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Breast Cancer Survival in African American and White Women: An Assessment of Modifiable Factors

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Breast Cancer Survival in African American and White Women: An Assessment of Modifiable Factors

by

Deirdra Forté Wilson

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Committee in charge:

Professor Mahasin S. Mujahid, Chair
Professor Arthur Reingold
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Abstract

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by

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Doctor of Philosophy in Epidemiology

University of California, Berkeley

Professor Mahasin S. Mujahid, Chair

Background: Breast cancer is the leading cancer diagnosis and the second leading cause of cancer-related death in the United States. However, the overall mortality rate declined more than 42% over the last 30 years due to advances in treatment and screening. Despite these advancements, the breast cancer mortality rate for Black women is persistently higher than any other group with a 41% gap in survival compared to White women. The cause of this disparity is complex and partially attributed to non-modifiable factors such as tumor biology and modifiable factors such as access to quality breast cancer treatment, reductions in obesity, and other chronic conditions. The purpose of this research is to examine the contributions of body mass index, comorbidity, and hospital characteristics to the breast cancer mortality disparity between Black and White women.

Methods: This dissertation assesses the contributions of comorbidity, obesity, and hospital characteristics to breast cancer mortality disparities between Black and White women. Chapter 1 provides an overview of breast cancer mortality trends, a review of the literature on the associations of modifiable factors associated with breast cancer mortality and presents the questions and hypotheses for the proceeding chapters. Chapter 2 is a systematic review of peer-reviewed articles to evaluate comorbidity as a primary contributor to breast cancer mortality disparities between Black and White women. Chapter 3 presents the findings of the evaluation of body mass index as a modifier of breast cancer and all-cause mortality disparities between Black and White women using a historical breast cancer cohort dataset. Chapter 5 presents findings from our study of the associations between hospital characteristics, breast cancer surgical volume and hospital area-level poverty, and breast cancer mortality and all-cause mortality. The final chapter provides a summary of our findings and suggestions for future research.

Significance: Identifying and addressing modifiable risk factors for breast cancer mortality is key to narrowing the breast cancer mortality gap between Black and White women. Obesity,

comorbidity, and hospital quality are three such modifiable factors. This research aims to contribute to existing knowledge and elucidate the roles of obesity, comorbidity, and hospital characteristics to adverse breast cancer outcomes among Black women.

Dedication

To my husband, Damon, who relentlessly loves, supports and believes in me, my daughter Naomi Rose who inspires me to be courageous in the pursuit of my dreams, my son Isaac Anthony who exudes pure joy and encourages me to bask in the satisfaction of life each day, and to my mother, Audrey, the woman who gave me the template for tenacity.

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Acknowledgment

Upon the shoulders of my ancestors, I stand.

My doctoral journey was supported by so many who paved the path of educational opportunities for African Americans before me and those who lead me, walked by my side and picked me up as I navigated the difficult path of this doctorate degree. I am grateful to you all. This dissertation would not have been possible without the mentorship of Dr. Mahasin Mujahid who helped resuscitate a body of work that was all but dead. Mahasin's encouragement enabled me to see the bigger picture of what my doctoral work contributes to the field and more importantly what I contribute to the discipline. I am fortunate to have worked with her and look forward to future collaborations.

Thanks also to my committee members: Dr. Art Reingold for his leadership of the department and support as I navigated the process to complete my doctoral work, Dr. Denise Herd, for serving on my committee and for seeing me when I thought I was not seen and Dr. Maureen Lahiff for simplifying complicated statistical concepts and guiding me through the Stata programming. I am grateful that you all decided to take up the mantle of my committee.

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Chapter 1
Introduction

1.1 Background and Significance

Breast Cancer: Significance and Scope of the Problem in the United States

The lifetime risk of developing breast cancer for women in the United States has increased over 50 years. A women's lifetime risk was 1 in 10 in the 1970s[1] and is now 1 in 8. [1-4] Breast cancer is the leading cause of cancer and the second leading cause of cancer death among women in the United States. [3] It is estimated that 287,850 new cases of invasive breast cancer will be diagnosed, and 43,250 breast cancer deaths will occur in the US in 2022. [3-5] The increase in breast cancer rates is most likely due to increases in breast cancer screening, obesity, and the increased use of hormone replacement therapy during the previous 15-20 years. [1]
Racial trends in breast cancer incidence mirror those of the overall incidence for all groups until 2005. Since 2005, age-adjusted breast cancer incidence among Black women has shown a steady increase compared to White women.[1] Today, Black women under the age of forty-five have the highest incidence rates of breast cancer compared to any other group. [2-4] Black women also have the shortest survival time from diagnosis and highest mortality rates compared to all other groups. [5,6] The 5-year breast cancer survival rate for White women increased from 85.1 percent in 1989 to 90.1 percent by 2013 and from 71.1 percent in 1989 to 82.7 percent in 2013 for Black women. Breast cancer mortality rates were 42% higher for Black women (28.0 per 100,000) compared to (19.9 per 100,000) among White women in the United States between 2015 and 2019.[4,7] These statistics highlight the persistent disparity in breast cancer survival and mortality for Black women compared to White women in the United States.

Causes of Racial Disparities in Breast Cancer are Poorly Understood

For more than 20 years, reports have been published documenting excess cancer mortality and poorer survival among Black women with breast cancer compared to White women.[6] The persistent disparities in breast cancer survival and mortality between Black and White women have been an area of extensive research for just as long. [8-13] Researchers have attempted to better understand these disparities by identifying biological factors that might contribute to the initiation and promotion of breast cancer disparities in Black women compared to White women. However, research suggests that individual-level biological risk factors alone do not account for these disparities. [13,14] In 2013, the Danforth model was developed that described how the *interaction* of these factors creates breast cancer disparities between Black and white women. [15] While this model has been instrumental in guiding research in the field, there are still gaps in knowledge around how specific biological and social contextual factors interact to promote these breast cancer mortality and survival disparities. Below, I describe the current state of evidence using the Danforth model as an organizing frame. (Figure 1)

What is known: Biological Factors and Disparities

Breast cancer is not a homogenous disease but is characterized by various tumor subtypes that vary in treatments and prognostic outcomes. Breast cancer tumor subtypes are most often defined by the presence or absence of hormone receptors and growth-promoting proteins. Black women are more often diagnosed with the most aggressive breast cancer subtype, triple-negative breast cancer, which is estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor 2 (HER2) negative. This basal-like subtype grows more rapidly than the more treatable Luminal A breast cancers with more favorable outcomes.[16-19] In an international study, Stark et al. found that women of African Ancestry were more likely to be diagnosed with this aggressive form of breast cancer compared to women of European Ancestry.[19] However, additional research suggests that over-representation in this more aggressive tumor subtype does not account for the poorer survival outcomes. For example, in a study of women with triple-negative breast cancer, Black women still had shorter survival and higher mortality than White women.[19]

What is known: Social Contextual Factors and Disparities

Social and contextual determinants such as socioeconomic status (SES), access to quality health care, and advanced stage at diagnosis are significant contributors to disparities in breast cancer survival and mortality. Further, the interactions between these determinants and the biological causes of breast cancer survival and mortality disparities are complex and difficult to disentangle.[9,20,21]

SES. Differences in socioeconomic status (e.g., education, income, employment status) have been proposed to explain differences in survival. In a study of race as an independent prognostic factor, Perkins et al. found that after controlling for other known prognostic factors such as socioeconomic status and stage at diagnosis, race was no longer a significant predictor of survival.[22] However, examining associations between socioeconomic status and breast cancer survival outcomes have been mixed, with some studies finding an association,[23-25] and other studies failing to find an association.[24,26]

Health Care Access. Limited or no access to quality health care has been implicated as one of the contributing factors to poor health outcomes among Black women with breast cancer. Research suggests that women with no insurance or public insurance receive worse breast cancer quality of care. For example, a study by Parikh-Patel and colleagues investigated the role of the type of health insurance and cancer outcomes and found that breast cancer patients without private insurance were 16-25% less likely to receive radiation treatment after surgery.[27] Moreover, research also documents significant racial disparities among women with a similar level of health care access. For example, a study from the Henry Ford Health Sciences Program in Detroit compared breast cancer survival in Black and White women with similar health care access.[28] Results indicated that despite this similar access, Black women were diagnosed at a later stage than White women. These findings suggest that all access isn't created equal, and examining the quality of access is an important area of investigation.

Stage. Advanced stage breast cancer diagnosis is also a well-documented cause of lower survival time and high breast cancer mortality among Black women compared to White women. [29-31] The reasons for advanced stage at diagnosis are complex and thought to be a combination of health care access and utilization, including quality of mammography services and aggressive tumor biology.[32,33] This contrasts with popular narratives that Black women do not utilize preventive health screening as frequently as White women. However, in a recent analysis of mammography screening practices in the US, Black women were as likely as White women to have had a mammogram in the last year.[5] Thus, inadequate screening for breast cancer is a function of more than just preferences or health care-seeking behavior. [6,34]
While it is clear that socioeconomic status, access to quality health care, and advanced stage at diagnosis significantly contribute to the disparities in survival and mortality between Black and White women, the contributions of other prevalent factors such as comorbidity, obesity, and hospital characteristics are less clear.

