.5
2012-2106 Ghana and 1975-1979 US Black women	542	3258	50.3	56.2	<0.0001	45.6	50.1	<0.0001	-5.9	-4.6

Sensitivity analyses – impact of the standard population on the adjusted mean age at diagnosis

There were no notable changes in the adjusted mean age at diagnosis when we used the US and European standard populations (**Table 5**).

Table 5: Sensitivity analyses assessing the impact of using different standard populations

	Ghana and US breast cancer cases diagnosed 2012-2016									
	Cases, N (%)		**Crude mean age (years) at diagnosis**		**P value (T-test)**	**Adjusted mean age (years) at diagnosis**		**P value (T test)**	**Difference in mean (Ghana – US)**	
Standard population	**Ghana**	**US**	**Ghana**	**US**		**Ghana**	**US**		**Crude**	**Adjusted**
World Health Organization	542	144100	50.30	61.58	<0.0001	45.55	55.13	<0.0001	-11.28	-9.58
United States	542	144100	50.30	61.58	<0.0001	46.46	56.18	<0.0001	-11.28	-9.72
European	542	144100	50.30	61.58	<0.0001	47.01	56.16	<0.0001	-11.28	-9.15
	Ghana breast cancer cases diagnosed 2012-2016 and US cases diagnosed 1975-1979									
World Health Organization	542	50496	50.30	60.63	<0.0001	45.55	53.58	<0.0001	-10.33	-8.03
United States	542	50496	50.30	60.63	<0.0001	46.46	54.81	<0.0001	-10.33	-8.35
European	542	50496	50.30	60.63	<0.0001	47.10	54.81	<0.0001	-10.33	-7.71

Breast cancer incidence rates in Ghana and the US 2012 – 2016

Both the crude and age standardized breast cancer incidence rates were lower among Ghanaian women compared to US women between 2012 and 2016. The crude breast cancer incidence rate in Ghana was 9.15 per 100,000 and 189.14 per 100,000 in the US. The age standardized breast cancer incidence rates in Ghana were 14.16 per 100,000 and 129.89 per 100,000 in the US. Age-specific incidence rates and the incidence rate differences between Ghana and the US increased with increasing age. Ghana's age specific incidence rate increases from 0.16 to 25.68 per 100,000, whereas the age specific rate for the US increases from 0.02 to 473.44 per 100,000. In addition, Ghana's incidence rate is 23.68 per 100,000 lower than the US's in the 30-34 years age group and 408 per 100,000 lower in the 60-64 years age group. (**Table 6**).

Table 6: Breast cancer incidence rates among women diagnosed with breast cancer 2012-2016 in the US and Ghana

	Ghana	**US all women**	
Crude incidence rate	9.15 per 100,000	189.14 per 100,000	
Age standardized incidence rate	14.16 per 100,000	129.89 per 100,000	
Age group (Years)	**Age specific incidence rate/100,000**		**Difference (Ghana-US)**
5 - 9	0.00	0.02	-0.02
10 - 14	0.00	0.00	0.00
15 - 19	0.16	0.10	0.06
20 - 24	1.04	1.99	-0.95
25 - 29	2.88	10.93	-8.05
30 - 34	10.12	33.80	-23.68
35 - 39	17.73	74.11	-56.38
40 - 44	26.86	174.71	-147.85
45 - 49	31.53	266.87	-235.34
50 - 54	35.67	320.81	-285.14
55 - 59	53.83	349.78	-295.95

60 - 64	34.59	442.59	-408.00
65 - 69	39.37	546.54	-507.17
70 - 74	23.20	591.61	-568.41
75+	25.68	473.44	-447.77

3.4 Discussion

In this population-based study of women diagnosed with breast cancer in Ghana and the US, we found that the mean age at breast cancer diagnosis is significantly lower among women in Ghana compared to the US. This discrepancy persisted even after accounting for differences between the two countries in population age structure and breast cancer screening. On average, women in Ghana were 11.3 years younger than women in the US. After adjusting for differences between the two countries' population age and breast cancer screening, on average, women in Ghana were 8 years younger than women in the US at breast cancer diagnosis.

In our study, the difference between Ghana and the US in mean age at breast cancer diagnosis for cases diagnosed 2012-2016 decreased from 11.3 years to 9.6 years after adjusting for differences between the two countries population age structure. Thus, 15% of the difference in mean age at diagnosis between Ghana and the US is explained by these population age structure differences. A study by Bidoli et al. reported that age at breast cancer diagnosis reflects the median age of the population, where one year increase in population age was associated with 0.26 increase in median age at breast cancer onset (82). However, the differences in methods and populations between our study and Bidoli et al. make estimates from these two studies incommensurable. The Bidoli et al. study assumed a linear relationship, across registries in the Eastern Mediterranean and Africa, between median age of the population and the median age at breast cancer diagnosis

while we used direct standardization of the mean age at cancer diagnosis. Also, our study included and pertains only to the US and Ghana populations while Bidoli et al.'s analysis is at the continent level, combining data from the Eastern Mediterranean and Africa.

We explored the possibility of breast cancer screening influencing the significant difference in the mean age at breast cancer diagnosis between Ghana and the US. Once we accounted for population age structure and screening effect, the difference in mean age at diagnosis between Ghana and the US decreased from 11.3 years to 8 years. This decrease is due to the fact that the mean age at diagnosis in the US was higher in the post-screening era (2012-2106) compared to the pre-screening era (1975-1979). Screening mammography in the US has been associated with an increase in breast cancer incidence rates especially among women 50 years and older, the ages at which routine screening is recommended, resulting in an increased the mean and median age at diagnosis (83). In spite of the many advantages of breast cancer screening, it is well recognized that some cancer cases detected by screening are indolent and unlikely to progress to clinically significant disease (94).

Even after taking into account differences in population age structures and screening, women in Ghana were 8 years younger at breast cancer diagnosis compared to women in the US. A possible explanation for this persisting difference in mean age at diagnosis is differences in the prevalence of risk factors among older women in Ghana compared to older women in the US. Older women in Ghana are more likely to have protective breast cancer risk profiles such as higher parity (95, 96) leading to a decreased breast cancer incidence rate among older women in Ghana compared to older women in the US. Consistent with this explanation, we observed that differences between Ghana

and the US in incidence of breast cancer increases with age. Specifically, at >=40 years, the incidence of breast cancer is substantially higher in the US compared to Ghana vs incidence rates at <40 years. This observation is similar to a previous study that found breast cancer incidence rates among women <40 years in North-Africa and France were similar but among women >=40 years the incidence was much higher in France (97).

The age standardized breast cancer incidence rate in Ghana was considerably lower at 14.16 per 100,000 compared to 129.89 per 100,000 in the US. Our estimate is also lower than the pooled West African breast cancer incidence rate of 24.2 per 100,000 reported by Adeloye et al (30). While population based, the KCR only reports information from 5 of 6 facilities in Kumasi that provide breast cancer care. However, data from KATH, the main cancer treatment hospital in Kumasi, is included in our sample so the registry likely captures the majority of cases in Kumasi (7, 67). Even when taking underestimation into account, the US incidence rate is still substantially higher compared to the Ghana rate. However, it is possible that over time the breast cancer incidence rates in Ghana will increase. Similar to other SSA countries, women in Ghana are living longer and their breast cancer risk profiles, especially among women in urban areas, are changing and becoming more similar to that of the US. For example, fertility rates in Ghana are declining (98), obesity rates are increasing (99) and life expectancy is increasing (100). The breast cancer risk profile in Ghana will continue to evolve and will likely lead to an increased incidence of breast cancer especially among older individuals. Research that evaluates the longitudinal changes in mean age at breast cancer diagnosis could help better understand the impact of these demographic shifts.

This study has several limitations. First, as previously stated, our estimate of incidence of breast cancer in Kumasi may have been underestimated. Second, while both SEER and KCR use ICD-O guidelines to identify incident cancer cases, the guideline versions are not identical. SEER uses the North American Association of Central Cancer Registries ICD-O guidelines while KCR uses the International Agency for Research on Cancer ICD-O guidelines (101, 102). In spite of these limitations, our study is the first to compare estimates from the only population-based registry in Ghana to nationally representative SEER data from the US. Our findings contribute valuable information on factors that may contribute to the persistent finding of the younger age at breast cancer diagnosis seen in Ghana.

3.5 Conclusion

Our study shows the importance of adjusting for differences in population age structures when comparing age at cancer diagnosis between countries. The younger age at diagnosis among women in Ghana compared to women in the US is partly due to population age structure differences. However, other factors such as breast cancer screening and differences in risk factor exposure among older women likely contribute to the age at diagnosis differences. Lastly, as the profile of breast cancer risk factors in Ghana becomes more like that of the US, the incidence of breast cancer in Ghana is expected to increase and may eventually reach current US levels. There is therefore an urgent need for evidence-based early detection and treatment interventions for the Ghanaian population.

CHAPTER 4. MANUSCRIPT 3: USE OF SURGERY AND RADIATION FOR TRIPLE NEGATIVE BREAST CANCER: ASSOCIATION WITH SURVIVAL

4.1 Introduction

Triple negative breast cancer (TNBC) is a breast cancer subtype associated with an aggressive clinical course. It is characterized by lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (i.e. ER-, PR- and HER2-) (2, 3). TNBC accounts for 12-15% of all invasive breast cancer cases in the United States and is more likely to be diagnosed among Black and younger women (13, 103). Compared to other subtypes, TNBC has the highest recurrence rates, poorest survival rates and is usually higher grade, and has larger tumor size at diagnosis (3, 4). Because TNBC tumors do not have HER2, progesterone, or estrogen receptors, neither hormone therapy nor medications that work by blocking HER2 are used to treat patients with TNBC (13). This raises the question of whether the poor prognosis of TNBC warrants a more aggressive surgical approach and whether there is value in expanded use of radiation therapy among women with TNBC who receive mastectomy.

Breast conserving surgery (BCS) and mastectomy are the two surgical options for breast cancer patients. Guidelines recommend that BCS should be followed by radiotherapy (i.e., breast conserving therapy, BCT) (104). While patients who receive mastectomy can receive radiotherapy, it is generally only recommended for cases with positive surgical margins or involved lymph nodes (26). The National Comprehensive Cancer Network (NCCN) surgical guidelines for breast cancer do not vary by breast cancer subtype (26). While randomized trials have shown that breast cancer patients

undergoing BCT or mastectomy have similar survival rates (105-107), to our knowledge, no randomized trials have compared different surgical treatments for TNBC.

Several observational studies have explored use of surgery and radiotherapy for TNBC but have conflicting findings. Two population-based studies found that TNBC patients treated with BCT had superior breast cancer specific survival (BCSS) and overall survival (OS) compared to those who received mastectomy or mastectomy and radiotherapy (108, 109). However, the studies had only 3 years of follow-up and did not adjust for comorbidities that may impact surgical treatment for breast cancer (110). Two single-institution studies also found that TNBC patients who received BCT had higher OS compared to those who received mastectomy or mastectomy with radiotherapy (111, 112). However, other single institution studies found no difference in OS among TNBC patients undergoing BCT or mastectomy (113, 114).

Our study aims to examine whether the poor prognosis of TNBC necessitates a more aggressive surgical approach (i.e., mastectomy instead of BCS) and whether radiotherapy after BCS or mastectomy improves OS and BCSS. The goal is to inform guidelines for surgical treatment in this population.

4.2 Materials and Methods

4.2.1 Data

We used the National Cancer Institute (NCI)'s linked Surveillance Epidemiology and End Results (SEER)-Medicare database, which combines SEER population-based cancer registries data and Medicare claims. The SEER cancer registries provide population-based cancer surveillance data covering approximately 30% of the United

States (115). SEER data include patient sociodemographic and tumor characteristics, first course of treatment, and follow-up vital statistics. Medicare is a federally funded insurance program that provides coverage to 97% of the US population age 65 years and older. SEER-Medicare links 93% of eligible cancer cases to their Medicare claims (87).

4.2.2 Study population

The study cohort included women age 66 years or older diagnosed with stage I - III TNBC as their first or only cancer between 2010 and 2015. We required the women to be enrolled in Medicare fee-for-service for at least 12 months before and after cancer diagnosis or until death. This ensured that women have complete claims. We excluded women who did not have a known month of diagnosis and whose diagnosis was based on autopsy or death certificate (**Appendix B**).

4.2.3 Patient characteristics

Patient demographic characteristics obtained from Medicare included age at diagnosis, race, and comorbidity. Other sociodemographic variables included US census region and census median household income. We used the Charlson Comorbidity Score to calculate comorbidity and categorized it as 0,1,2 and 3+ (116). Patient-level tumor characteristics obtained from SEER included tumor size and stage at diagnosis.

4.2.4 Treatment

The four treatments considered were: 1) breast conserving surgery (BCS); 2) BCS and radiotherapy (i.e., breast conserving therapy, BCT); 3) mastectomy; and 4) mastectomy and radiotherapy. We used MedPAR, Outpatient, and Carrier files to identify the treatments (**Appendix C**) (117-119).

4.2.5 Outcome

Our outcomes were breast cancer-specific survival (BCSS) and overall survival (OS). Survival was defined as number of months from cancer diagnosis to death. Cause and date of death information were obtained from SEER. We used SEER's death date because it is linked to cause of death information. Observations were censored at the date of death or end of the observation period (December 31, 2015).

4.2.6 Statistical Analysis

We used Pearson's chi-square test to compare clinical and sociodemographic characteristics among the four treatment groups.

Overall survival (OS)

The Kaplan-Meier method was used to assess the cumulative incidence of all-cause mortality by treatment. The log rank test was used to test differences between the survival curves. Cox proportional hazards regression was used to evaluate the effect of treatment method on OS controlling for tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region, and Charlson comorbidity score.

Inverse Probability of Treatment Weighting (IPTW)

Separately, we also used an IPTW Cox proportional hazards regression to evaluate the effect of treatment method on OS. To reduce treatment selection bias, we estimated propensity scores and used them in IPTW. Weighting patients by the inverse probability of the treatment received is another way to remove the association between the baseline covariates and treatment received (120). We used polytomous logistic regression to estimate the probability of treatment conditional on these baseline variables: tumor size, tumor stage, age at diagnosis, race, census tract median household income,

US census region, and Charlson comorbidity score. The inverse of each person's estimated probability of getting each treatment is the IPTW. We stabilized and truncated the IPTW to reduce variance induced by patients with extreme weights (121, 122). Stabilized IPTW was calculated by multiplying the IPTW by the estimated probability of receiving the treatment that each individual received (123). The stabilized IPTW were truncated at the 1st and 99th percentile (121). After IPTW, we used Pearson's chi-square to test the balance of the baseline variables and all variables were balanced.

Breast cancer specific survival (BCSS)

We used the Fine and Gray competing risk approach, where death due to breast cancer was the event of interest and death from other causes was considered a competing risk (124). We used a competing risk approach because individuals dying from other causes impacts the number of individuals who can die from breast cancer (125). Cumulative incidence functions (CIF) were used to estimate the incidence of death due to breast cancer by treatment. Gray's test was used to test differences between the CIFs. We used a Fine and Gray subdistribution hazard model to evaluate the effect of treatment method on BCSS while controlling for demographic and clinical characteristics. Separately, we also used an IPTW Fine and Gray subdistribution hazard model to evaluate the effect of treatment method on BCSS. The stabilized and truncated IPTW method is described above.

We assessed the proportional hazard assumption in each analysis by specifying an interaction of treatment with survival time. The proportional hazard assumption was not violated.

Treatments pair comparison and effect by stage

For each of the OS and BCSS models, we did pairwise comparisons to determine whether pairs of treatments differed, using Tukey's multiple comparison test to compare each pair and adjust for multiple comparisons. To examine whether the overall treatment effects were the same within each stage, we split the dataset by stage (I, II, and III) and re-did the analysis described above.

Sensitivity analysis

We conducted a series of sensitivity analyses to confirm that our findings did not vary based on analytic decisions. First, we confirmed that removing the <11 individuals who survived for less than one month after diagnosis did not impact model estimates. (We report the number of women excluded as "<11" to comply with the SEER-Medicare DUA which does not allow reporting of numbers less than 11 (126)). A second set of sensitivity analyses confirmed that using specific age and tumor size categories did not impact our results. We tested this by running the models described above with age as a continuous predictor, and categorizing the tumor sizes into smaller sub-categories (≤2 cm, > 2 and ≤ 5 cm, > 5 and ≤ 10 cm, and >10cm). Third, we adjusted for chemotherapy receipt.

All statistical tests were two-sided, and the level of significance was set at $p < 0.05$. All analyses used SAS (PC SAS 9.4, SAS Institute, Inc., Cary, NC). This study was considered exempt by the Institutional Review Board at the University of Minnesota.

4.2.7 Results

Population description

A total of 4598 women met our inclusion criteria (**Appendix A**). Of these, 94% (N = 4,333) received surgery (mastectomy or BCS). Of the 4,333, 49% (N=2,110) were

treated with BCT, 28% (N=1,219) with mastectomy, 14% (N=602) with mastectomy and radiotherapy (RT) and 9% (N=402) with BCS. All the sociodemographic and clinical characteristics differed by treatment group except race. However, all the characteristics were balanced when we used stabilized and truncated IPTWs (all $p>0.05$). Compared to women who received other treatments, women who received BCT were younger, more likely to be stage I, had smaller tumors (≤2 cm), had lower Charlson comorbidity scores, were more likely to live in the Northeast US census region,and to be in the highest census tract median household income (>$60,000) (**Table 7**).

Table 7: Baseline patient demographic and clinical characteristics

	BCS (N= 402)		BCT (N = 2110)		Mastectomy (N= 1219)		Mastectomy + Radiotherapy (N= 602)		P value[a]	IPTW P value[a]
Characteristics	N	%	N	%	N	%	N	%		
Age at diagnosis (years)									<0.0001	0.86
66-74	135	33.58	1254	59.43	533	43.72	348	57.81		
75-84	139	34.58	716	33.93	474	38.88	185	30.73		
85+	128	31.84	140	6.64	212	17.39	69	11.46		
Race									0.35	0.72
White	331	82.34	1746	82.75	994	81.54	499	82.89		
Black	50	12.44	283	13.41	156	12.80	77	12.79		
Other	21	5.22	81	3.84	69	5.66	26	4.32		
Region									<0.0001	0.21
Midwest	57	14.18	268	12.70	166	13.62	92	15.28		
Northeast	71	17.66	479	22.70	188	15.42	110	18.27		
South	107	26.62	486	23.03	376	30.84	165	27.41		
West	167	41.54	877	41.56	489	40.11	235	39.04		
Stage									<0.0001	0.29
I	199	49.50	1274	60.38	428	35.11	51	8.47		
II	173	43.03	731	34.64	623	51.11	231	38.37		
III	30	7.46	105	4.98	168	13.78	320	53.16		
Tumor size									<0.0001	0.42
≤2 cm	211	52.49	1370	64.93	481	39.46	120	19.93		
> 2 and ≤ 5 cm	164	40.80	665	31.52	586	48.07	277	46.01		
> 5 cm	27	6.72	75	3.55	152	12.47	205	34.05		
Charlson Comorbidity Score									<0.0001	0.37

0	245	60.95	1569	74.36	810	66.45	443	73.59		
1	84	20.90	331	15.69	203	16.65	95	15.78		
2	30	7.46	111	5.26	118	9.68	38	6.31		
3+	43	10.70	99	4.69	88	7.22	26	4.32		
Census tract median household income									<0.0001	0.99
<$40,000	87	21.64	346	16.40	281	23.05	111	18.44		
$40,001 - $50,000	69	17.16	280	13.27	191	15.67	105	17.44		
$50,001 - $60,000	60	14.93	325	15.40	197	16.16	95	15.78		
>$60,000	156	38.81	1055	50.00	462	37.90	257	42.69		
Missing	30	7.46	104	4.93	88	7.22	34	5.65		

[a] P values based on Pearson $\chi 2$. Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy

Overall survival

The treatment groups differed significantly according to the Kaplan-Meier (KM) curves (p value <0.0001) (**Figure**). The unadjusted KM curves show higher overall survival for women who received BCT compared to those who received BCS, mastectomy, or mastectomy + RT. Specifically, the 5-year overall survival rates for women who underwent BCT, mastectomy, mastectomy + RT, and BCS were 81.44%, 57.16%, 47.18%, and 51.07% respectively (**Table 8**).

Findings from our multivariate and IPTW Cox proportional hazard models were similar (**Table 9a, Appendix D**). Here we present output from the multivariate Cox proportional hazard models. The three other treatments differed significantly from BCT after controlling for sociodemographic and clinical characteristics. Women who received BCS, or mastectomy or mastectomy + RT had significantly higher hazard of death compared to women who had BCT (hazard ratios (HR), 95% confidence interval (CI): 3.05, [2.43 - 3.83]; 2.03, [1.70 - 2.43]; 1.74, [1.39 - 2.17] respectively) (**Table 9a**). In pairwise comparisons adjusted for multiple comparisons (**Table 9b**), five pairs of treatment differed significantly. Women who had BCS or mastectomy or mastectomy+ RT had significantly higher hazard of death compared to those who had BCT (adjusted p values <0.0001), and women who had BCS had significantly higher hazards of death compared to those who had mastectomy or mastectomy + RT (HR, adjusted p values: 1.50, 0.0008 and 1.75, 0.0001, respectively). However, the hazard of death did not differ between those who had mastectomy vs mastectomy + RT (adjusted p value 0.39).

Several factors were independent predictors of increased hazard of death (**Table 9a**). Women with tumor size > 5 cm had higher hazard of death than those whose tumor

size was ≤2 cm (HR, 95% CI: 1.61, [1.23 - 2.10]). Women whose tumors were stage II or III had higher hazard of death than those whose tumors were stage I (HR, 95% CI: 2.03 [1.54 - 2.68]; 4.10 [3.06 - 5.50] respectively). Lastly, older women (75-84 and 85+ years) had higher a hazard of death than younger women (66-74 years), women with higher Charlson comorbidity score had a higher hazard of death than those with lower scores, and women who lived in the Midwest and South US census regions had a higher hazard of death compared to those who lived in the West.

Figure 4. Overall survival: Kaplan Meier Curves by treatment

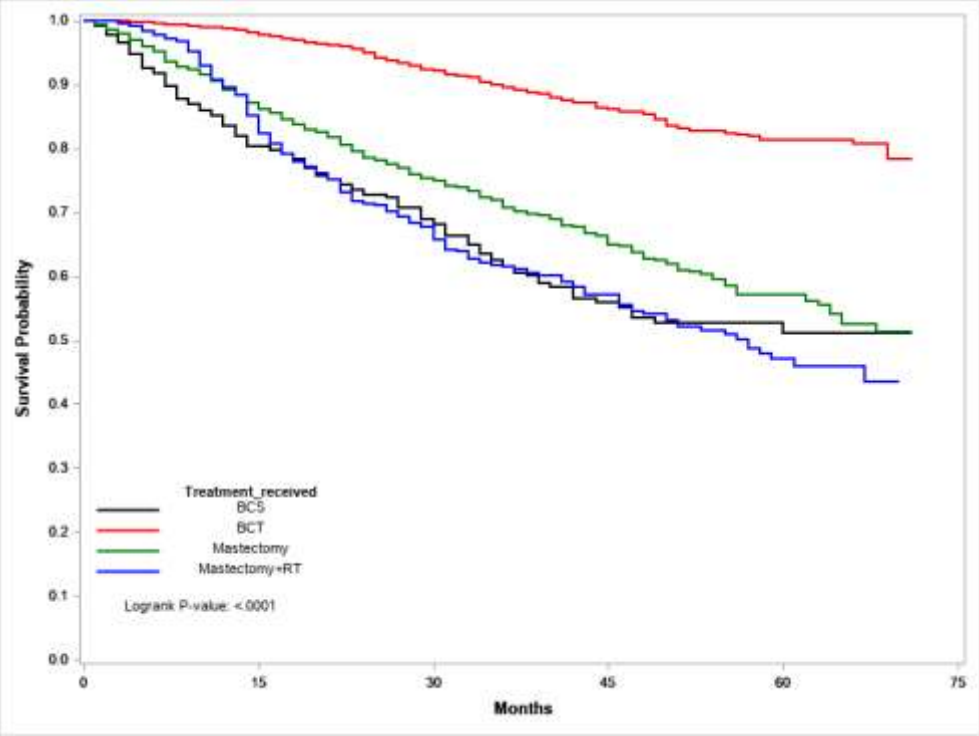


Table 8: 5 year all-cause and breast cancer mortality cumulative incidence

	BCT	**Mastectomy**	**Mastectomy + RT**	**BCS**
5 year all-cause mortality cumulative incidence (%)	81.44	57.16	47.18	51.07
5 year breast cancer mortality cumulative incidence (%)	8.35	18.56	36.02	20.44

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; HR

Table 9a: Multivariate Cox proportional hazards model predicting all-cause mortality

	HR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	3.05	2.43 - 3.83	<0.0001
Mastectomy	2.03	1.70 - 2.43	<0.0001
Mastectomy + RT	1.74	1.39 - 2.17	<0.0001
Tumor size			
≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.09	0.85 -1.41	0.49
> 5 cm	1.61	1.23 - 2.10	0.0005
Stage			
I	1.00 (Reference)		
II	2.03	1.54 - 2.68	<0.0001
III	4.10	3.06 - 5.50	<0.0001
Age at diagnosis (years)			
66-74	1.00 (Reference)		
75-84	1.52	1.30 - 1.77	<0.0001
85+	2.49	2.076-2.98	<0.0001
Race			
White	1.00 (Reference)		
Black	0.89	0.72 - 1.09	0.24
Other	0.98	0.71 - 1.35	0.90
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	1.26	1.05 -1.50	0.01
2	1.49	1.18 - 1.89	0.001
3+	2.30	1.85 - 2.87	<0.0001
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.07	0.87 - 1.33	0.52
50,001 - 60,000	1.00	0.80 - 1.24	0.97
>60,000	0.90	0.75 - 1.09	0.29
Missing	1.02	0.76 - 1.35	0.92
Region			
Midwest	1.24	1.02 - 1.52	0.03
Northeast	0.97	0.80 - 1.18	0.74
South	1.21	1.02 - 1.44	0.03
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio

Table 9b: Pairwise Comparison - multivariate Cox proportional hazards model predicting all-cause mortality

Treatment	**HR**	**95% CI**	**P value[a]**
BCS vs BCT	3.05	2.43 - 3.84	<0.0001
BCS vs Mastectomy + RT	1.75	1.35 - 2.27	0.0001
BCS vs Mastectomy	1.50	1.22 - 1.85	0.0008
Mastectomy + RT vs BCT	1.74	1.39 - 2.17	<0.0001
Mastectomy vs BCT	2.03	1.70 - 2.43	<0.0001
Mastectomy vs Mastectomy + RT	1.17	0.96 - 1.42	0.39

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons
Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Breast cancer specific survival

Gray's test indicated that the treatment groups differed significantly in their CIFs (p value <0.0001) (**Figure 5**). The unadjusted CIFs showed lower cumulative incidence of death due to breast cancer for women who received BCT compared to those who received mastectomy, mastectomy + RT, or BCS. The 5-year cumulative incidence of death due to breast cancer for women who underwent BCT, mastectomy, mastectomy + RT, and BCS were 8.35%, 18.56%, 36.02%, and 20.44%, respectively (**Table 8**).