What is known: Health Status and Health Care

Comorbidity. Comorbidity, the coexistence of multiple diseases in addition to a primary condition of interest, [35] is becoming more common as the aging US population 2004. [36] Given that comorbidities and cancer both increase with age, breast cancer patients often have preexisting comorbidities at the time of diagnosis. The number and severity of comorbid conditions potentially affect breast cancer progression, treatment, and outcomes.[37,38] In a review of the impact of comorbidity on cancer survival, Sogaard et al. concluded that treatment effectiveness is compromised in patients with comorbidity. [39] In a study of Danish breast cancer patients, Land and colleagues reported that older patients were more likely to receive breast cancer treatment according to National guidelines. The effect of comorbidity remained after the adjustment for stage and age at diagnosis. [40] They also reported that comorbidities and other prognostic factors were mediators in racial disparities of all-cause mortality. [40] The mediating effect of comorbidities in the disparities of breast cancer survival was also reported by Tammemagi et al. In a study of breast cancer survival disparities between Black and White patients in a large health system in Detroit, Michigan. They reported that Black breast cancer patients had a higher comorbidity burden compared to White breast cancer patients, and this disproportionate burden accounted for 50% of the racial disparities in all-cause mortality.[41]

Obesity. Obesity and obesity-related diseases have become more prevalent in the United States in 20 years. Researchers have reported the correlation between obesity as measured by body mass index (BMI) and overall breast cancer survival. [42-44] However, few studies explore relationships between obesity and obesity-related diseases to the disparities in breast cancer survival. It is a logical assumption that if obesity and obesity-related diseases such as type II diabetes affect breast cancer survival and if black women are disproportionately obese, poor breast cancer survival among black women may be partly due to obesity. The direction of this relationship, however, is unclear. Obesity can have both a direct and indirect effect on breast cancer survival. Obesity is indirectly associated with breast cancer survival through its impact on the stage at diagnosis. Women who are obese often have larger and denser breasts, making

it more difficult to detect small breast tumors.[45,46] As a result, obese women are more likely to be diagnosed with late-stage breast cancer and have poorer survival rates.[47-49] Obesity may directly affect breast cancer through several biological mechanisms that stimulate tumor growth.[50-52] Triple-negative breast cancer is more prevalent among women experiencing obesity, [48,51,53] and research suggests that obesity may trigger or promote triple-negative breast cancers through increased levels of circulating insulin and insulin-like growth factors that promote a more aggressive form of cellular proliferation. [53,54]

Hospital Factors. Patient-level factors undoubtedly contribute substantially to disparities in breast cancer outcomes. However, disparities remain once these patient-level factors are accounted for in the analysis. As a result, researchers have looked at factors outside the patient's behavior and biology that may contribute to poor outcomes. Variations in the type and quality of care patients receive across hospitals have become central to this changed focus. Breslin et al. reported that hospital quality factors such as cancer care specific volume and racial mix are important mediators of the racial disparities in breast cancer outcomes, explaining 36% of the excess mortality in Black patients. [14,55,56] Differences in the quality of care Black and other minoritized groups receive are documented in various research studies and health issues. [57,58] The National Health Care Disparities report documented that although access to care and barriers to care declined between 2002 and 2011, [57] Black and Latino patients received worse care than White patients in more than 40% of the quality measures used in the report. In a study conducted on the quality of lung cancer care in an integrated health care system, Ryoo et al. reported that differences within the Veterans Health Administration varied across facilities despite uniform quality requirements and measures, possibly contributing to disparities in lung cancer outcomes among Veteran patients. [59] Current research points to a need to assess the hospital factors such as volume and quality as contributors to disparities in breast cancer outcomes.

Gaps in Knowledge

Despite the current knowledge about the individual contributors to breast cancer survival and mortality disparities, there are some important limitations. While valuable, the current understanding of the biological contributions does not explain the persistent disparities at all ages and stages of breast cancer diagnosis. [60] Further, the convergence of biological, social, contextual, health status, and health care factors has not been adequately researched. Current evidence supports the theory that health status and care factors may play a more significant role in determining breast cancer outcomes than previously thought. Obesity, other comorbidities, and hospital factors are three such factors that may significantly contribute to the persistent disparities in breast cancer survival observed. However, there are gaps in the current disparities research literature regarding these three factors. First, most studies assessing the relationship between comorbid conditions and breast cancer have focused on overall survival, not the disparities in survival between Black and White women in the US. [37,38,61] Only recently has literature that focuses on the contributions of specific comorbid conditions to racial disparities.[62-64]

Second, there is limited research on the moderating effects of obesity on racial disparities in breast cancer survival despite the higher prevalence of obesity among Blacks. In a recent study, Gallagher et al. presents evidence that insulin resistance, as a result of obesity, mediates the relationship between race and breast cancer survival [65]. However, to date, no papers have examined the moderating effects of obesity on race and breast cancer survival. This is a promising and important area of research, and results may inform treatment guidelines. Finally, there has been little focus on how hospital system factors may interact with race to contribute to breast cancer survival disparities. As the gaps in modifiable social contextual factors such as access to care and regular mammography screening are filled, it is apparent that identifying hospital system-level factors that may contribute to persistent disparities can help close the survival disparities gap. [14,66]

Overall, these gaps highlight the lack of evidence to support the underlying causes of disparities in breast cancer survival and mortality and the need for further research to disentangle the complex interrelationships of the biological, social, contextual, health status, and health care factors that contribute to this problem.

1.2 Specific aims

The overall goal of this research is to examine the role of factors that contribute to racial disparities in breast cancer outcomes. Specifically, the contributions of comorbidity, obesity, and hospital factors. I will investigate the contributions of obesity, co-morbidity, and hospital factors to breast cancer survival disparities between Black and White women using an adaptation (Figure1) of the Danforth "Model of the initiation and progression of Breast Cancer Disparities" as the theoretical framework. [15]

This goal will be achieved by the following research aims (Figure 1):

Research Aim 1: To conduct a systematic review of the literature of the body of evidence linking comorbid conditions as the primary contributor to racial disparities in breast cancer survival.

Research Aim 2: To examine the racial differences in breast cancer overall survival and mortality and determine if differences are modified by obesity.

Hypotheses:

1) *The associations between race and overall breast cancer survival and mortality are modified by obesity.*
2) *The associations between race and overall breast cancer survival and mortality will be stronger among obese women.*

Research Aim 3: To examine associations between hospital breast cancer surgical volume and breast cancer mortality and determine if the hospital site of diagnosis contributes to racial/ethnic differences in breast cancer mortality.

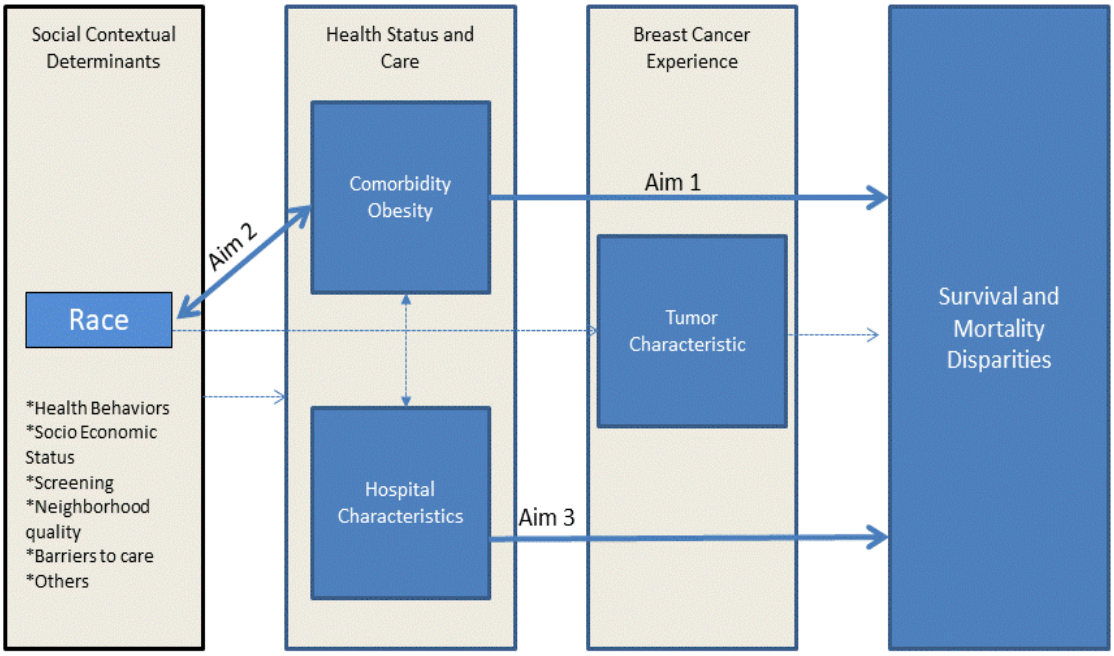
Hypotheses:

1) Hospital factors will be associated with breast cancer mortality.
2) Racial differences in breast cancer mortality will be reduced after adjusting for the hospital site of diagnosis.