As with overall survival, findings were similar from our multivariate and IPTW Fine and Gray subdistribution hazard models (**Table 10a, Appendix E**). Here we present output from the multivariate Fine and Gray subdistribution hazard model. The three other treatments differed significantly from BCT after controlling for sociodemographic and clinical characteristics. Women who had BCS or mastectomy or mastectomy + RT had significantly higher hazard of death due to breast cancer compared to women who had BCT (subdistribution hazard ratios (sHR), 95% CI: 2.67, [1.88 - 3.80]; 1.64, [1.26 - 2.12], 1.95, [1.45 - 2.63]; respectively) (**Table 10a**)

In pairwise comparisons adjusted for multiple comparisons (**Table 10b**), four pairs of treatments differed. Women who had BCS, or mastectomy or mastectomy+ RT had a significantly higher hazard of death due to breast cancer compared to those who had BCT (adjusted p values <0.0001, 0.001, <0.0001 respectively). Also, women who had BCS had significantly higher hazards of death due to breast cancer compared to those who had mastectomy (sHR, 1.63, adjusted p value 0.02). However, the hazard of death due to breast cancer did not differ significantly for those who had mastectomy vs mastectomy + RT or BCS vs mastectomy + RT (adjusted p values 0.56 and 0.40).

Several factors were independent predictors of increased hazard of death due to breast cancer (**Table 10a**). Women with tumor size > 5 cm had higher hazard of death due to breast cancer than those whose tumor size was ≤2 cm (sHR 1.69, 95% CI [1.20 - 2.39]). Women whose tumors were stage II or III had higher hazard of death due to breast cancer than those whose tumors were stage I (sHR, 95% CI: 3.04 [2.03 - 4.54]; 6.67 [4.38 - 10.15] respectively). Lastly, women who were 85+ years had higher hazard of death due to breast cancer than those whose who were 66 -74 years.

The overall pattern persisted when we divided the data into three subsets defined by stage. In stages I and II, BCT was associated with significantly higher OS and BCSS compared to BCS, mastectomy, or mastectomy + RT. However, among stage III women BCT, mastectomy, or mastectomy + RT did not differ significantly in BCSS while BCT and mastectomy + RT did not differ significantly in OS (**Tables 11a, 11b, 12a, and 12b**).

With regard to the sensitivity analysis, excluding individuals who survived for less than a month, using age at diagnosis as continuous, smaller tumor size categories and

adjusting for chemotherapy did not change our findings notably (**Appendices F,G, H, I, J, K, L, M, N, O, P, Q**).

Figure 5: Cumulative incidence of death due to breast cancer

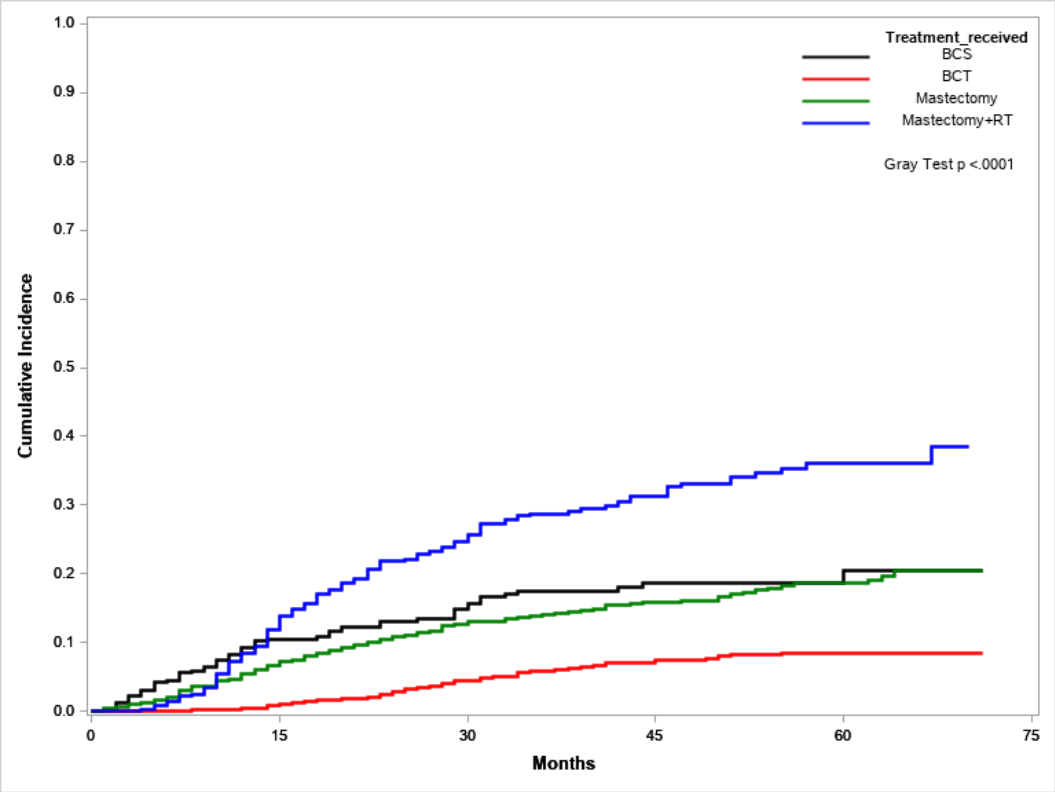


Table 10a: Fine-Gray Subdistribution hazard model for breast cancer death

	sHR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.67	1.88 - 3.80	<0.0001
Mastectomy	1.64	1.26 - 2.12	0.0002
Mastectomy + RT	1.95	1.45 - 2.63	<0.0001
Tumor size			
≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.15	0.82 - 1.61	0.41
> 5 cm	1.69	1.20 - 2.39	0.003
Stage			
I	1.00 (Reference)		
II	3.04	2.03 - 4.54	<0.0001
III	6.67	4.38 - 10.15	<0.0001
Age at diagnosis (years)			

66-74	1.00 (Reference)		
75-84	1.13	0.92 - 1.40	0.25
85+	1.51	1.16 - 1.97	0.003
Race			
White	1.00 (Reference)		
Black	0.74	0.55 - 1.02	0.06
Other	0.64	0.38 - 1.08	0.09
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	0.96	0.74 - 1.25	0.76
2	1.30	0.94 - 1.80	0.12
3+	1.23	0.84 - 1.81	0.29
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.03	0.76 - 1.40	0.85
50,001 - 60,000	1.03	0.76 - 1.39	0.85
>60,000	0.85	0.65 - 1.11	0.22
Missing	1.01	0.67 - 1.52	0.97
Region			
Midwest	1.32	1.00 - 1.73	0.05
Northeast	0.89	0.63 - 1.18	0.41
South	1.26	1.00 - 1.60	0.05
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio

Table 10b: Pairwise comparison - Fine-Gray Subdistribution hazard model for breast cancer death

	sHR	**95% CI**	**P value[a]**
BCS vs BCT	2.67	1.88 - 3.80	<0.0001
BCS vs Mastectomy + RT	1.37	0.93 - 2.03	0.40
BCS vs Mastectomy	1.63	1.18 - 2.27	0.02
Mastectomy + RT vs BCT	1.95	1.45 - 2.63	<0.0001
Mastectomy vs BCT	1.64	1.26 - 2.12	0.001
Mastectomy vs Mastectomy + RT	0.84	0.64 - 1.09	0.56

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons
Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Table 11a: Multivariate Cox proportional hazards model predicting all-cause mortality by stage

	Stage I			Stage II			Stage III		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Treatment									
BCT	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
BCS	2.69	1.82-3.97	<0.0001	2.61	1.88-3.62	<0.0001	6.50	3.5-11.93	<0.0001
Mastectomy	1.84	1.31-2.58	0.0005	1.98	1.55-2.55	<0.0001	2.57	1.64-4.03	<0.0001
Mastectomy + RT	3.34	1.76-6.34	0.0002	2.22	1.60-3.09	<0.0001	1.45	0.96-2.20	0.09

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio.
Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Table 11b: Pairwise comparison - Multivariate Cox proportional hazards model predicting all-cause mortality by stage

	Stage I			Stage II			Stage III		
Treatment	**HR**	**95% CI**	**P value[a]**	**HR**	**95% CI**	**P value[a]**	**HR**	**95% CI**	**P value[a]**
BCS vs BCT	2.69	1.82-3.97	<0.0001	2.61	1.88-3.62	<0.0001	6.50	3.54-11.93	<0.0001
BCS vs Mastectomy + RT	0.80	0.4-1.60	0.93	1.17	0.81-1.70	0.84	4.47	2.71-7.39	<0.0001
BCS vs Mastectomy	1.46	0.98-2.19	0.25	1.31	0.98-1.76	0.26	2.53	1.54-4.16	0.002
Mastectomy + RT vs BCT	3.34	1.76-6.34	0.001	2.22	1.60-3.09	<0.0001	1.45	0.96-2.20	0.3
Mastectomy vs BCT	1.84	1.31-2.58	0.003	1.98	1.55-2.55	<0.0001	2.57	1.64-4.03	0.0002
Mastectomy vs Mastectomy + RT	0.55	0.29-1.06	0.28	0.89	0.66-1.20	0.88	1.77	1.33-2.35	0.0005

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons
Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio.
Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Table 12a: Fine-Gray Subdistribution hazard model for breast cancer death by stage

	Stage I			Stage II			Stage III		
	sHR	**95% CI**	**P value**	**sHR**	**95% CI**	**P value**	**sHR**	**95% CI**	**P value**
Treatment									
BCT	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
BCS	2.46	1.15 - 5.27	0.02	1.97	1.19-3.25	0.01	5.35	2.40-11.91	<0.0001
Mastectomy	1.35	0.71 - 2.58	0.36	1.65	1.17-2.33	0.004	1.78	1.01-3.14	0.05
Mastectomy + RT	4.87	1.88 - 12.58	0.001	2.25	1.48-3.42	0.0002	1.71	1.04-2.81	0.03

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Table 12b: Pairwise comparison - Fine-Gray Subdistribution hazard model for breast cancer death by stage

	Stage I			Stage II			Stage III		
Treatment	**sHR**	**95% CI**	**P value[a]**	**sHR**	**95% CI**	**P value[a]**	**sHR**	**95% CI**	**P value[a]**
BCS vs BCT	2.46	1.15 - 5.27	0.09	1.97	1.19 - 3.25	0.04	5.35	2.40 - 11.91	0.0002
BCS vs Mastectomy + RT	0.51	0.17 - 1.48	0.60	0.88	0.50 - 1.53	0.97	3.12	1.59 - 6.15	0.01
BCS vs Mastectomy	1.82	0.82 - 4.05	0.45	1.19	0.75 - 1.90	0.88	3.01	1.50 - 6.01	0.01
Mastectomy + RT vs BCT	4.87	1.88 - 12.58	0.006	2.25	1.48 - 3.42	0.0009	1.71	1.04 - 2.81	0.14
Mastectomy vs BCT	1.35	0.71 - 2.58	0.80	1.65	1.17 - 2.33	0.02	1.78	1.01 - 3.14	0.19
Mastectomy vs Mastectomy + RT	0.28	0.10 - 0.74	0.06	0.74	0.49 - 1.10	0.43	1.04	0.72 - 1.51	0.99

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Table 12b: Pairwise comparison - Fine-Gray Subdistribution hazard model for breast cancer death by stage

	Stage I			Stage II			Stage III		
Treatment	**sHR**	**95% CI**	**P value[a]**	**sHR**	**95% CI**	**P value[a]**	**sHR**	**95% CI**	**P value[a]**
BCS vs BCT	2.46	1.15 - 5.27	0.09	1.97	1.19 - 3.25	0.04	5.35	2.40 - 11.91	0.0002
BCS vs Mastectomy + RT	0.51	0.17 - 1.48	0.60	0.88	0.50 - 1.53	0.97	3.12	1.59 - 6.15	0.01
BCS vs Mastectomy	1.82	0.82 - 4.05	0.45	1.19	0.75 - 1.90	0.88	3.01	1.50 - 6.01	0.01
Mastectomy + RT vs BCT	4.87	1.88 - 12.58	0.006	2.25	1.48 - 3.42	0.0009	1.71	1.04 - 2.81	0.14
Mastectomy vs BCT	1.35	0.71 - 2.58	0.80	1.65	1.17 - 2.33	0.02	1.78	1.01 - 3.14	0.19
Mastectomy vs Mastectomy + RT	0.28	0.10 - 0.74	0.06	0.74	0.49 - 1.10	0.43	1.04	0.72 - 1.51	0.99

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

4.3 Discussion

This population-based study found that receiving BCT was associated with lower 5-year cumulative incidence of all-cause and breast cancer specific death compared with mastectomy, mastectomy + RT, or BCS. These findings persisted in the multivariate and IPTW Cox proportional and Fine and Gray sub-distribution hazard models, in which individuals who had BCT had a lower hazard of all-cause and breast cancer specific mortality compared to those who had mastectomy, mastectomy + RT, or BCS. Similar patterns were observed in stage-specific analysis. BCT was associated with significantly higher OS and BCSS among women who had stage I or stage II disease. Although BCT did not differ significantly from mastectomy and mastectomy + RT in stage III, women who had BCT had better OS and BCSS than did women who received other treatments. We note that the analysis of stage III, where the sample size was only 623, had lower statistical power compared to stage I (N=1952) and stage II (N=1758).