Specific aim 1 will be achieved by conducting a systematic review and analysis of peer-reviewed literature. Specific aim 2 will be achieved by analyzing the Kaiser Comorbidity dataset, a Surveillance, Epidemiology, and End Results (SEER) linked historical cohort of incident breast cancer diagnosed from 1978-1986 among Black and White women receiving care at a Northern California Kaiser Permanente facility. Specific aim 3 will be achieved by analyzing the Kaiser Comorbidity dataset and the California Office of Statewide Health Planning and Development (OSHPD) data on hospital characteristics.

1.3 Tables and Figures

Figure 1: Summary Graphic of Specific Aims



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Chapter 2

Comorbidities and Racial Disparities in Breast Cancer Survival: A Systematic Review

2.1 Introduction

Despite a lower incidence of breast cancer, African American women have higher breast cancer mortality than White women, and this racial disparity has persisted for more than 30 years.[1-3] As a result, extensive research has focused on identifying the factors underlying racial disparities in breast cancer outcomes.[4,5] Early research focused on screening practices and stage at diagnosis as the primary contributor to these disparities, given that African American women are more likely to be diagnosed at later stages when the tumor is more invasive.[2] Additional research considered tumor prognostic features, including tumor size, nuclear grade, and histologic subtype. African American women are more likely, compared to White women, to be diagnosed with larger tumors and triple-negative disease.[6] However, studies have documented that racial disparities persist after adjustment for these factors. For example, Zhou et al. found that although racial disparities in breast cancer survival were most pronounced among those with triple-negative disease, disparities existed within every other breast cancer subtype, including subtypes with more favorable prognoses.[7] There is a need to consider other factors, such as comorbidity, that may also contribute to these pervasive disparities.

Comorbidity is the coexistence of multiple diseases, as "co-occurrence of medical conditions is a common and increasingly frequent phenomenon with many consequences."[8,9] The existence of comorbidity at the time of breast cancer diagnosis is common because many comorbid conditions and breast cancer incidence are related to aging.[10] Some comorbid conditions increase the risk of , interfere with breast cancer treatment and increase the risk of breast cancer and all-cause mortality . Obesity is an example of a comorbid condition associated with the initiation and progression of breast cancer through various pathways. In a review of the literature, Brown et al. describe the contributions of obesity to post-menopausal breast cancer initiation through a dysregulated metabolism, inflammation, and the endogenous production of estrogens.[11] Specifically, obesity may lead to the dysregulation of the cytokine, adipokine, and growth factor mechanism leading to the initiation and progression of breast cancer tumors. Obesity is also associated with low-grade chronic inflammation that increases tumor cell proliferation and migration to various sites in the body.[12] Increased adipose tissue also leads to the excess production of endogenous estrogen, a known contributor to breast cancer cell proliferation.[12] Finally, overweight and obese women often receive intentionally reduced doses of adjuvant therapy due to a lack of consensus regarding weight-based dosing protocols, a practice that leads to increased mortality.[12-14] Thus, obesity and other comorbid conditions may play a critical role in adverse cancer-related outcomes.

Studies have shown that pre-existing and comorbid conditions that develop after diagnosis, increase the risk of adverse outcomes among breast cancer patients.[12,14,15] However, fewer studies have examined the contribution of comorbidity to racial disparities and breast cancer outcomes. Given that Black women are more likely to have comorbidities including obesity,

hypertension, and diabetes than White women, it is plausible that comorbid conditions are significant contributors to breast cancer mortality disparities.[16,17] Thus, the goal of this systematic review was to examine the literature on comorbidity is a contributor to the survival disparities between Black and White women diagnosed with invasive breast cancer. Our primary research question was: Are racial differences in breast cancer survival attenuated and no longer statistically significant after adjustment for comorbid conditions? Additionally, we assessed what percent of the racial disparity in breast cancer survival was explained by comorbidity across studies.

2.2 Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines were followed for this systematic review. Research articles examining comorbidity as an explanatory factor for breast cancer mortality differences between Black and White women were published in peer-reviewed academic journals.

The search was limited to the English language and studies of human subjects only. All searches were performed in October 2021. A hand search was also conducted of the reference lists of articles identified in the initial search. Table 1 shows the search strategy and terms used for PubMed, Embase, and the hand search.

Inclusion Criteria

Studies were included if they: 1) focused on women with breast cancer and included both African American/Black and White women, 2) were conducted in the United States, 3) included an empirical analysis, 4) included at least one measure of comorbidity and 5) examined breast cancer survival or mortality as the primary study outcome.

Study Selection

All identified articles were exported into Covidence open-access software for systematic reviews and then screened. . Abstracts were reviewed for relevance against inclusion/exclusion criteria and reasons for exclusion were recorded. Next, the full text of articles were reviewed against inclusion/exclusion criteria, and reasons for exclusion were also recorded.

Data Extraction

Data were extracted from included studies using a data extraction form to collect study year, study authors, study design, sample size, study population, comorbidity assessed, percent with comorbidity, endpoint assessed, results explaining comorbidity association with breast cancer survival, and main conclusions.

Synthesis of Results

A narrative synthesis was performed, summarizing and integrating findings to respond to this review's objective. Significant study findings (i.e., hazard ratios) were examined to see if there

was a consistent relationship between comorbidity and race disparity for breast cancer survival or morbidity.

Quality

Quality was assessed using the Medical Education Research Study Quality Instrument (MERSQI),[18] on 10 criteria: study design, sampling, type of data, the validity of evaluation instrument, data analysis, and outcomes. Each category is scored from 0 to 3, with a total possible MERSQI score of 18. For this systematic review, the "validity of evaluation instrument" domain was excluded resulting in a maximum score of 15 (Supplemental Table 1).

2.3 Results

Three hundred and seventy-four manuscripts were identified in the initial screening process, and 123 duplicates were removed. An additional 191 manuscripts were excluded based on the inclusion and exclusion criteria, such as geographically located within the United States, focus on Black and White women, study design, and comorbidity measure. The remaining 60 full-text articles were read and assessed for eligibility. An additional 48 were removed based on a closer examination of their fit with the inclusion and exclusion criteria. Twelve studies were included in the final sample. Figure 1 provides the screening and inclusion process for this review.

Table 2 displays the characteristics of the 12 studies identified in this systematic review. All studies used a longitudinal study design, 10 of which were retrospective cohort studies,[7,15,19-26] and 2 prospective cohort studies.[14,27] Studies ranged in size from 906 participants to 41,020 and participants were between 20 and 80 years of age. Seven studies used cancer surveillance data, 4 of which used data from the Surveillance Epidemiology and End Results Program (SEER),[15,21,25,26], and 3 used data from other surveillance systems or disease registries (e.g. Metropolitan Detroit Cancer Surveillance System).[14,22,23] The remaining 5 studies used data from community samples of women.[7,19,20,24,27]

A variety of comorbidity measures were used across studies. Seven studies used a comorbidity index,[7,20-22,24-26] three studies calculated a count of comorbidities from a specified list,[14,19] two studies included a comorbidity index and examined obesity or hypertension (HTN) separately,[15,27] and one study examined type II diabetes as the sole comorbid condition.[23] The most commonly used indices include the Modified National Cancer Institute Index (MNCII) and the Charlson Comorbidity Index (CCI).,.[28-30] Although some studies included a wide range of comorbidities, many studies did not list which comorbidities were assessed. The range of comorbidities in the final sample of research papers ranged from hypertension, heart disease, diabetes, renal disease, lung disease, BMI, lifestyle factors, arthritis, respiratory disease, stroke, other cancers, kidney disease, urinary tract disease, circulatory disease, and gastro-intestinal disease.

Comorbidity Measured via Sum of Number of Comorbid Conditions.

Three studies used the sum total of comorbid conditions as a measure of comorbidity. Each of these studies found that Black women are at greater risk of dying when compared to White

women (see Table 2).[1,14,19,20] Eley et al. found the risk of dying for Black women to be 2.2 times the risk of White women (95% confidence interval, 1.8-2.8).[19] Satariano and Ragland found the number of comorbid conditions was strongly associated with an increased risk for death from all causes.[14] They also found that, after further adjustments were made, the number of comorbid conditions was not significantly associated with increased risk of breast cancer death ($p>0.2$), but patients with 2 or more comorbid conditions were at increased risk of death from other causes ($p<0.001$).[14] A study by Tammemagi et al. found that Black breast cancer patients are more likely to die from competing causes rather than of breast cancer.[20] Overall, the three studies that measured comorbidity using the sum of comorbid conditions reached the same conclusion, that comorbidity does not explain racial disparities in breast cancer specific survival.

Comorbidity Measured via Charlson Comorbidity Index (CCI)

The 7 studies that used the Charlson Comorbidity Index, found an association between comorbidity and breast cancer survival (Table 2). Overall, studies using the CCI reported that comorbidity only accounted for a small amount of the disparity in breast cancer survival between Black and White women after adjusting for significant covariates.

Specific Comorbidities Measured

Three studies measured breast cancer survival outcomes with specific comorbidities, such as diabetes, hypertension, and obesity.[15,23,27] While both Samson, et al. and Lu, et al. found no significant association of diabetes or obesity to breast cancer survival disparities, respectively,[23,27] Braithwaite found that hypertension alone explained 30.3% of racial disparity in all cause survival (Table 2).[15]

Quality

The MERSQI scores of review articles ranged from 10-13 across studies which is below the median MERSQI scores published across systematic reviews.[18]

2.4 Discussion

This research investigated whether comorbidity is a contributor to the survival disparities between Black and White women diagnosed with invasive breast cancer. Research revealed limited evidence that comorbidity, in general, is not a major driver of survival disparities between Black and White women diagnosed with invasive breast cancer. Instead, the type of comorbidity may be a better prognostic indicator of breast cancer survival than the number of comorbid conditions. Black women have a higher prevalence of hypertension, which was found to significantly account for 30% of racial disparity in survival rates when compared with White women.[15] Other specific comorbidities, such as diabetes and obesity, were not found to have any significant associations with breast cancer mortality.[23,27] In general, the twelve articles reviewed did not suggest that comorbidity is accountable for any breast cancer survival rate disparities.

Comorbidity

The articles that used a sum total of the number of comorbid conditions a participant simply measured the number of comorbidities; however, each of the three studies that used their own comorbidity index had varying amounts of comorbidities in their coding, as opposed to having one cohesive scale between all studies. For example, Elay, et al. coded the comorbid illnesses as "0," "1," or "2 or more,"[19] whereas Satariano and Ragland[14] coded the comorbid illnesses as "0," "1," "2," or "3 or more" and Tammemagi et al.[20] coded the comorbid illnesses as "0," "1," "2," "3," or "4 or more." The statistical coding discrepancies between the three studies who used the sum total rather than the Charlson Comorbidity Index does not appear to have influenced the results and conclusions. Findings suggest that comorbidity is not associated with breast cancer survival and does not account for survival disparities between Black and White women. However, women with significant comorbidity burden (two or more) appear to be at higher risk of mortality from causes other than breast cancer, irrespective of race.

Racial Differences in Comorbidity

Black women are repeatedly found to have a higher prevalence of comorbidities when compared to White women,[20,21,25,27] however, there is no statistical evidence to suggest that comorbidity explains racial disparities in breast cancer-specific survival. [20,21,23,25,27] Some comorbidities, such as hypertension, have a higher prevalence in the Black population and should be included in the Charlson Comorbidity Index to enhance the CCI's prognostic value for Black adults. While the Charlson Comorbidity Index does yield statistically significant associations, "it is necessary to investigate whether the prognostic value of this index for specific subgroups of women can be improved by including conditions with greater prevalence or severity in those subgroups of women".[19] If the comorbidity index included additional conditions that were more prevalent in Black adults, the results could be used to more accurately capture the association between comorbidities and breast cancer survival.

Comorbidity and Breast Cancer Mortality

Quantity of comorbid conditions may account for at least some of the disparity in breast cancer survival between Black and White women.[19] Studies that measured the sum of number of comorbid conditions found that increased number of comorbidities was associated with increased mortality and other adverse outcomes.[14,19] While comorbidity was shown to be associated with 3-year breast cancer survival,[14] comorbidity still does not fully explain the disparity in survival outcomes for Black and White women with invasive breast cancer.

Specific comorbid conditions were found to be associated with breast cancer outcomes. Obesity, hypertension, and diabetes were of particular interest due to their high prevalence in the general population; however, only hypertension was able to empirically account for about 30% of the disparity in breast cancer survival between Black and White women.[15,23,27] Hypertension is more prevalent in Black adults and therefore needs to be further investigated in regard to breast cancer outcomes. Although many studies used CCI data, the highly prevalent

condition of hypertension is unrepresented in the CCI. Hypertension has been shown to predict mortality among Black adults.[15] Hypertension may have a stronger effect on survival among Black women than on White women, wherein one study found that if accounted for approximately 30% of the racial disparity in breast cancer survival.[15] Although the CCI is overrepresented in the current sample of reviewed papers, the omission of hypertension in this index may affect the validity of the overall findings. Additionally, there is a need to examine hypertension, breast cancer survival, and racial disparity in contemporary cohorts, which should include this factor. If hypertension has such an effect on breast cancer survival, then doctors and patients can monitor the comorbid hypertension and potentially improve survival rates for Black women.

Methodological Issues

The studies in this review varied widely by study population, sampling and other research methodology which may explain differences in the reported findings of an association between comorbidities and breast cancer survival. Studies where patients had similar sociodemographic backgrounds and were treated at the same institutions, reported associations between comorbidity and breast cancer outcomes. For example, in studies conducted using SEEER data or data of patients that received care at Kaiser Permanente Northern California, [15,26] and other studies that used a SEER sample,[21,26] comorbidity accounted for some of the difference in breast cancer survival between Black and White women. Eley et al. used samples from multiple locations, including Northern California, and found an association between comorbidity and breast cancer survival.[19] On the other hand, studies that used samples of patients from the Detroit area of Michigan (MDCSS) did not report an association between comorbidity and racial disparities in breast cancer survival.

Sample size varied substantially across studies as did the distribution of Black and White women in the studies. In several studies, the sample size of Black women was significantly smaller than White women. In other studies, Black women were a much greater portion of the sample than White women which may have affected the statistical power. Curtis et al. examined approximately 36,000 White women and under 2500 Black women.[21] Another study by Santorelli et al. examined approximately 63000 Black women and approximately 4900 White women.[25] As such, a more thorough examination of how racial disparity and comorbidities may impact breast cancer survival would require data with more alignment in sample sizes, controls, and measurement differences.

Currently, there is no consensus on how comorbidity should be measured and calculated for use as a prognostic indicator for breast cancer mortality. Weighted measures such as the Charlson Comorbidity Index and the National Cancer Institute Index and non-weighted measures such as the sum of the total conditions may have contributed to inconsistent results across studies. Thus, future studies need to play close attention to these methodological considerations to determine the most ideal research settings, sampling methods, geographic locations, and the ideal measure or index to assess the contribution of comorbidity to racial disparities in breast cancer survival outcomes.

Limitations and Future Considerations

Limitations of this study include possible confounding variables and incongruence of measured variables between studies. The studies analyzed in this review were thorough and accounted for many possible confounding variables, such as socioeconomic factors, access to healthcare, age, occupation, and much more. However, many breast cancer prognostic indicators were surprisingly not measured consistently throughout the existing literature. For example, estrogen receptor status, progesterone receptor status, and human epidermal growth factor 2 (HER2) status are substantial prognostic indicators when considering breast cancer survival and mortality; however, only two studies explored them.[7,24] Thus, residual cofounding is a major limitation across studies.

The studies examined in this review analyzed either solely a quantitative comorbidity index, such as the sum of total number of comorbidities (independent of type of comorbidity), or a comorbidity index, such as the CCI and NCI (which accounts for both quantity and type of comorbidity). Future research should measure both the sum of the total number of comorbidities as well as the CCI to investigate whether the number of comorbidities – regardless of type – are significantly associated with breast cancer survival rate discrepancy between Black and White women. Future research should also account for the four main subtypes of breast cancer, include hypertension in the comorbidity index, and include data regarding possible confounders such as menopause status, parity, and age of participants. Finally, considering the extensive research in the realm of biological factors, future studies need to consider other factors, such as social and economic factors that may be associated with the mortality gap.

2.5 Conclusion

Racial disparities in breast cancer mortality have been a research priority for decades. While socioeconomic factors appear to be a major underlying cause of this gap, there has been much debate regarding additional contributing factors, such as other medical conditions which exist in combination with breast cancer. Results of this systematic review suggest that comorbidity, in general, does not account for racial disparities in breast cancer survival. However, studies also suggest that specific comorbidities, such as hypertension, may account for a large percentage of breast cancer survival disparities. Future research should continue to investigate the potential role of comorbidity and examine the complex interplay between comorbidity and other social and environmental factors in relation to these disparities.

2.6 Tables and figures

Tables

Table 1. Search strategy and terms.

PubMed	Embase
((((((((((("Comorbidity"[Mesh] OR comorbidity OR comorbidities OR multi morbidities OR multimorbidity OR coexisting diseases) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) OR (("Diabetes Mellitus"[Mesh] OR diabetes mellitus) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) OR (("Obesity"[Mesh] OR obesity) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) OR (("Pulmonary Disease, Chronic Obstructive"[Mesh] OR Chronic Obstructive pulmonary disease OR COPD) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) OR (("Cardiovascular Diseases"[Mesh] OR Cardiovascular Diseases OR hypertension) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) AND (("Health Status Disparities"[Mesh] OR Health disparities) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) AND (("Breast Neoplasms"[Mesh] OR Breast Cancer OR breast	((((('breast cancer'/exp OR breast) AND cancer OR 'breast tumor'/exp OR breast) AND tumor) AND 'human'/de AND [female]/lim AND [english]/lim) AND ((('survival'/exp OR survival OR 'mortality'/exp OR mortality) AND [english]/lim) AND 'human'/de AND [female]/lim) AND ((((('health disparity'/exp OR 'race difference'/exp OR health) AND disparity OR race) AND difference AND [english]/lim) AND 'human'/de AND [female]/lim) AND (((((('multiple chronic conditions'/exp OR multiple) AND chronic AND conditions) AND 'human'/de AND [female]/lim) OR (('comorbidity'/exp OR comorbidity) AND 'human'/de AND [female]/lim) OR ((('charlson comorbidity index'/exp OR charlson) AND comorbidity AND index) AND 'human'/de AND [female]/lim) OR ((('elixhauser comorbidity index'/exp OR elixhauser) AND comorbidity AND index) AND 'human'/de AND [female]/lim)) OR

neoplasms) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms])) AND ((("Survival"[Mesh]) OR "Mortality"[Mesh] OR mortality OR survival) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms]) AND Humans[Mesh] AND English[lang] AND Female[MeSH Terms]	(('hypertension'/exp OR hypertension) AND 'human'/de AND [female]/lim) OR ((('diabetes mellitus'/exp OR diabetes) AND mellitus) AND 'human'/de AND [female]/lim) OR ((('cardiovascular disease'/exp OR cardiovascular) AND disease) AND 'human'/de AND [female]/lim) OR (('obesity'/exp OR obesity) AND 'human'/de AND [female]/lim))

Table 2: Results of selected studies on the association between comorbidity and breast cancer survival disparities between Black and White Women.