Based on results from randomized trials of surgical treatment for breast cancer, we would have expected women undergoing BCT or mastectomy to have similar hazards of death after accounting for clinical and demographic factors (105-107). Our finding of worse OS and BCSS for women receiving mastectomy than BCT suggests other factors could have differed between these groups of women that are not accounted for in our analyses. Possible factors include clinical factors such as margin status and non-clinical factors such as provider and patient preferences, which are not included in SEER-Medicare (127). However, our findings are consistent with reports by Chen et al. (108) and Wang et al. (109), who studied TNBC. Another explanation for better survival rates

among those who had BCT compared to mastectomy is our outcomes of interest, OS and BCSS. Two observational studies found that among early-stage TNBC patients, BCT and mastectomy did not differ in terms of locoregional recurrence (112-114). Unfortunately, we could not assess recurrence in our study since SEER-Medicare does not include information about recurrence.

Our study, which used the SEER-Medicare database, has several advantages over the Chen et al. and Wang et al studies, which used SEER data. These advantages include adjustment for patient comorbidity, which may impact the treatment received (110), accounting for competing risks of death from non-breast cancer causes, and longer follow-up time (5 compared to 3 years). Also, the sensitivity of SEER data in identifying radiation therapy is low, so using SEER-Medicare data allowed us to have more complete and accurate radiation information (128). Lastly, unlike previous studies on TNBC surgical and radiotherapy treatments (108, 109, 111-114), we assessed all surgical and radiotherapy combination options available to patients with TNBC, thus providing a more comprehensive understanding of the effectiveness of these treatments.

The NCCN guidelines recommend that early-stage breast cancer patients receive radiation therapy following BCS because omitting radiotherapy after BCS is associated with increased risk of recurrence and mortality (129). However, 9% of patients in our study had BCS without radiation, which is similar to the proportion reported in previous studies (130, 131). As expected, in the multivariate analysis, women who received BCS had the lowest OS and BCSS. In our study, most women who received BCS without radiation had smaller tumors that were diagnosed at an earlier stage. Early-stage smaller tumors, which have a lower risk of recurrence, may have contributed to these women not

receiving radiation after BCS. However, given that radiation after BCS reduces recurrence even among women with better-prognosis tumors (e.g., early-stage and ER positive) (132) and the aggressive biology of TNBC, omission of radiotherapy after BCS is problematic and deserves attention.

In our study, we did not observe any differences by race in survival outcomes after controlling for treatment, socio-demographic and clinical characteristics. These findings are consistent with several studies that found that among TNBC patients, racial groups did not differ in OS and BCSS after controlling for treatment and socio-demographic characteristics (108, 109, 113, 133, 134). Although we did not find racial disparities in survival it is important to note that TNBC is more likely to be diagnosed among Black women and has a worse prognosis than other subtypes so there is still an urgent need for better treatment strategies for TNBC (3).

This study had several limitations. First, we only included individuals who were at least 66 years old and enrolled in Medicare fee-for-service, so our findings may not generalize to a younger population or those enrolled in health maintenance organizations. Second, we were unable to assess recurrence because SEER does not collect this information. Third, we could not control for some clinical factors such as margin status and non-clinical factors such as patient and physician preferences, which may impact treatment receipt. We used IPTW and multivariate analysis to reduce selection bias for factors for which we could obtain data. Despite these limitations, our study, which used population-based data and is a nationally representative sample of elderly individuals, contributes valuable new information on the effectiveness of surgical treatment for TNBC in this population.

4.4 Conclusion

This population-based cohort study of TNBC patients found that BCT is associated with higher OS and BCSS compared to BCS, mastectomy, or mastectomy and radiation. These findings persisted in the subsets of stage I and II patients. However, in the subset of stage III patients BCT, mastectomy, and mastectomy + RT did not differ significantly although the estimated treatment effects were of similar sizes.

CHAPTER 5. OVERALL DISCUSSION

This dissertation contributes to the existing body of knowledge on breast cancer incidence patterns, diagnosis, and treatment outcomes in Ghana and the US. Manuscript 1 explores how women navigate the complex pathways to breast cancer diagnosis and treatment in Ghana and Manuscript 2 assesses factors contributing to the current breast cancer incidence patterns in Ghana. Manuscript 3 examines the optimal surgical treatment for women with triple negative breast cancer (TNBC) – the most aggressive breast cancer subtype that is also more likely to be diagnosed among Black women in the US and women in Ghana.

In Manuscript 1 of this dissertation, we evaluated the breast cancer care continuum in Ghana from the perception of women with breast cancer. Patient's perspectives and experiences are essential in the implementation of optimal healthcare interventions. Our study is the first to trace women's pathways to breast cancer diagnosis and treatment in detail in Ghana. We found that women go through approximately seven steps from symptom detection to receiving allopathic breast cancer treatment in Ghana. Further, the pathway is not linear, with some women looping back repeatedly to earlier steps or skipping steps altogether. In addition, the women frequently move among

different management approaches including alternative therapy (e.g. faith healing and traditional medicine). Based on the findings from the interviews with women who have been diagnosed with breast cancer, we propose a comprehensive framework showing the pathways of care to breast cancer diagnosis and treatment. This framework can be used to identify locally relevant interventions that can be implemented to improve early detection and timely treatment of breast cancer in Ghana. Theoretical frameworks are important as they provide a systematic approach to understanding heath seeking behavior by building on existing knowledge (135-137). However, most existing frameworks do not include the role of alternative therapy providers and are therefore not applicable to settings where patients commonly seek care from these providers. Our study showed that alternative therapy providers play a major role in the breast cancer care continuum in Ghana. Our findings indicate that alternative therapy and allopathic medicine are not mutually exclusive contrary to the way they are currently presented in the literature. We recommend integration of alternative therapy providers in breast cancer diagnosis and management strategies. In an integrated system, alternative therapy providers can play a triage role, where they refer women with breast cancer related symptoms to allopathic medicine and offer psychosocial support as the women receive allopathic medicine. Additional research is warranted to assess how incorporating alternative therapy providers improves early detection of breast cancer, access and adherence to treatment. Findings from this study may be applicable to other countries where use of traditional medicine and faith healing is common.

Manuscript 2 examined factors accounting for the younger age at diagnosis pattern that is evident in Ghana. Similar to previous studies comparing age at diagnosis in

sub-Saharan Africa (SSA) to North America and Europe, we found that women in Ghana were diagnosed at a younger age compared to women in the US. This phenomenon has previously been interpreted as women in SSA being at a higher risk for breast cancer compared to women in Europe and North America. However, our study refutes this notion; we showed that the younger age at diagnosis is partly due to population age structure differences. Using a US historical cohort (cases diagnosed 1975-1979) we showed that breast cancer screening is a second factor that contributes to the average lower mean age at diagnosis in Ghana. We argue that cohort effects, where older women in Ghana have more protective breast cancer risk profiles compared to older women in the US, is a third factor that may also contribute to this younger age diagnosis pattern in Ghana. Previous research has shown that breast cancer incidence is growing rapidly in SSA as the population ages and prevalence of risk factors increases, and incidence rates in SSA will likely reach those in Western countries (1). There is an urgent need for increased breast cancer control interventions across the cancer continuum from screening to treatment and palliative care. These interventions should also include tapping into the expertise of alternative therapy providers who are readily available and trusted by women in Ghana as evidenced in Manuscript 1. More research is needed on the impact of the changing risk profile in Ghana on breast cancer incidence and mortality patterns. Further, Manuscript 2 highlights the necessary role of population-based cancer registries in understanding breast cancer incidence patterns. Using data from a population-based cancer registry in Ghana, we were able to identify potential factors contributing to the patterns of breast cancer in Ghana. Population-based cancer registries are a comprehensive source of data necessary to describe cancer burden, etiology, treatment

outcomes, and for monitoring and evaluating cancer management interventions. Out of 46 countries in SSA, only 25 have a population-based cancer registry; thus, most breast cancer incidence estimates are based on data from the International Association of Cancer Registries (IARC) GLOBOCAN database (30, 138) However, due to lack of cancer incidence data in most SSA countries GLOBOCAN cancer incidence rates for some SSA countries are derived from rates from neighboring countries (139). Limited accurate population-based data is a hindrance for cancer control in SSA.

Lastly, in Manuscript 3 we examined the optimal treatment for women with TNBC. Black women in the US and women in West African countries like Ghana are more likely to be diagnosed with TNBC. We found that women treated with BCS followed by radiotherapy (i.e breast conserving therapy (BCT)) had a better prognosis than those treated with mastectomy or mastectomy and radiotherapy. These findings suggest that TNBC is not a contraindication for breast conserving surgery (BCS) SEER-Medicare is the only comprehensive source of population-based cancer data in the US that provides treatment information and allows for long-term follow up of cancer patients. Using these data, we provided real-world evidence that is essential for tailoring surgical treatment guidelines for TNBC patients in the US. Currently, high quality sources of cancer treatment and outcomes data do not exist in Ghana. Given the epidemiologic similarities of Ghanaian women and Black women in the US, findings from this study may also inform treatment guidelines for patients with TNBC in Ghana and/or form the basis for a more definitive study. However, in considering the applicability of these results to Ghana, it is important to note that the study population was at least 66 years old and differences in treatment resources between the two countries

might impact treatment recommendations. Lastly, we noted that our findings of worse survival outcomes among women receiving mastectomy compared to BCT might be due to factors that differed between the two groups that were not accounted for in our analysis. Further confirmation of our findings, in randomized clinical trials, is necessary.

Findings from this dissertation are timely due to the rapidly rising burden of breast cancer in SSA and persistant disparities in the US. The framework from Manuscript 1 findings is useful for designing breast cancer control programs in Ghana and other LMICs with similar healthcare structures or health related belief systems. Manuscript 2 provides insight on the younger age at diagnosis patterns in Ghana and highlights the need for urgent action on breast cancer control in Ghana. Manuscript 3 findings inform treatment guidelines for triple negative breast cancer and call for quality data to assess treatment outcomes in Ghana.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin; 2021;0:1-41.
2. Russnes HG, Lingjaerde OC, Borresen-Dale AL, Caldas C. Breast Cancer Molecular Stratification: From Intrinsic Subtypes to Integrative Clusters. Am J Pathol. 2017;187(10):2152-62.
3. Metzger-Filho O, Sun Z, Viale G, Price KN, Crivellari D, Snyder RD, et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. J Clin Oncol. 2013;31(25):3083-90.
4. Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. Medicine. 2016;95(35).
5. Fregene A, Newman LA. Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in African-American women? Cancer. 2005;103(8):1540-50.
6. Clegg-Lamptey JN, Aduful HK, Yarney J, Adu-Aryee NA, Vanderpuye V, Kyereh M, et al. Profile of breast diseases at a self-referral clinic in Ghana. West African journal of medicine. 2009;28(2):114-7.
7. Laryea DO, Awuah B, Amoako YA, Osei-Bonsu E, Dogbe J, Larsen-Reindorf R, et al. Cancer incidence in Ghana, 2012: evidence from a population-based cancer registry. BMC Cancer. 2014;14:362-.
8. Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016. National Cancer Institute; 2019.
9. Gonzalez-Angulo AM, Broglio K, Kau SW, Eralp Y, Erlichman J, Valero V, et al. Women age < or = 35 years with primary breast carcinoma: disease features at presentation. Cancer. 2005;103(12):2466-72.
10. Azubuike SO, Muirhead C, Hayes L, McNally R. Rising global burden of breast cancer: the case of sub-Saharan Africa (with emphasis on Nigeria) and implications for regional development: a review. World J Surg Oncol. 2018;16(1):63.
11. Akarolo-Anthony SN, Ogundiran TO, Adebamowo CA. Emerging breast cancer epidemic: evidence from Africa. Breast Cancer Res. 2010;12(4):S8.
12. Cody HS, 3rd. Current surgical management of breast cancer. Curr Opin Obstet Gynecol. 2002;14(1):45-52.
13. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363(20):1938-48.
14. Gangi A, Chung A, Mirocha J, Liou DZ, Leong T, Giuliano AE. Breast-conserving therapy for triple-negative breast cancer. JAMA Surg. 2014;149(3):252-8.
15. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736-50.
16. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, et al. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res. 2015;5(10):2929-43.