Author, Year	Comorbidity Index, Individual Condition	Data Source, Ages, and Sample Size	Study Design	HR (95% CI)	Main Findings
Eley, et al., 1994	Sum of number of comorbid conditions	Atlanta, New Orleans, San Francisco, Oakland N = 1130 AA= 612 WW = 518 Ages 20 to 79	Retrospective Cohort, Frequency Matched Design	Race, comorbidities HR=2.0, CI (1.5-2.7); Race, comorbidities, and covariates HR=1.3, CI (0.9-1.8)	Comorbidity accounts for some of the disparity in breast cancer survival between AA and WW.
Tammemagi, et al., 2005	Sum of number of comorbid conditions; Charlson Comorbidity Index score	Detroit N = 906 AA=264, WW=642 Age ≤40 to > 80	Retrospective Cohort	Race, comorbidities HR = 1.5, CI (1.09-2.05)	Comorbidity did not explain racial disparities in breast cancer specific survival.
Curtis, et al., 2008	Charlson Comorbidity Index score	United States N = 41,020 AA = 2479 WW = 35,878 Other = 2258 Ages: ≥ 68	Retrospective Cohort	Race, covariates, and comorbidity HR = 1.10, CI (0.10-1.22)	Comorbidity accounts for little of the disparity in breast cancer survival between AA and WW after adding significant covariates to the model.
Lu, et al., 2011	Sum of comorbidities; Obesity (BMI) (5 years prior to diagnosis)	Atlanta, Detroit, Los Angeles, Philadelphia, Seattle. N = 4538 AA = 1604 WW = 2934 Ages: 35-64	Prospective Cohort	Race, BMI, AA, HR = 1.20, CI (0.99-1.46)	Obesity does not account for the disparity in breast cancer survival between AA and WW.
Izano, et al., 2014	Charlson Comorbidity Index score	Detroit N=975 AA=170 WW=829 Ages=40-84	Retrospective Cohort	Race, CCI, AA, HR=1.07, CI (0.83-1.36)	Comorbidity is **not** associated with breast cancer survival and does not account for disparities

					in survival between AA and WW.
Samson, et al., 2016	Type 2 Diabetes Mellitus (T2DM)	South Carolina N = 1462 AA = 725 WW = 737	Retrospective Cohort	Race, T2DM OR = 1.52, CI (0.61-3.77)	No significant association of diabetes to breast cancer survival disparities.
Kabat, et al., 2016	Charlson Comorbidity Index score	New York N = 3890 AA = 1394 WW = 853 Other = 1643 Ages: 61.5±13.6	Retrospective Cohort	Race, Clinical variable (including CCI) OR = 1.00, CI = (0.81-1.22)	No significant association of clinical variables inclusive of CCI to breast cancer survival disparities.
Santorelli, et al., 2017	National Cancer Institute (NCI) index	United States N = 68,090 AA = 63,120 WW = 4,970 Age = 65+	Retrospective Cohort	Race, Tumor Characteristics, NCI index HR 1.11, CI = 0.94-1.31	Comorbidity does not explain breast cancer-specific survival disparities.
Zhao, et al., 2021	Deyo/Charlson Comorbidity Index (D/CCI)	Chicago N = 2795 AA = 1067 WW = 1521 Other = 207 Age = N/A	Retrospective Cohort	Race, Tumor Characteristics, D/CCI HR = 1.78, CI = (1.35 - 2.36)	Comorbidity reduces but does not eliminate disparities in breast cancer survival
Braithwaite, et al., 2009	Charlson Comorbidity Index; Hypertension	Northern California N=1254 AA=416 WW=838 Ages: 40 - 80	Retrospective Cohort	Race, hypertension, HR = 1.40, CI (1.08–1.82), vs. HR = 1.32, CI (1.00–1.73)	Hypertension accounts for 20% of disparity in breast cancer survival between AA and WW women.
West, et al., 1997	Charlson Comorbidity Index (CCI)	California N = 1196 AA = 418 WW = 850 Age: All ages	Retrospective Cohort	Race, comorbidity RR is 1.23 (P = 0.10), 2.58 (P < 0.001), and 3.44 (P < 0.001) for comorbidity categories 1, 2, and 3+, respectively.	Comorbidity is associated with the survival of women with breast cancer, independently of other factors. The Charlson index has prognostic significance for both Black and White populations.

Satariano & Ragland, 1994	Comorbidity index developed based on the total number of conditions present.	Detroit N = 936 AA = N/A WW = N/A Age: 40 – 84	Longitudinal, Observational	Stage of disease, survival, comorbidity (P = 0.02).	Patients who had 3 or more comorbid conditions had a 20-fold higher rate of mortality from causes other than breast cancer.

AA=African American/Black women; WW=White women; T2DDM=Type II diabetes mellitus

Table 3: Quality Assessment. Data assessed using the Medical Education Research Quality Instrument (MERQI).

Article	Study Design	Sampling	Type of data	Data Analysis	Outcomes	Score
Eley, et al., 1994	Retrospective Cohort (2)	Random sampling of AA and frequency matched to WW by age group and geo graphic location (3)	Clinical variables abstracted from medical records (3)	Cox proportional hazards models and Cox proportional hazards multivariate regression (3)	Breast cancer mortality (3)	13
Tammemagi , et al., 2005	Historical/ Retrospective Cohort (2)	Cohort from 1985 -1990 was identified from the Henry Ford Health System Tumor Registry. (1)	Clinical variables abstracted from medical records (3)	Cox proportional hazards models and Cox proportional hazards multivariate regression (3)	Breast cancer survival and mortality (3)	13
Curtis, et al., 2008	Retrospective Cohort (2)	Cohort of women ≥ 68 with incident breast cancer between1994-1999 identified from SEER-Medicare database. (1)	Clinical variable abstracted from SEER-Medicare data (3)	Cox proportional hazards models and Cox proportional hazards multivariate regression (3)	Breast cancer survival (3)	12
Lu, et al., 2011	Prospective Cohort (3)	Cohort sampled from the Women's Contraceptive and Reproductive Experiences (CARE) case-control study (0.5)	Clinical variables abstracted from SEER; Exposure variables collected via interview (self-reported BMI and comorbidities) (3)	Multivariate Cox proportional hazards regression (3)	Breast Cancer mortality (3)	12.5

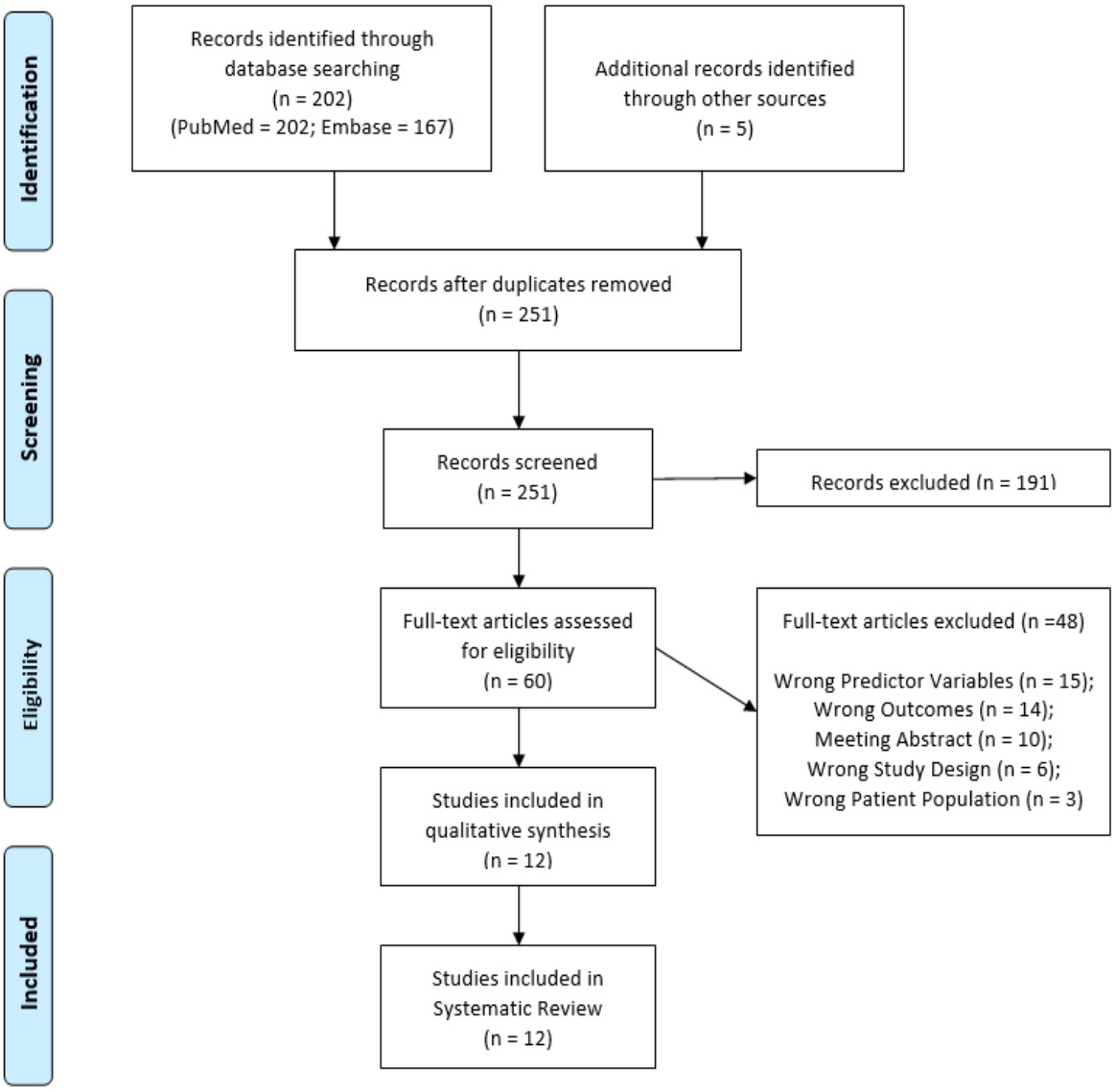
Izano, et al., 2014	Retrospective Cohort (2)	Cohort sampled from the Health and Functioning in Women (HFW) study/ BCA cases identified – Metropolitan Detroit Cancer Surveillance System (MDCSS) (1)	Clinical variables abstracted from MDCSS; Exposure variables collected via interview (self-reported BMI) (3)	Cox proportional hazards regression (3)	Breast cancer mortality (3)	12
Samson, et al., 2016	Retrospective Cohort (2)	Cohort sampled from the South Carolina Central Cancer Registry (SCCCR) and Medicaid records (1)	Clinical variables abstracted from SCCCR and Diabetes diagnosis abstracted from Medicaid records (3)	Conditional logistic regression (2.5)	Breast Cancer mortality (3)	11
Kabat, et al., 2016	Retrospective Cohort (2)	Cohort sampled from the Montefiore Medical Clinical Looking Glass System (CLG) (1)	Clinical variable abstracted from the CLG (1)	Cox proportional hazards models and regression (3)	Breast cancer mortality (3)	10
Santorelli, et al., 2017	Retrospective Cohort (2)	SEER-Medicare linked data (1)	Clinical variable abstracted from SEER-Medicare data (3)	Proportional hazards model for competing risk (3)	Breast Cancer mortality (3)	12

Zhao, et al., 2021	Retrospective Cohort (2)	The Chicago Multiethnic Epidemiologic Breast Cancer Cohort (ChiMEC) (1)	Clinical variables abstracted from medical record, risk factor data collected via questionnaire. (3)	Cox proportional hazards models (3)	Breast Cancer Survival (3)	12
Braithwaite, et al., 2009	Retrospective Cohort (2)	Kaiser Permanente Northern California Medical Care Program (KPMCP) and SEER data. (1)	Clinical variables abstracted from KPMCP and SEER data. (3)	Cox proportional hazards regression (3)	Breast Cancer Survival (3)	12
West, et al., 1997	Retrospective Cohort (2)	KPMCP data, Bay Area Metropolitan Statistical Area, and SEER data (1)	Clinical variables abstracted from KPMCP and SEER data. (3)	Cox proportional hazards models (3)	Breast Cancer Survival (3)	12
Satariano & Ragland, 1994	Longitudinal, Observational (2)	Metropolitan Detroit Cancer Surveillance System (MDCSS) (1)	Clinical variables abstracted from MDCSS; Social and behavioral variables collected via interview. (3)	Cox proportional hazards models (3)	Breast Cancer Mortality (3)	12

Numbers in parentheses represent scores for individual criterion

Figures

Figure 1. Flowchart of literature search strategy and exclusion criteria.



Supplemental Table 1. Medical Education Research Quality Instrument for Quantitative Studies

Domain	MERSQI Item	Score	Max Score
Study design	Single group cross-sectional or single group posttest only	1	3
	Single group pretest & posttest	1.5	
	Nonrandomized, 2 groups	2	
	Randomized controlled trial	3	
Sampling	*Institutions studied*:		3
	1	0.5	
	2	1	
	3	1.5	
	Response rate, %:		
	Not applicable		
	<50 or not reported	0.5	
	50-74	1	
	>75	1.5	
Type of data	Assessment by participants	1	3
	Objective measurement	3	
Validity of evaluation instrument	*Internal structure:*		3
	Not applicable		
	Not reported	0	
	Reported	1	
	Content:		
	Not applicable		
	Not reported	0	
	Reported	1	
	Relationships to other variables:		
	Not applicable		
	Not reported	0	
	Reported	1	
Data analysis	*Appropriateness of analysis:*		3
	Inappropriate for study design or type of data	0	
	Appropriate for study design, type of data	1	
	Complexity of analysis:		
	Descriptive analysis only	1	
	Beyond descriptive analysis	2	
Outcomes	Satisfaction, attitudes, perceptions, opinions, general facts	1	3
	Knowledge, skills	1.5	
	Behaviors	2	
	Patient/health care outcome	3	
Total possible score*			**18**

*Scores range from 5 to 18; for this study, excluding validity of evaluation instrument
Adapted from Reed DA et al, JAMA 2007;298:1002–9.

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Chapter 3 The Contribution of Obesity to Racial Disparities in Breast Cancer Mortality

3.1 Background

Breast cancer is the leading cause of cancer among women and the second leading cause of cancer-related death.[1,2] Over the past two decades, a primary goal of breast cancer researchers and advocates has been to reduce both the incidence and mortality of breast cancer among women in the United States. This goal has been met with moderate success. Breast cancer mortality declined by 42% for all groups of women in the United States from 1989 to 2019, and this decline is most likely attributed to improvements in early detection and treatment.[1,2] However, during this same period, the racial disparity in mortality widened between White and Black women.[1,3] Persistently high breast cancer mortality rates among Black women are thus a significant public health concern.

Although the exact causes of the disproportionate burden of breast cancer mortality in Black women are unknown, common explanations include an advanced stage at diagnosis and aggressive tumor subtypes. [4,5] In the past, Black women were less likely than White women to have undergone recent mammography screening, contributing to later detection and more advanced-stage tumors. [6,7] However, improvements in outreach and access have resulted in screening rates that are about the same between the two groups.[3] Despite improvements in screening rates, Black women are still more likely to be diagnosed with advanced stage and aggressive tumor subtypes, two factors contributing to increased mortality.[5,8-11] Data on the disparity in breast cancer tumor diagnosis stage is consistent across epidemiologic breast cancer studies. A large retrospective cohort study using data from 11 registries that participated in the Surveillance, Epidemiology, and End Results (SEER) program found that Black women were 2.5 times more likely to be diagnosed with stages 3 or 4 breast cancer tumors than non-Hispanic White women.[5] Additional studies have also reported a greater proportion of advanced-stage tumors among Black women. [12-14] In addition, the most aggressive types of breast cancer, triple-negative breast cancers such as estrogen receptor-negative and progesterone receptor-negative, and excess human epidermal growth factor receptor 2 (HER2) proteins are more common among Black women than among women of other ethnicities.[14,15]

The causes of triple-negative breast cancer are unclear, but one theory is that obesogenic factors promote the growth and progression of triple-negative breast cancer tumors. Rigorous studies and systematic reviews have examined the association between overweight and obesity at the time of breast cancer diagnosis to poorer breast cancer survival and increased breast cancer mortality. These studies have consistently reported that breast cancer patients who are overweight or obese, based on their body mass index (BMI) at diagnosis, experience decreased breast cancer survival and have higher mortality rates compared to breast cancer patients of normal weight.[16] In a systematic review of 82 studies on the association between obesity and breast cancer-specific mortality, Chan et al. found that obesity was associated with increased mortality and poorer survival among pre and post-menopausal women.[16] Similar finding were reported in a 2016 review of the literature. Jiralerspong et al reported a 35- 40% increased

risk of breast cancer recurrence and breast cancer-specific mortality among pre and post-menopausal women classified as obese.[17]

Despite the strong evidence that these studies and systematic reviews present, the role obesity plays in breast cancer survival and mortality disparities between Black and White women is less clear. . In a study of 4,538 Black and White women ages 35 to 64 years old, Lu et al. reported that obesity was associated with higher overall and breast cancer-specific mortality in White women but not Black women and concluded that it is unlikely that obesity explains the survival disparities between Black and White women.[18] Specifically, after controlling for tumor stage, age, education, study site, and comorbidities, obesity was not associated with differences in mortality between Black and White women. Lu and colleagues argued that other factors (cultural, psychological, behavioral, social, and environmental) might affect breast cancer progression and obesity, and other biological factors.[18] In a study of 1,351 racially diverse women, Kwan et al. investigated the association of body size with breast cancer-specific mortality and found an association only for Asian American women.[19] Ultimately, the evidence to support the role of obesity in explaining the mortality and survival gap among Africa American and White women is inconsistent and highlights the need for further study.