17. Clarke CA, Keegan TH, Yang J, Press DJ, Kurian AW, Patel AH, et al. Age-specific incidence of breast cancer subtypes: understanding the black-white crossover. J Natl Cancer Inst. 2012;104(14):1094-101.
18. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. The Lancet Oncology. 2012;13(11):1141-51.
19. Ewertz M, Duffy SW, Adami HO, Kvale G, Lund E, Meirik O, et al. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. International journal of cancer. 1990;46(4):597-603.
20. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet. 2008;371(9612):569-78.
21. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet. 1997;350(9084):1047-59.
22. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic Density and the Risk and Detection of Breast Cancer. N Engl J Med. 2007;356(3):227-36.
23. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet. 2001;358(9291):1389-99.
24. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(11):1329-33.
25. Comen E, Davids M, Kirchhoff T, Hudis C, Offit K, Robson M. Relative contributions of BRCA1 and BRCA2 mutations to "triple-negative" breast cancer in Ashkenazi Women. Breast Cancer Res Treat. 2011;129(1):185-90.
26. National Comprehensive Cancer Network National Comprehensive Cancer Network 2020 [Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419
27. Waks AG, Winer EP. Breast Cancer Treatment: A Review JAMA. 2019;321(3):288-300.
28. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer: National Cancer Institute: Surveillance, Epidemiology, and End Results Program 2018 [Available from: https://seer.cancer.gov/statfacts/html/breast.html
29. Yedjou CG, Sims JN, Miele L, Noubissi F, Lowe L, Fonseca DD, et al. Health and Racial Disparity in Breast Cancer. Adv Exp Med Biol. 2019;1152:31-49.
30. Adeloye D, Sowunmi OY, Jacobs W, David RA, Adeosun AA, Amuta AO, et al. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. Journal of Global Health. 2018;8(1):010419.
31. International Agency for Research on Cancer. Ghana Source: Globocan 2018. [Available from https://gco.iarc.fr/today/data/factsheets/populations/288-ghana-fact-sheets.pdf.]

32. Ohene-Yeboah M, Adjei E. Breast Cancer in Kumasi, Ghana. Ghana Medical Journal. 2012;46(1):8-13.
33. Naku Ghartey Jnr F, Anyanful A, Eliason S, Mohammed Adamu S, Debrah S. Pattern of Breast Cancer Distribution in Ghana: A Survey to Enhance Early Detection, Diagnosis, and Treatment. Int J Breast Cancer. 2016;2016:3645308.
34. Edmund DM, Naaeder SB, Tettey Y, Gyasi RK. Breast cancer in Ghanaian women: what has changed? Am J Clin Pathol. 2013;140(1):97-102.
35. Stalsberg H, Adjei EK, Owusu-Afriyie O. No difference in the prevalence of benign breast changes between women from Ghana and Norway: an autopsy study. Breast Cancer Res Treat. 2015;151(1):177-82.
36. Mensah A, Yarney J, Nokoe KS, Opoku S, Clegg-Lamptey JN. Survival Outcomes of Breast Cancer in Ghana: An Analysis of Clinicopathological Features2016. 1-11 p.
37. Thomas AS, Kidwell KM, Oppong JK, Adjei EK, Osei-Bonsu E, Boahene A, et al. Breast Cancer in Ghana: Demonstrating the Need for Population-Based Cancer Registries in Low- and Middle-Income Countries. Journal of global oncology. 2017;3(6):765-72.
38. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
39. Clegg-Lamptey J, Dakubo J, Attobra YN. Why Do Breast Cancer Patients Report Late or Abscond During Treatment in Ghana? A Pilot Study. Ghana Medical Journal. 2009;43(3):127-31.
40. Scherber S, Soliman AS, Awuah B, Osei-Bonsu E, Adjei E, Abantanga F, et al. Characterizing Breast Cancer Treatment Pathways in Kumasi, Ghana from Onset of Symptoms to Final Outcome: Outlook towards Cancer Control. Breast Dis. 2014;34(4):139-49.
41. Dedey F, Wu L, Ayettey H, Sanuade OA, Akingbola TS, Hewlett SA, et al. Factors Associated With Waiting Time for Breast Cancer Treatment in a Teaching Hospital in Ghana. Health Educ Behav. 2016;43(4):420-7.
42. Kohler RE, Gopal S, Miller AR, Lee CN, Reeve BB, Weiner BJ, et al. A framework for improving early detection of breast cancer in sub-Saharan Africa: A qualitative study of help-seeking behaviors among Malawian women. Patient Educ Couns. 2017;100(1):167-73.
43. Bonsu AB, Ncama BP. Recognizing and appraising symptoms of breast cancer as a reason for delayed presentation in Ghanaian women: A qualitative study. PLoS One. 2019;14(1):e0208773.
44. Agbeko AE, Arthur J, Bayuo J, Kaburi BB, Kyei I. Seeking healthcare at their 'right' time; the iterative decision process for women with breast cancer. BMC Cancer. 2020;20(1):1011.
45. Scott SE, Walter FM, Webster A, Sutton S, Emery J. The model of pathways to treatment: conceptualization and integration with existing theory. Br J Health Psychol. 2013;18(1):45-65.
46. Bairati I, Fillion L, Meyer FA, Hery C, Larochelle M. Women's perceptions of events impeding or facilitating the detection, investigation and treatment of breast cancer. Eur J Cancer Care (Engl). 2006;15(2):183-93.

47. Moustakas C. Phenomenological research methods. Thousand Oaks, California 1994 2020/07/28.
48. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health. 2015;42(5):533-44.
49. Grady MP, editor Qualitative and Action Research: A Practitioner Handbook1998.
50. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant. 2018;52(4):1893-907.
51. Frie KG, Kamaté B, Traoré CB, Ly M, Kantelhardt EJ. Tackling Late-Stage Diagnosis of Breast Cancer Patients in Sub-Saharan Africa: A Case Study From Mali. Journal of global oncology. 2018;4(Supplement 2):64s-s.
52. Grosse Frie K, Kamaté B, Traoré CB, Coulibaly B, Mallé B, Kantelhardt EJ. Health system organisation and patient pathways: breast care patients' trajectories and medical doctors' practice in Mali. BMC Public Health. 2019;19(1):204.
53. Moodley J, Cairncross L, Naiker T, Momberg M. Understanding pathways to breast cancer diagnosis among women in the Western Cape Province, South Africa: a qualitative study. BMJ open. 2016;6(1):e009905.
54. Moodley J, Cairncross L, Naiker T, Constant D. From symptom discovery to treatment - women's pathways to breast cancer care: a cross-sectional study. BMC Cancer. 2018;18(1):312-.
55. Brown CA, Kohler RE, John O, Motswetla G, Mmalane M, Tapela N, et al. Multilevel Factors Affecting Time to Cancer Diagnosis and Care Quality in Botswana. Oncologist. 2018;23(12):1453-60.
56. Stamatovic L, Vasovic S, Trifunovic J, Boskov N, Gajic Z, Parezanovic A, et al. Factors influencing time to seeking medical advice and onset of treatment in women who are diagnosed with breast cancer in Serbia. Psychooncology. 2018;27(2):576-82.
57. QSR International Pty Ltd. (2018) NVivo (Version 12), [Available from https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home.
58. Miles MB. Qualitative data analysis : a methods sourcebook: Third edition. Thousand Oaks, Califorinia : SAGE Publications, Inc., [2014]; 2014.
59. Mays N, Pope C. Rigour and qualitative research. BMJ. 1995;311(6997):109-12.
60. Carter N, Bryant-Lukosius D, DiCenso A, Blythe J, Neville AJ. The use of triangulation in qualitative research. Oncol Nurs Forum. 2014;41(5):545-7.
61. Birt L, Scott S, Cavers D, Campbell C, Walter F. Member Checking: A Tool to Enhance Trustworthiness or Merely a Nod to Validation? Qual Health Res. 2016;26(13):1802-11.
62. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for Reporting Qualitative Research: A Synthesis of Recommendations. Acad Med. 2014;89(9):1245-51.
63. Abor P, Abekah-Nkrumah G, Abor J. An examination of Hospital Governance in Ghana. Leadersh Health Serv. 2008;21:47-60.
64. James PB, Wardle J, Steel A, Adams J. Traditional, complementary and alternative medicine use in Sub-Saharan Africa: a systematic review. BMJ Glob Health. 2018;3(5):e000895.

65. Yarney J, Donkor A, Opoku SY, Yarney L, Agyeman-Duah I, Abakah AC, et al. Characteristics of users and implications for the use of complementary and alternative medicine in Ghanaian cancer patients undergoing radiotherapy and chemotherapy: a cross- sectional study. BMC Complement Altern Med. 2013;13:16.
66. Boateng MA, Danso-Appiah A, Turkson BK, Tersbøl BP. Integrating biomedical and herbal medicine in Ghana - experiences from the Kumasi South Hospital: a qualitative study. BMC Complement Altern Med. 2016;16:189.
67. O'Brien KS, Soliman AS, Awuah B, Jiggae E, Osei-Bonsu E, Quayson S, et al. Establishing effective registration systems in resource-limited settings: cancer registration in Kumasi, Ghana. Journal of registry management. 2013;40(2):70-7.
68. Arias D, Taylor L, Ofori-Atta A, Bradley EH. Prayer Camps and Biomedical Care in Ghana: Is Collaboration in Mental Health Care Possible? PLoS One. 2016;11(9):e0162305.
69. Furin J. The Role of Traditional Healers in Community-Based HIV Care in Rural Lesotho. J Community Health. 2011;36(5):849-56.
70. Gureje O, Appiah-Poku J, Bello T, Kola L, Araya R, Chisholm D, et al. Effect of collaborative care between traditional and faith healers and primary health-care workers on psychosis outcomes in Nigeria and Ghana (COSIMPO): a cluster randomised controlled trial. The Lancet. 2020;396(10251):612-22.
71. Krah E, de Kruijf J, Ragno L. Integrating Traditional Healers into the Health Care System: Challenges and Opportunities in Rural Northern Ghana. J Community Health. 2018;43(1):157-63.
72. Centers for Disease Control and Prevention. What Is Breast Cancer Screening? Available from: https://www.cdc.gov/cancer/breast/basic_info/screening.htm
73. Devi BC, Tang TS, Corbex M. Reducing by half the percentage of late-stage presentation for breast and cervix cancer over 4 years: a pilot study of clinical downstaging in Sarawak, Malaysia. Ann Oncol. 2007;18(7):1172-6.
74. Mena M, Wiafe-Addai B, Sauvaget C, Ali IA, Wiafe SA, Dabis F, et al. Evaluation of the impact of a breast cancer awareness program in rural Ghana: a cross-sectional survey. International journal of cancer. 2014;134(4):913-24.
75. Opoku SY, Benwell M, Yarney J. Knowledge, attitudes, beliefs, behaviour and breast cancer screening practices in Ghana, West Africa. The Pan African Medical Journal. 2012;11:28.
76. Zelle SG, Nyarko KM, Bosu WK, Aikins M, Niëns LM, Lauer JA, et al. Costs, effects and cost-effectiveness of breast cancer control in Ghana. Trop Med Int Health. 2012;17(8):1031-43.
77. Kantelhardt EJ, Muluken G, Sefonias G, Wondimu A, Gebert HC, Unverzagt S, et al. A Review on Breast Cancer Care in Africa. Breast Care. 2015;10(6):364-70.
78. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg. 2009;208(3):341-7.
79. Chollet-Hinton L, Olshan AF, Nichols HB, Anders CK, Lund JL, Allott EH, et al. Biology and Etiology of Young-Onset Breast Cancers among Premenopausal African American Women: Results from the AMBER Consortium. Cancer Epidemiol Biomarkers Prev. 2017;26(12):1722-9.