Based on current evidence, obesity at the time of breast cancer diagnosis has a role in the initiation and progression of breast cancer, causing poorer survival and increased mortality. What is less clear is whether this association explains the poorer survival and higher breast cancer mortality among Black women. Because rates of overweight and obesity have increased dramatically over the last 20 years and Black women have the highest rates, it is plausible that obesity may have a significant role in explaining persistent breast cancer survival and mortality disparities in this group.[20] Thus, to address this gap in knowledge, we examined racial differences in all-cause and breast cancer-specific mortality and whether these differences were modified by obesity status. We hypothesized that Black women would have higher all-cause and breast cancer-specific mortality and that associations would be modified by obesity such that racial differences would be most pronounced among overweight and obese women.

3.2 Methods

Data Sources

A historical cohort study was conducted of Black and White women with invasive breast cancer as part of the Kaiser Permanente Northern California Medical Care Program (KPMCP) Co-morbidity Study.[21] The purpose of the KPMCP Co-morbidity study was to examine whether Black patients seen at Kaiser Hospitals have a higher prevalence of concurrent health conditions (i.e., comorbidities), such as hypertension, heart disease, and diabetes, and a higher prevalence of obesity than White patient, which may contribute to their risk of breast cancer death.

Cases were identified by the Northern California Cancer Center's (NCCC) Surveillance, Epidemiology, and End Results (SEER) cancer surveillance program. White and Black patients with histologically confirmed invasive breast cancer were eligible for inclusion in the original study. All cases were diagnosed between January 1, 1973, and December 31, 1986, and were

enrolled members of the KPMCP of Northern California. Patient data were abstracted by medical record review at KPMCP Northern California. Trained abstractors at KPMCP retrieved data on co-morbid conditions present at the time of breast cancer diagnosis and height and weight through a review of KPMCP medical records. These data were then linked to NCCC SEER surveillance data, including sociodemographic data, breast tumor histology, stage at diagnosis, estrogen receptor status, and breast cancer treatment.

Vital status and cause of death were updated for study participants in October 2002 for the current study. The update was completed by linking the NCCC patient registry number to the corresponding California vital records identification number to obtain updated data on survival and cause of death. In some cases, the patient registry number had changed, for example, when a patient was reported from more than one source, given a unique registry for both, and then consolidated. In such cases, changes in patient registry numbers were resolved by using patient identifying information such as name, address, and date of birth. The Human Subjects Review Boards of the NCCC (IRB # 2002-011) and the University of California Berkeley (OPHS # 2003-8-43) approved this work before the limited data set was accessed.

Study Population

Case selection for this historical cohort was based on the original KPMCP criteria. 1) Black or White (Non-Hispanic, White) race; 2) diagnosed with histologically confirmed invasive breast cancer between January 1, 1978, and December 31, 1985; 3) diagnosed at one of the seven KPMCP Hospitals in Northern California; 4) resident of either Alameda, Contra Costa, Marin, San Francisco, or San Mateo Counties at diagnosis; 5) and alive at the time of diagnosis. A total of 1258 breast cancer cases, 417 Black and 841 white women, met the specified eligibility criteria.

Exclusion Criteria

An additional 220 patients were excluded based on the exclusion criteria for the current study. Seven patients were excluded when the KPMCP data and vital records were merged for the following reasons. Three patients were no longer in the NCCC databases and could not be matched by name because the data set was de-identified; one recoded as in situ cancer instead of invasive, and one patient was not a resident of one of the five counties included in the study at the time of diagnosis, and 2 patients were deleted because they were duplicates. An additional 170 patients were deleted due to missing height and weight needed to calculate BMI. Forty patients with missing registry stage at diagnosis were also excluded from the cohort. Two additional patients were excluded because of missing cause of death information, and one was excluded because of less than one month of survival time. The final sample includes 1038 women, 351 Black women, and 687 White women (Figure 1).

Study Variables

Outcome Measures

Breast cancer-specific mortality and overall mortality were outcome measures for the study. California vital records data were used to collect information on the vital status of patients in the study. Death information and cause of death were abstracted and matched to the patient records. Deaths were categorized as breast cancer (International Classification of Diseases

codes ICD-9-174-175, ICD10-C50) and non-breast cancer deaths. Breast cancer deaths are considered deaths where breast cancer was recorded as the primary or underlying cause of death. Overall, mortality was considered death from any reason during the follow-up period. Patients in the historical cohort were followed from the time of diagnosis to the final vital status update in October 2002, with an average of 13 years of follow-up.

Race and other Demographic Characteristics

Self-identified race was abstracted from the KPMCP medical records of each patient (Black, White). [22] Women of other races were not included in the study as the study aimed to investigate the disparities in breast cancer mortality between Black and White women. Age at the time of diagnosis was calculated from the patient's date of birth. Marital status, tumor receptor status, and date of the last mammogram were evaluated but not included in the final tables or analysis because they lacked statistical significance in descriptive analyses.

Anthropometric Measurement and Clinical Covariates

Several measures were calculated from the KPMCP patient records. Body Mass Index (BMI) was calculated using the patient's height at the time of diagnosis, recorded in feet and inches, and the patient's weight at diagnosis recorded in pounds, and categorized based on the World Health Organization cut points for weight categories. [23] BMI categories included in analyses included underweight (BMI<20), normal weight (20≤BMI<25), overweight (25≤BMI<30), and obese (BMI≥30). SEER categories for cancer tumor stage were used for this study. The SEER cancer tumor stage categories account for tumor size, lymph node status, and metastases in the stage classification of a breast cancer tumors. SEER categories of local, regional /remote were used for this study.[24]

Statistical Analyses

Frequency stratified by race was used to report the distribution of demographic and clinically relevant variables in the study population. Pearson's chi-square tests examined associations between clinically relevant variables and all-cause and breast cancer-specific mortality. Variables included the patient's race, age at diagnosis, stage at diagnosis, and BMI categories.

Age-adjusted Kaplan Meier survival curves and the log-rank test were used to compare the survival time distributions for overall mortality and breast cancer-specific mortality by race and BMI. Cox proportional hazard regression models were used to estimate hazard ratios and 95% confidence intervals for the association between race and all-cause and breast cancer-specific mortality, before and after adjustment for confounders. Estimates were considered statistically significant for a p-value was less than 0.05. Each model was tested to verify that the assumption of proportional hazards was not violated and no violations were observed.

Models were adjusted for age and stage at diagnosis and included cross-product terms to test for effect modification by BMI categories. Effect modification was assessed using an overall Wald test, and a p-value less than 0.20 was considered statistically significant. [25] The linear combination of estimators (lincom) command was used to calculate the hazard ratios for race

separately for each BMI category. All statistical analyses were performed using STATA version 12.0 software. [26]

3.3 Results

A total of 1038 women were included in this study. The mean age at breast cancer diagnosis was 56 years (SD=13), 60% were White women, and 40% were Black women. Black women were more likely to be younger at diagnosis (<45 years: 34% for Black women, 19 % for White women), have a more advanced stage at diagnosis (Regional/distal stage: 48.7% for Black women vs. 37.7% for White women) and more likely to be obese (30.5% Black women vs. 15.4% White women, Table 1). During the follow-up period of 13 years, 624 women (60%) died from all causes (65% White women, 35% Black women), and 351 (30%) women died from breast cancer (60% White, 40% Black women). In bivariate analyses, breast cancer mortality increased with age, and was higher for women diagnosed with regional/remote stage tumors. All-cause mortality increased with age and was highest among women over 64 and for women diagnosed with regional/distal stage breast cancer tumors (Table 2).

In age-adjusted models, all-cause and breast cancer-specific mortality were higher among Black women than White women (HR, 95% C.I.: 1.30, 1.10 to 1.54 for all-cause mortality; 1.39, 1.11 to 1.76 for breast-cancer specific mortality). Additional adjustment for stage and obesity status attenuated these results (HR, 95% C.I.: 1.14, 0.96 to 1.36 for all-cause mortality; 1.14, 0.90 to 1.45for breast-cancer specific mortality; Table 3).