80. Ghana Statistical Services. Population & Housing Census National Analytical Report 2013. http://www.statsghana.gov.gh/gssmain/fileUpload/pressrelease/2010_PHC_National_Analytical_Report.pdf.
81. United States Census. 2010 Census Summary File 1, 2011. https://www2.census.gov/programs-surveys/decennial/2010/technical-documentation/complete-tech-docs/summary-file/sf1.pdf.
82. Bidoli E, Virdone S, Hamdi-Cherif M, Toffolutti F, Taborelli M, Panato C, et al. Worldwide Age at Onset of Female Breast Cancer: A 25-Year Population-Based Cancer Registry Study. Sci Rep. 2019;9(1):14111.
83. Verdial FC, Etzioni R, Duggan C, Anderson BO. Demographic changes in breast cancer incidence, stage at diagnosis and age associated with population-based mammographic screening. J Surg Oncol. 2017;115(5):517-22.
84. Centers for Disease Control and Prevention. Mammography. Available from: https://www.cdc.gov/nchs/fastats/mammography.htm.
85. Amoako YA, Awuah B, Larsen-Reindorf R, Awittor FK, Kyem G, Ofori-Boadu K, et al. Malignant tumours in urban Ghana: evidence from the city of Kumasi. BMC Cancer. 2019;19(1):267.
86. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER). 2018. Available from: https://seer.cancer.gov/about/factsheets/SEER_Overview.pdf
87. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care. 2002;40(8 Suppl):Iv-3-18.
88. National Cancer Institute. Registry Groupings in SEER Data and Statistics. Available from: https://seer.cancer.gov/registries/terms.html
89. National Cancer Institute. Download U.S. Population Data - 1969-2019. Available from: https://seer.cancer.gov/popdata/download.html
90. Ghana Statistical Services. https://statsghana.gov.gh/index.php
91. Stapleton SM, Oseni TO, Bababekov YJ, Hung Y, Chang DC. Race/ethnicity and age distribution of breast cancer diagnosis in the united states. JAMA Surgery. 2018;153(6):594-5.
92. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: A new WHO standard. 2001.
93. American Cancer Society. History of ACS Recommendations for the Early Detection of Cancer in People without Symptoms. Available from: https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/overview/chronological-history-of-acs-recommendations.html
94. Jørgensen KJ, Gøtzsche PC, Kalager M, Zahl PH. Breast Cancer Screening in Denmark: A Cohort Study of Tumor Size and Overdiagnosis. Ann Intern Med. 2017;166(5):313-23.
95. Gaisie S. Fertility Trend in Ghana. African Population Studies (ISSN: 0850-5780) Vol 20 Num 2. 2013;20.
96. Smith SK, Ahmed B. A demographic analysis of the population growth of states, 1950-1980. J Reg Sci. 1990;30(2):209-27.
97. Corbex M, Bouzbid S, Boffetta P. Features of breast cancer in developing countries, examples from North-Africa. Eur J Cancer. 2014;50(10):1808-18.

98. Blanc AK, Grey S. Greater than expected fertility decline in Ghana: untangling a puzzle. J Biosoc Sci. 2002;34(4):475-95.
99. Lartey ST, Magnussen CG, Si L, Boateng GO, de Graaff B, Biritwum RB, et al. Rapidly increasing prevalence of overweight and obesity in older Ghanaian adults from 2007-2015: Evidence from WHO-SAGE Waves 1 & 2. PLoS One. 2019;14(8):e0215045.
100. Mba CJ. Population Ageing in Ghana: Research Gaps and the Way Forward. J Aging Res. 2010;2010:672157.
101. National Cancer Institute Surveillance and End Results Program. ICD-O-3 Coding Materials [Available from: https://seer.cancer.gov/icd-o-3/.
102. International Association of Cancer Registries. International Classification of Diseases for Oncology (ICD-O). http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577
103. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109(9):1721-8.
104. Warburton R, Chiu CG, Roberts A, et al. Current surgical management of breast cancer. BCMJ 2018; 60:92-98.
105. Lichter AS, Lippman ME, Danforth DN, Jr., d'Angelo T, Steinberg SM, deMoss E, et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. J Clin Oncol. 1992;10(6):976-83.
106. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
107. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. N Engl J Med. 2002;347(16):1233-41.
108. Chen Q-X, Wang X-X, Lin P-Y, Zhang J, Li J-J, Song C-G, et al. The different outcomes between breast-conserving surgery and mastectomy in triple-negative breast cancer: a population-based study from the SEER 18 database. Oncotarget. 2016;8(3):4773-80.
109. Wang SE, Sun Yd, Zhao SJ, Wei F, Yang G. Breast conserving surgery (BCS) with adjuvant radiation therapy showed improved prognosis compared with mastectomy for early staged triple negative breast cancer patients Running title: BCS had better prognosis than mastectomy for early TNBC patients. Math Biosci Eng. 2019;17(1):92-104.
110. Zhou J, Enewold L, Zahm SH, Jatoi I, Shriver C, Anderson WF, et al. Breast conserving surgery versus mastectomy: the influence of comorbidities on choice of surgical operation in the Department of Defense health care system. Am J Surg. 2013;206(3):393-9.
111. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer

treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. J Clin Oncol. 2011;29(21):2852-8.
112. Adkins FC, Gonzalez-Angulo AM, Lei X, Hernandez-Aya LF, Mittendorf EA, Litton JK, et al. Triple-Negative Breast Cancer Is Not a Contraindication for Breast Conservation. Ann Surg Oncol. 2011;18(11):3164.
113. Zumsteg ZS, Morrow M, Arnold B, Zheng J, Zhang Z, Robson M, et al. Breast-Conserving Therapy Achieves Locoregional Outcomes Comparable to Mastectomy in Women with T1-2N0 Triple-Negative Breast Cancer. Ann Surg Oncol. 2013;20(11):3469-76.
114. Parker CC, Ampil F, Burton G, Li BDL, Chu QD. Is breast conservation therapy a viable option for patients with triple-receptor negative breast cancer? Surgery. 2010;148(2):386-91.
115. Duggan MA, Anderson WF, Altekruse S, Penberthy L, Sherman ME. The Surveillance, Epidemiology, and End Results (SEER) Program and Pathology: Toward Strengthening the Critical Relationship. The American journal of surgical pathology. 2016;40(12):e94-e102.
116. National Cancer Institute Division of Cancer Control & Population Sciences. SEER-Medicare: Selecting the Appropriate Comorbidity SAS Macro. Available from https://healthcaredelivery.cancer.gov/seermedicare/considerations/calculation.html.
117. Gabriela Dieguez CF, David Rotter. The cost burden of blood cancer care. A longitudinal analysis of commercially insured patients diagnosed with blood cancer. 2018.
118. Gibson DC, Chou L-N, Raji MA, Baillargeon JG, Kuo Y-F. Opioid Prescribing Trends in Women Following Mastectomy or Breast-Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone. The oncologist. 2020;25(4):281-9.
119. Killelea BK, Long JB, Chagpar AB, Ma X, Soulos PR, Ross JS, et al. Trends and clinical implications of preoperative breast MRI in Medicare beneficiaries with breast cancer. Breast Cancer Res Treat. 2013;141(1):155-63.
120. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
121. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656-64.
122. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of Stabilized Inverse Propensity Scores as Weights to Directly Estimate Relative Risk and Its Confidence Intervals. Value Health. 2010;13(2):273-7.
123. Pezzi A, Cavo M, Biggeri A, Zamagni E, Nanni O. Inverse probability weighting to estimate causal effect of a singular phase in a multiphase randomized clinical trial for multiple myeloma. BMC Med Res Methodol. 2016;16(1):150.
124. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.
125. Bolch CA, Chu H, Jarosek S, Cole SR, Elliott S, Virnig B. Inverse probability of treatment-weighted competing risks analysis: an application on long-term risk of urinary adverse events after prostate cancer treatments. BMC Med Res Methodol. 2017;17(1):93.

126. National Cancer Institute SEER-Medicare Data Use Agreement (DUA). Available from: https://healthcaredelivery.cancer.gov/seermedicare/obtain/seerdua.pdf.
127. Gu J, Groot G, Boden C, Busch A, Holtslander L, Lim H. Review of Factors Influencing Women's Choice of Mastectomy Versus Breast Conserving Therapy in Early Stage Breast Cancer: A Systematic Review. Clin Breast Cancer. 2018;18(4):e539-e54.
128. Noone A-M, Lund JL, Mariotto A, Cronin K, McNeel T, Deapen D, et al. Comparison of SEER Treatment Data With Medicare Claims. Med Care. 2016;54(9):e55-e64.
129. Vinh-Hung V, Verschraegen C, Project FTBCS. Breast-Conserving Surgery With or Without Radiotherapy: Pooled-Analysis for Risks of Ipsilateral Breast Tumor Recurrence and Mortality. JNCI: Journal of the National Cancer Institute. 2004;96(2):115-21.
130. Longacre C, Neprash H, Shippee N, Tuttle T, Virnig B. Travel, Treatment Choice, and Survival Among Breast Cancer Patients: A Population-Based Analysis. Women's Health Reports. 2021;2:1-10.
131. Guidolin K, Lock M, Vogt K, McClure JA, Winick-Ng J, Vinden C, et al. Recurrence and mortality after breast-conserving surgery without radiation. Curr Oncol. 2019;26(6):380-8.
132. Viani GA, Stefano EJ, Afonso SL, De Fendi LI, Soares FV, Leon PG, et al. Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials. Radiat Oncol. 2007;2:28.
133. Pacheco JM, Gao F, Bumb C, Ellis MJ, Ma CX. Racial differences in outcomes of triple-negative breast cancer. Breast Cancer Res Treat. 2013;138(1):281-9.
134. Warner ET, Tamimi RM, Hughes ME, Ottesen RA, Wong Y-N, Edge SB, et al. Racial and Ethnic Differences in Breast Cancer Survival: Mediating Effect of Tumor Characteristics and Sociodemographic and Treatment Factors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(20):2254-61.
135. Walter F, Webster A, Scott S, Emery J. The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis. J Health Serv Res Policy. 2012;17(2):110-8.
136. Scott S, Walter F. Studying Help-Seeking for Symptoms: The Challenges of Methods and Models2010. 531-47 p.
137. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer. 2012;106(7):1262-7.
138. Omonisi AE, Liu B, Parkin DM. Population-Based Cancer Registration in Sub-Saharan Africa: Its Role in Research and Cancer Control. JCO Global Oncology. 2020(6):1721-8.
139. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.

APPENDICES

Appendix A: Interview Guide

Section 1

Introduction:

Thank you for taking the time to talk to us about your journey seeking care for breast cancer. My name is (Research Assistant name) and this is Waruiru who is a student. Waruiru is working on research on the pathway to breast cancer care among women in Ghana. We hope that the information gathered from these interviews will help us better understand Ghanaian women's journey in seeking care for breast cancer from symptom detection to treatment and ways to ensure that women get the best breast cancer care soonest possible.

We will be recording the session because we do not want to miss any of your input. We know you have helpful comments and we cannot write fast enough to get them all down. We will not include any names or other identifiable information and what you say is confidential. Do you have any questions for me? Do I have your permission to start the interview?

Icebreaker:

What Ghanaian food do you enjoy making?

Main question:

Please tell us the story of your journey from when you detected bodily change to when you started receiving breast cancer treatment

Below are the probes (only ask the probes if the patient did not provide this information)

1. Please tell us the first change or symptom that you noticed in
2. your breast?
    - Time of discovery (date & year)
    - Please tell us how you discovered the symptom or change in
    - your breast?
    - What happened after the discovery?
    - What did you think the symptom was?
    - Was it a serious issue to you?
    - So what did you do after the discovery
        - Did you get any treatment related to the symptom?
3. Please tell us what you thought was the cause of the breast symptoms?
    - Why did you think that was the cause?
4. Please tell us if you shared the information with anybody?
    - Who?
    - Why?
    - When?
    - What did the person tell you?
5. Did you see a doctor about the symptom?
    - Where (facility)? Why this facility?

- When (date & year)?
- Why early? Or why delay?
- What happened at the hospital?
- What did the doctor say?
- What did the doctor do for you?
- Any labs?
- Any referral? Why, when and to where?

6. Please can you share with me the journey from when your symptom
7. was assessed by the doctor to diagnosis?
    - What happened?
    - What were you asked to do?
    - The various investigations requested
    - Where did you do each of these?
    - cost
8. Were you actually told that you have breast cancer?
    - When (Date)
    - Who informed you? And Where?
    - How did you feel
    - So what happened next?
    - Who did you inform about your breast cancer? Why?
    - Any referral? By who? When and to where?
9. So have you received any treatment so far?
    - What type?
    - When did you start?
    - How long have you been on treatment?
10. Please can you share with me your experiences with the treatment so far
11. and if there are factors that have impacted your ability to continue receiving treatment
    - Side effects
    - Cost
    - Any insurance
    - Any labs
    - How long it takes you to get to the facility
    - Any support?

12. (Research Assistant summarize what the patient said to check accuracy)

13. Is there any other thing you may want to share with us.

Thank you for taking the time to share your journey with us. We now have a short survey that we would like you to fill. Please let us know if any question is not clear

Section 2

Qn No.	Question	Answers
1	Please how old are you (years)?	Years:
2	What is your marital status	☐ Single ☐ Married/Partnered/Cohabiting ☐ Widowed/Divorced/Separated
3	What is your highest level of education?	☐ Primary school ☐ High school ☐ Technical college diploma ☐ Bachelor degrees ☐ Masters ☐ Other (specify)
4	What is your religion	☐ Christian ☐ Muslim ☐ Other (specify)
5	Are you employed?	☐ Yes ☐ No (SKIP to question 7)
6	If employed, who do you work for?	☐ Government ☐ Self-employed ☐ Other (specify)
7	Do you have health insurance?	☐ Yes ☐ No
8	Has anyone in your family ever had cancer?	☐ Yes ☐ No (SKIP to question 11)
9	Your relation to them?	☐ Father ☐ Mother ☐ Grandmother ☐ Grandfather ☐ Sibling ☐ Child ☐ Husband
10	If anyone in your family has had cancer, what type of cancer did they have?	☐ Breast ☐ Other

Appendix B. Cohort inclusion and exclusion criteria

Criteria	Total Cohort	Number Lost	Percent Lost
Total breast cancer cases in SEER-Medicare diagnosed between 2010-2015	225428		
Restrict to breast cancer is the only cancer or first of many	204861	20567	9.12
Restrict to female	203205	1656	0.81
Restrict to not diagnosed by autopsy or death certificate	202017	1188	0.58
Restrict to known month of diagnosis	201267	750	0.37
Restrict to triple negative breast cancer (TNBC)	16010	185257	92.05
Restrict to age 66 years and older at diagnosis	9205	6805	42.50
Restrict to Medicare fee for service (Parts A and B) and no HMO enrollment 12 months prior and post diagnosis or until death	5194	4011	43.57
Restrict to stage I-III	4598	596	11.47

Appendix C: Radiation and surgery codes

Treatment	Code type	Specific codes
Radiation	ICD 9 diagnosis codes	V58.0, v66.1, v67.1
	ICD 9 procedure codes	92.2, 92.20, 92.21, 92.22, 92.23, 92.24, 92.25, 92.26, 92.27, 92.28, 92.29, 92.3, 92.30, 92.31, 92.32, 92.33, 92.39 92.4, 92.41
	ICD 10 procedure codes	3E0F304, 3E0F704, 3E0F804, 3E0G304, 3E0G704, 3E0G804, 3E0H304, 3E0H704, 3E0H804, 3E0J304, 3E0J704, 3E0J804, 3E0L304, 3E0L704, 3E0M304, 3E0M704, 3E0Y304, 3E0Y704, DBY07ZZ, DBY17ZZ, DBY27ZZ, DBY57ZZ, DBY67ZZ, DBY77ZZ, DDY57ZZ, DDY77ZZ, DMY07ZZ, DMY17ZZ, DWY27ZZ, DWY37ZZ, D7040ZZ, D7050ZZ, D7060ZZ, DB000ZZ, DB010ZZ, DB020ZZ, DB050ZZ, DB060ZZ, DB070ZZ, DD050ZZ, DD070ZZ, DH060ZZ, DH080ZZ, DM000ZZ,

		DM010ZZ, DW020ZZ, DW030ZZ, D71497Z, D71498Z, D71499Z, D7149BZ, D7149CZ, D7149YZ, D714B7Z, D714B8Z, D714B9Z, D714BBZ, D714BCZ, D714BYZ, D71597Z, D71598Z, D71599Z, D7159BZ, D7159CZ, D7159YZ, D715B7Z, D715B8Z, D715B9Z, D715BBZ, D715BCZ, D715BYZ, D71697Z, D71698Z, D71699Z, D7169BZ, D7169CZ, D7169YZ, D716B7Z, D716B8Z, D716B9Z, D716BBZ, D716BCZ, D716BYZ, DB1097Z, DB1098Z, DB1099Z, DB109BZ, DB109CZ, DB109YZ, DB10B7Z, DB10B8Z, DB10B9Z, DB10BBZ, DB10BCZ, DB10BYZ, DB1197Z, DB1198Z, DB1199Z, DB119BZ, DB119CZ, DB119YZ, DB11B7Z, DB11B8Z, DB11B9Z, DB11BBZ, DB11BCZ, DB11BYZ, DB1297Z, DB1298Z, DB1299Z, DB129BZ, DB129CZ, DB129YZ, DB12B7Z, DB12B8Z, DB12B9Z, DB12BBZ, DB12BCZ, DB12BYZ, DB1597Z, DB1598Z, DB1599Z, DB159BZ, DB159CZ, DB159YZ, DB15B7Z, DB15B8Z, DB15B9Z, DB15BBZ, DB15BCZ, DB15BYZ, DB1797Z, DB1798Z, DB1799Z, DB179BZ, DB179CZ, DB179YZ, DB17B7Z, DB17B8Z, DB17B9Z, DB17BBZ, DB17BCZ, DB17BYZ, DD1597Z, DD1598Z, DD1599Z, DD159BZ, DD159CZ, DD159YZ, DD15B7Z, DD15B8Z, DD15B9Z, DD15BBZ, DD15BCZ, DD15BYZ, DD1797Z, DD1798Z, DD1799Z, DD179BZ, DD179CZ, DD179YZ, DD17B7Z, DD17B8Z, DD17B9Z, DD17BBZ, DD17BCZ, DD17BYZ, DM1097Z, DM1098Z, DM1099Z, DM109BZ, DM109CZ, DM109YZ, DM10B7Z, DM10B8Z, DM10B9Z, DM10BBZ, DM10BCZ, DM10BYZ, DM1197Z, DM1198Z, DM1199Z, DM119BZ, DM119CZ, DM119YZ, DM11B7Z, DM11B8Z, DM11B9Z, DM11BBZ, DM11BCZ, DM11BYZ, DW1297Z, DW1298Z, DW1299Z, DW129BZ, DW129CZ, DW129YZ, DW12B7Z, DW12B8Z, DW12B9Z, DW12BBZ, DW12BCZ, DW12BYZ, DW1397Z, DW1398Z, DW1399Z, DW139BZ, DW139CZ, DW139YZ, DW13B7Z, DW13B8Z, DW13B9Z, DW13BBZ, DW13BCZ, DW13BYZ, D7041ZZ, D7042ZZ, D7051ZZ, D7052ZZ, DB001ZZ, DB002ZZ, DB011ZZ, DB012ZZ, DB021ZZ, DB022ZZ,

		DB051ZZ, DB052ZZ, DB071ZZ, DB072ZZ, DD051ZZ, DD052ZZ, DD071ZZ, DD072ZZ, DM001ZZ, DM002ZZ, DM011ZZ, DM012ZZ, DW021ZZ, DW022ZZ, D7043ZZ, D7053ZZ, D7063ZZ, DB003ZZ, DB013ZZ, DB023ZZ, DB053ZZ, DB073ZZ, DD053ZZ, DD073ZZ, DM003ZZ, DM013ZZ, DW023ZZ, D7044ZZ, D7045ZZ, D7054ZZ, D7055ZZ, DB004ZZ, DB005ZZ, DB014ZZ, DB015ZZ, DB024ZZ, DB025ZZ, DB054ZZ, DB055ZZ, DB074ZZ, DB075ZZ, DD054ZZ, DD055ZZ, DD074ZZ, DD075ZZ, DM004ZZ, DM005ZZ, DM014ZZ, DM015ZZ, DW024ZZ, DW025ZZ, 0BH001Z, 0BH031Z, 0BH041Z, 0BH071Z, 0BH081Z, 0BHK01Z, 0BHK31Z, 0BHK41Z, 0BHK71Z, 0BHK81Z, 0BHL01Z, 0BHL31Z, 0BHL41Z, 0BHL71Z, 0BHL81Z, 0DHP01Z, 0DHP31Z, 0DHP41Z, 0DHP71Z, 0DHP81Z, 0HHT01Z, 0HHT31Z, 0HHT71Z, 0HHT81Z, 0HHU01Z, 0HHU31Z, 0HHU71Z, 0HHU81Z, 0HHV01Z, 0HHV31Z, 0HHV71Z, 0HHV81Z, 0HHW01Z, 0HHW31Z, 0HHW71Z, 0HHW81Z, 0HHWX1Z, 0HHX01Z, 0HHX31Z, 0HHX71Z, 0HHX81Z, 0HHXX1Z, 0WH801Z, 0WH831Z, 0WH841Z, 0WH901Z, 0WH931Z, 0WH941Z, 0WHB01Z, 0WHB31Z, 0WHB41Z, 0WHQ01Z 0WHQ31Z, 0WHQ41Z, 0WHQ71Z, 0WHQ81Z, 0XH401Z, 0XH431Z, 0XH441Z, 0XH501Z, 0XH531Z, 0XH541Z, CW73NZZ, CW73YZZ, D7Y4FZZ, D7Y5FZZ, DBY0FZZ, DBY1FZZ, DBY2FZZ, DBY5FZZ, DBY7FZZ, DDY5FZZ, DDY7CZZ, DDY7FZZ, DMY0FZZ, DMY1FZZ, DWY2FZZ D7043Z0, D7053Z0, D7063Z0, DB003Z0, DB013Z0, DB023Z0, DB053Z0, DD053Z0, DD073Z0, DW023Z0
	CPT/HCPCs codes	19296, 19297, 32701, 61793, 61796, 61797, 61798, 61799, 61800, 63620, 63621, 32701, 61793, 77373, G0173, G0251, G0339, G0340, 0082T, 77371-77399 , 77401-77427, 77427-77499, 77520-77525, 77750-77799 G0173, G0174, G0242, G0243, G0251, G0338-G0340, G6002-G6017, 0073T, 0082T

	Revenue center codes	0330,0333
Mastectomy	ICD 9 procedure codes	85.33, 85.34, 85.4, 85.41, 85.43, 85.45, 85.47, 85.35, 85.36, 85.42, 85.44, 85.46, 85.48
	ICD 10 procedure codes	0H0T0JZ, 0H0U0JZ, 0HTT0ZZ, 0HTU0ZZ, 0KTH0ZZ, 0KTJ0ZZ, 0H0V0JZ, 0HTV0ZZ, 0KTH0ZZ, 0KTJ0ZZ, 0H5T0ZZ, 0H5U0ZZ, 0H5V0ZZ
	CPT/HCPC codes	19140, 19180, 19182, 19200, 19220, 19240, 19260, 19271, 19272, 19300, 19303-19307
Breast conserving surgery	ICD 9 procedure codes	85.2, 85.20, 85.21, 85.22, 85.23, 85.24, 85.25
	ICD 10 procedure codes	0H5T3ZZ, 0H5T8ZZ, 0H5U3ZZ, 0H5U8ZZ, 0H5V3ZZ, 0H5V8ZZ, 0HBT0ZZ, 0HBT3ZZ, 0HBT7ZZ, 0HBT8ZZ, 0HBU0ZZ, 0HBU3ZZ, 0HBU7ZZ, 0HBU8ZZ, 0HBV0ZZ, 0HBV3ZZ, 0HBV7ZZ, 0HBV8ZZ, 0HBY0ZZ, 0HBY3ZZ, 0HBY7ZZ, 0HBY8ZZ, 0HTY0ZZ, 0H5W0ZZ, 0H5W3ZZ, 0H5W7ZZ, 0H5W8ZZ, 0H5WXZZ, 0H5X0ZZ, 0H5X3ZZ, 0H5X7ZZ, 0H5X8ZZ, 0H5XXZZ, 0HBW0ZZ, 0HBW3ZZ, 0HBW7ZZ, 0HBW8ZZ, 0HBWXZZ, 0HBX0ZZ, 0HBX3ZZ, 0HBX7ZZ, 0HBX8ZZ, 0HBXXZZ, 0HTWXZZ, 0HTXXZZ
	CPT/HCPCs codes	38790, 38792, 38900, 78800, 78801

Appendix D: IPTW cox proportional hazards model predicting all-cause mortality

	HR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	3.44	2.56 - 4.62	<0.0001
Mastectomy	1.91	1.57 - 2.32	<0.0001
Mastectomy + RT	2.21	1.65 - 2.97	<0.0001

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR hazard ratio

Appendix E: IPTW Fine-Gray Subdistribution hazard model for breast cancer death

	sHR	95% CI	P value
Treatment			
BCT	1.00 (Reference)		
BCS	3.25	2.45 - 4.32	<0.001
Mastectomy	1.65	1.31 - 2.08	<0.001
Mastectomy + RT	2.59	2.02 - 3.32	<0.001

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio

Appendix F: Multivariate Cox proportional hazards model predicting all-cause mortality after excluding those who survived for only one month

	HR	95%CI	P value
Treatment			
BCT	1.00 (Reference)		
BCS	2.99	2.37 - 3.76	<0.0001
Mastectomy	2.00	1.67 - 2.40	<0.0001
Mastectomy + RT	1.76	1.41 - 2.20	<0.0001
Tumor size			
≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.09	0.85 - 1.41	0.49
> 5 cm	1.58	1.20 - 2.06	0.0009
Stage			
I	1.00 (Reference)		
II	2.06	1.55 - 2.72	<0.0001
III	4.10	3.05 - 5.51	<0.0001
Age at diagnosis (years)			
66-74	1.00 (Reference)		
75-84	1.52	1.30 - 1.77	<0.0001
85+	2.49	2.08 - 2.98	<0.0001
Race			
White	1.00 (Reference)		
Black	0.89	0.73 - 1.09	0.26
Other	0.94	0.67 - 1.30	0.70
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	1.25	1.05 - 1.50	0.01
2	1.49	1.18 - 1.89	0.001
3+	2.30	1.84 - 2.87	<0.0001

Census tract median household income			
<$40,000	1.00 (Reference)		
$40,001 - $50,000	1.07	0.86 - 1.33	0.54
$50,001 - $60,000	0.98	0.79 - 1.23	0.88
>$60,000	0.91	0.75 - 1.10	0.33
Missing	1.03	0.78 - 1.37	0.83
Region			
Midwest	1.24	1.016-1.516	0.03
Northeast	0.96	0.785-1.165	0.66
South	1.20	1.006-1.426	0.04
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio

Appendix G: Pairwise comparison - Multivariate Cox proportional hazards model predicting all-cause mortality after excluding those who survived for a month or less

Treatment	**HR**	**95% CI**	**P value[a]**
BCS vs BCT	2.99	2.37 - 3.76	<0.0001
BCS vs Mastectomy + RT	1.70	1.31 - 2.20	0.0004
BCS vs Mastectomy	1.49	1.21 - 1.84	0.0011
Mastectomy + RT vs BCT	1.76	1.41 - 2.20	<0.0001
Mastectomy vs BCT	2.00	1.67 - 2.40	<0.0001
Mastectomy vs Mastectomy + RT	1.14	0.94 - 1.38	0.57

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Appendix H: Fine-Gray Subdistribution hazard model for breast cancer death after excluding those who survived for a month or less

	sHR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.65	1.86 - 3.77	<0.0001
Mastectomy	1.63	1.25 - 2.11	0.0002
Mastectomy + RT	1.96	1.46 - 2.64	<0.0001
Tumor size			

≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.15	0.82 - 1.60	0.43
> 5 cm	1.69	1.20 - 2.40	0.003
Stage			
I	1.00 (Reference)		
II	3.10	2.07 - 4.65	<0.0001
III	6.69	4.38 - 10.20	<0.0001
Age at diagnosis (years)			
66-74	1.00 (Reference)		
75-84	1.11	0.90 - 1.38	0.33
85+	1.51	1.16 - 1.97	0.002
Race			
White	1.00 (Reference)		
Black	0.73	0.53 - 1.00	0.05
Other	0.60	0.35 - 1.03	0.07
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	0.95	0.73 - 1.24	0.71
2	1.27	0.92 - 1.77	0.15
3+	1.21	0.82 - 1.79	0.33
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.02	0.75 - 1.38	0.92
50,001 - 60,000	1.04	0.77 - 1.40	0.81
>60,000	0.83	0.64 - 1.09	0.19
Missing	1.01	0.67 - 1.52	0.97
Region			
Midwest	1.32	1.01 - 1.74	0.05
Northeast	0.89	0.67 - 1.18	0.4
South	1.25	0.98 - 1.58	0.07
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio

Appendix I: Pairwise comparison - Fine-Gray Subdistribution hazard model for breast cancer death after excluding those who survived for a month or less

	sHR	**95% CI**	**P value[a]**

BCS vs BCT	2.65	1.86 - 3.77	<0.0001
BCS vs Mastectomy + RT	1.35	0.91 - 2.00	0.44
BCS vs Mastectomy	1.63	1.17 - 2.26	0.02
Mastectomy + RT vs BCT	1.96	1.46 - 2.64	<0.0001
Mastectomy vs BCT	1.63	1.25 - 2.11	0.001
Mastectomy vs Mastectomy + RT	0.83	0.63 - 1.08	0.52

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Appendix J: Continuous age and tumor size broke further - Multivariate Cox proportional hazards model predicting all-cause mortality

	HR	**95%CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.93	2.33 - 3.68	<0.0001
Mastectomy	1.98	1.65 - 2.37	<0.0001
Mastectomy + RT	1.73	1.38 - 2.16	<0.0001
Tumor size			
≤1 cm	1.00 (Reference)		
> 1 and ≤ 2 cm	1.64	1.21 - 2.22	0.002
> 2 and ≤ 5 cm	1.62	1.13 - 2.33	0.009
> 5 and ≤ 10 cm	2.47	1.68 - 3.64	<0.0001
> 10 cm	2.16	1.39 - 3.36	0.0007
Stage			
I	1.00 (Reference)		
II	1.94	1.47 - 2.58	<0.0001
III	3.86	2.87 - 5.18	<0.0001
Age at diagnosis (years)			
1 year	1.05	1.04 - 1.06	<0.0001
Race			
White	1.00 (Reference)		
Black	0.91	0.74 - 1.11	0.36
Other	0.97	0.70 - 1.34	0.85
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	1.25	1.05 - 1.50	0.01
2	1.47	1.16 - 1.86	0.002
3+	2.27	1.82 - 2.83	<0.0001

Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.07	0.87 - 1.33	0.52
50,001 - 60,000	0.99	0.80 - 1.24	0.96
>60,000	0.90	0.75 - 1.09	0.28
Missing	0.98	0.74 - 1.30	0.89
Region			
Midwest	1.24	1.01 - 1.51	0.04
Northeast	0.97	0.80 - 1.18	0.79
South	1.22	1.03 - 1.45	0.02
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio

Appendix K: Pairwise comparison - Continuous age and tumor size broke further - Multivariate Cox proportional hazards model predicting all-cause mortality

Treatment	**HR**	**95% CI**	**P value[a]**
BCS vs BCT	2.93	2.33 - 3.68	<0.0001
BCS vs Mastectomy + RT	1.70	1.31 - 2.20	0.0004
BCS vs Mastectomy	1.48	1.21 - 1.8	0.001
Mastectomy + RT vs BCT	1.73	1.38 - 2.16	<0.0001
Mastectomy vs BCT	1.98	1.65 - 2.37	<0.0001
Mastectomy vs Mastectomy + RT	1.14	0.94 - 1.39	0.53

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR- hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Appendix L: Continuous age and tumor size broke further - Fine-Gray Subdistribution hazard model for breast cancer death

	sHR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.67	1.89 - 3.78	<0.0001
Mastectomy	1.63	1.26 - 2.11	0.0002
Mastectomy + RT	1.94	1.44 - 2.61	<0.0001
Tumor size			

≤1 cm	1.00 (Reference)		
> 1 and ≤ 2 cm	2.04	1.19 - 3.50	0.01
> 2 and ≤ 5 cm	2.06	1.17 - 3.62	0.01
> 5 and ≤ 10 cm	2.96	1.64 - 5.36	0.0003
> 10 cm	3.27	1.75 - 6.12	0.0002
Stage			
I	1.00 (Reference)		
II	2.92	1.96 - 4.35	<0.0001
III	6.38	4.21 - 9.66	<0.0001
Age at diagnosis (years)			
1 year	1.02	1.01 - 1.03	0.006
Race			
White	1.00 (Reference)		
Black	0.75	0.55 - 1.03	0.07
Other	0.65	0.38 - 1.09	0.1
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	0.95	0.73 - 1.23	0.69
2	1.30	0.93 - 1.80	0.12
3+	1.23	0.84 - 1.81	0.29
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.03	0.76 - 1.39	0.87
50,001 - 60,000	1.04	0.77 - 1.40	0.81
>60,000	0.85	0.65 - 1.11	0.22
Missing	1.01	0.67 - 1.52	0.98

Region			
Midwest	1.31	1.00 - 1.73	0.05
Northeast	0.89	0.67 - 1.18	0.42
South	1.27	1.01 - 1.61	0.04
West	1.00 (Reference)		

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio

Appendix M: Pairwise comparison - Continuous age and tumor size broke further - Fine-Gray Subdistribution hazard model for breast cancer death

	sHR	**95% CI**	**P value[a]**
BCS vs BCT	2.67	1.89 - 3.78	<0.0001
BCS vs Mastectomy + RT	1.38	0.93 - 2.04	0.37
BCS vs Mastectomy	1.64	1.19 - 2.27	0.01
Mastectomy + RT vs BCT	1.94	1.44 - 2.61	<0.0001
Mastectomy vs BCT	1.63	1.26 - 2.11	0.001
Mastectomy vs Mastectomy + RT	0.83	0.64 - 1.10	0.57

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region and Charlson comorbidity score.

Appendix N: Multivariate Cox proportional hazards model predicting all-cause mortality including chemotherapy adjustment

	HR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.80	2.22 - 3.51	<0.0001
Mastectomy	1.92	1.60 - 2.30	<0.0001
Mastectomy + RT	1.84	1.47 - 2.31	<0.0001
Tumor size			
≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.08	0.84 -1.39	0.54
> 5 cm	1.52	1.17 – 1.99	0.002
Stage			
I	1.00 (Reference)		
II	2.29	1.73 – 3.04	<0.0001
III	4.92	3.65 – 6.62	<0.0001

Age at diagnosis (years)			
66-74	1.00 (Reference)		
75-84	1.28	1.09 - 1.51	0.003
85+	1.81	1.48 - 2.22	<0.0001
Race			
White	1.00 (Reference)		
Black	0.88	0.72 - 1.07	0.21
Other	0.96	0.70 - 1.33	0.82
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	1.24	1.04 -1.49	0.02
2	1.43	1.13 - 1.81	0.003
3+	2.17	1.74 - 2.71	<0.0001
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.03	0.83 - 1.28	0.78
50,001 - 60,000	0.96	0.77 - 1.20	0.72
>60,000	0.89	0.74 - 1.08	0.22
Missing	0.98	0.73 - 1.30	0.87
Region			
Midwest	1.19	0.97 - 1.45	0.09
Northeast	0.96	0.79 - 1.17	0.69
South	1.17	0.98 - 1.39	0.08
West	1.00 (Reference)		
Chemotherapy			
Yes	1.00 (Reference)		
No	1.71	1.45 – 2.02	<0.0001

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio

Appendix O: Pairwise Comparison - multivariate Cox proportional hazards model predicting all-cause mortality including chemotherapy adjustment

Treatment	**HR**	**95% CI**	**P value[a]**
BCS vs BCT	2.80	2.22 - 3.51	<0.0001
BCS vs Mastectomy + RT	1.52	1.17 – 1.97	0.009
BCS vs Mastectomy	1.46	1.19 - 1.80	0.002
Mastectomy + RT vs BCT	1.84	1.47 - 2.31	<0.0001
Mastectomy vs BCT	1.92	1.60 - 2.30	<0.0001

Mastectomy vs Mastectomy + RT	1.05	0.85 - 1.27	0.98

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; HR – hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region, Charlson comorbidity score and chemotherapy.

Appendix P: Fine-Gray Subdistribution hazard model for breast cancer death including chemotherapy adjustment

	sHR	**95% CI**	**P value**
Treatment			
BCT	1.00 (Reference)		
BCS	2.61	1.83 - 3.73	<0.0001
Mastectomy	1.61	1.24 - 2.09	0.0004
Mastectomy + RT	1.97	1.47 - 2.66	<0.0001
Tumor size			
≤2 cm	1.00 (Reference)		
> 2 and ≤ 5 cm	1.15	0.82 - 1.60	0.42
> 5 cm	1.67	1.18 - 2.36	0.004
Stage			
I	1.00 (Reference)		
II	3.11	2.07 - 4.68	<0.0001
III	6.91	4.50 - 10.61	<0.0001
Age at diagnosis (years)			
66-74	1.00 (Reference)		
75-84	1.10	0.88 - 1.36	0.41
85+	1.41	1.05 - 1.90	0.02
Race			
White	1.00 (Reference)		
Black	0.74	0.54 - 1.01	0.06
Other	0.64	0.38 - 1.07	0.09
Charlson Comorbidity Score			
0	1.00 (Reference)		
1	0.96	0.74 - 1.24	0.74
2	1.29	0.93 - 1.78	0.13
3+	1.21	0.82 - 1.78	0.34
Census tract median household income			
<40,000	1.00 (Reference)		
40,001 - 50,000	1.02	0.75 - 1.40	0.88
50,001 - 60,000	1.02	0.76 - 1.38	0.89

>60,000	0.84	0.64 - 1.10	0.21
Missing	1.00	0.66 - 1.51	0.99
Region			
Midwest	1.31	0.99 - 1.72	0.05
Northeast	0.89	0.67 - 1.18	0.41
South	1.26	0.99 - 1.59	0.05
West	1.00 (Reference)		
Chemotherapy			
Yes	1.00 (Reference)		
No	1.12	0.88 – 1.43	0.36

Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio

Appendix Q. Pairwise comparison - Fine-Gray Subdistribution hazard model for breast cancer death including chemotherapy adjustment

	sHR	**95% CI**	**P value[a]**
BCS vs BCT	2.61	1.83 - 3.73	<0.0001
BCS vs Mastectomy + RT	1.33	0.89 – 1.98	0.51
BCS vs Mastectomy	1.62	1.17 - 2.27	0.02
Mastectomy + RT vs BCT	1.97	1.47 - 2.66	<0.0001
Mastectomy vs BCT	1.61	1.24 - 2.09	0.002
Mastectomy vs Mastectomy + RT	0.82	0.62 - 1.07	0.46

[a] The Tukey multiple comparison test was used to compare each pair and adjust for multiple comparisons Abbreviations: BCS – breast conserving surgery; BCT – breast conserving therapy; RT – radiotherapy; sHR Subdistribution hazard ratio. Covariates adjusted for include: tumor size, tumor stage, age at diagnosis, race, census tract median household income, US census region, Charlson comorbidity score and chemotherapy.