There was evidence that the HR for Black vs. White participants varied by BMI category (Figure 2; Figure 3). In age-adjusted Kaplan Meir plots, Black-White disparities in breast cancer-specific mortality appeared most pronounced among overweight and obesity categories. Black-White disparities were pronounced for all-cause mortality in all BMI categories except for women classified as normal weight. Upon further statistical tests for effect modification, we found marginal evidence that obesity modified Black-White disparities in breast cancer mortality (p=0.20, Figure 4). Among women in the overweight BMI category, there was a 54% higher rate of breast cancer mortality for Black women compared to White women after adjusting for age and stage, however, the confidence interval included the null hypothesis value of 1 (HR, 95% C.I. 1.54, 0.80 to 2.57). Black-White differences in breast cancer mortality were less pronounced for women who were in the obese and normal weight category (HR, 95% C.I. 1.01, 0.52 to 1.69 for obesity; 1.07, 0.72 to 1.62), and Black women had a lower risk of breast cancer mortality compared to White women who were in the underweight category (HR, 95% C.I. 0.50, 0.14 to 1.53). There was no evidence that obesity status modified Black-White differences in all-cause mortality (p=0.920).

3.4 Discussion

In a population of Black and White female members of a managed care organization, we found that Black women diagnosed with invasive breast cancer had a higher overall and breast-cancer-specific mortality rate in age-adjusted models, but further adjustment for BMI and stage

at diagnosis attenuated these differences. We also found marginal evidence of effect modification by BMI. Black-White disparities in breast cancer mortality appeared to be most pronounced among women in the overweight category.

This is one of the first studies to examine Black-White differences in breast cancer and all-cause mortality within levels of obesity. Studies have investigated associations between BMI/obesity and survival outcomes within racial/ethnic groups, and results suggest that associations were present among White and Asian women but not among Black women.[18,19] In age-adjusted Kaplan-Meir plots, we found that Black women in the obese BMI category had the lowest survival compared to Black women in other BMI categories and White women of all BMI categories. However, racial disparities in breast cancer mortality were most pronounced in the overweight BMI category, although this effect modification was of marginal statistical significance. This finding may be because White women in the obese BMI category also had poorer survival contributing to smaller differences. Future studies are needed to investigate this trend. If our results are corroborated, then a focus on overweight and not obesity might provide an opportunity to improve breast cancer mortality outcomes for Black women.

When we examined age-adjusted survival differences in all-cause mortality between racial groups, we found that Black women in the obese BMI category also had the lowest survival curves compared to all other groups, but there were large Black-White differences in all-cause mortality for every category of BMI except for the underweight category. However, there was no evidence of effect modification when we adjusted for age and stage. We know from previous research that significant racial/ethnic disparities exist across a wide range of health behaviors, health factors, chronic disease, and mortality outcomes.[27] Our findings that racial disparities in all-cause mortality persist across BMI categories are consistent with this larger body of research. In addition, a growing body of research suggests that cumulative daily chronic stress from the experience of discrimination can overwhelm the immune system and become an important factor in early death for black individuals.[28] Future studies should continue to investigate this trend suggesting that Black women may be particularly vulnerable to premature death.

Current research suggests that tumor biology is an important prognostic indicator. Women diagnosed with breast cancer at ages less than 50 are more likely to be diagnosed with hormone receptor-negative (HR-) or triple-negative breast tumors (estrogen receptor, progesterone receptor, and HER2 negative) that are less responsive to traditional breast cancer treatments. [29] Tumor biology differences between Black and White women in this study population may partly explain the differences observed in survival.

Previous studies found that equal access to medical care was associated with longer breast cancer survival for Black and White women diagnosed with invasive breast cancer. [30-32] Women in this study had access to preventive and treatment health services as they were all a part of the same health maintenance organization (HMO). Despite equal access to preventive and treatment services, we found racial disparities. [33] One explanation may be differences in healthcare-seeking behaviors and other barriers to seeking preventive care and timely

treatment, but these variables were not measured. Health seeking barriers associated with survival differences found in other studies were delays in receiving treatment after the initial diagnosis of breast cancer and the lack of adherence to the treatment recommendations (i.e., foregoing hormonal therapy).[34]

This study is not without limitations. Data were obtained from a historical cohort that was not originally designed to assess the contributions of obesity to racial/ethnic differences in mortality outcomes. Moreover, trends in breast cancer diagnosis, treatment, and survival over time preclude us from extrapolating these results to current associations. Another limitation was data availability. Key covariates related to breast cancer and all-cause mortality, such as family history, tumor characteristics such as grade, and breast cancer treatment, were not available for a large enough sample of women. The dataset also lacked information on social factors (e.g., socioeconomic position), which we know are key drivers of racial/ethnic differences in health outcomes. Thus we cannot rule out residual confounding. Body mass index was calculated using overall weight and height, however, there is evidence that suggests that waist-to-hip ratio or other anthropometric measures may be better measures of body fat distribution.[35] In addition, body weight was obtained at diagnosis, which could underestimate the patient's weight if weight loss was a cancer-related symptom. However, based on similar studies, researchers found no evidence to suggest significant variations in weight in the 3-5 years before diagnosis.[36,37] Furthermore, generalizability of study results may be limited to women within the Northern California Kaiser health system because of known differences between members of an HMO and the general population. Finally, we were limited in statistical power, which may have compromised our ability to detect effect modification.

3.5 Conclusion

Racial disparities in breast cancer survival remain a significant public health issue. Although our results did not provide conclusive evidence that obesity is a major contributor to these disparities, future research should continue to investigate obesity and other factors that may account for these disparities in different contexts. Future research should also consider the social determinants for which race is a proxy. These determinants may offer a more complete picture of the factors that contribute to disparities in breast cancer and all cause survival between Black and White women.

3.6 Tables and figures

Table 1: Distribution of Selected Characteristics at Diagnosis of Patients with Breast Cancer by Race, Kaiser Permanente Northern California Medical Care Program

	Overall		Race	
	(N=1,038)		White (N=687)	Black (N=351)
	N	%	%	%
Age at diagnosis, years (mean, SD)	55.9 (13.3)		57.7 (13.0)	52.4 (13.1)
<45	250	24.1	19.0	34.2
45-54	212	20.4	19.8	21.7
55-64	297	28.6	31.2	23.6
65-74	279	26.9	30.0	20.5
Stage				
Local	608	58.6	62.3	51.28
Regional	401	38.6	35.2	45.30
Remote	29	2.79	2.47	3.42
BMI (kg/m^2) (mean, SD)	26.2 (5.4)		25.3 (4.9)	28.0 (5.9)
<20 (underweight)	69	6.7	7.7	4.6
20-24.9 (normal weight)	441	42.5	48.0	32.0
25-29.9 (overweight)	315	30.4	29.0	33.3
≥30 (obese)	213	20.5	15.4	30.5

Table 2: Proportion of All-Cause and Breast Cancer Specific Deaths by Study Covariates

	N=1038	All-Cause Mortality		Breast Cancer Mortality	
		Yes (N=624)	No (N=414)	Yes (N=308)	No (N=730)
		%	%	N	%
Race					
White participants	687	65.0	68.6	60.0	68.9
Black participants	351	35.0	31.4	40.0	31.1
Age at diagnosis, years					
<45	250	17.0	34.8	25.0	23.7
45-54	212	19.2	22.2	25.0	18.5
55-64	297	26.0	32.6	28.9	28.5
≥65	279	37.8	10.4	21.1	29.3
Stage					
Local	608	49.7	72.0	34.1	68.9
Regional/Remote	430	50.3	28.0	65.9	31.1
BMI (kg/m^2)					
<20 (underweight)	69	6.4	7.0	6.1	6.8
20-24.9 (normal weight)	441	38.6	48.3	38.0	44.4
25-29.9 (overweight)	315	31.3	29.0	28.9	31.0
≥30 (obese)	213	23.7	15.7	27.0	17.8

Table 3: Hazard Ratio Estimates and 95% Confidence Interval for the Association between Race, All Cause, and Breast-Cancer Specific Mortality

N=1038	All-Cause Mortality		Breast Cancer Specific Mortality	
	Model 1 HR [95% C.I.]	**Model 2 HR [95% C.I.]**	**Model 1 HR [95% C.I.]**	**Model 2 HR [95% C.I.]**
Race				
White participants	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Black participants	1.30 [1.10, 1.54]	1.14 [0.96, 1.36]	1.39 [1.11, 1.76]	1.14 [0.90 to 1.45]
Age at diagnosis				
<45	1.0 (Ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
45-54	1.41 [1.10, 1.83]	1.36 [1.04, 1.77]	1.23 [0.89, 1.69]	1.15 [0.84, 1.59]
55-64	1.40 [1.10, 1.80]	1.38 [1.08, 1.77]	1.02 [0.75, 1.38]	.97 [0.71, 1.33]
65+	2.95 [2.30, 3.74]	3.06 [2.41, 3.89]	0.94 [0.67, 1.31]	0.97 [0.69, 1.37]
Stage				
local		1.0 (ref)		1.0 (ref)
Regional/Remote		2.25 [1.92, 2.64]		3.50 [2.76, 4.45]
BMI (kg/m^2)				
<20 (underweight)		1.43 [1.02, 2.00]		1.34 [0.82, 2.19]
20-24.9 (normal weight)		1.0 (ref)		1.0 (ref)
25-29.9 (overweight)		1.15 [0.95, 1.39]		1.11 [0.84, 1.46]
≥30 (obese)		1.30 [1.05 to 1.61]		1.50 [1.12 to 2.02]

Model 1: age-adjusted; Model 2: +stage, BMI

Figure 1: Sample size flow chart

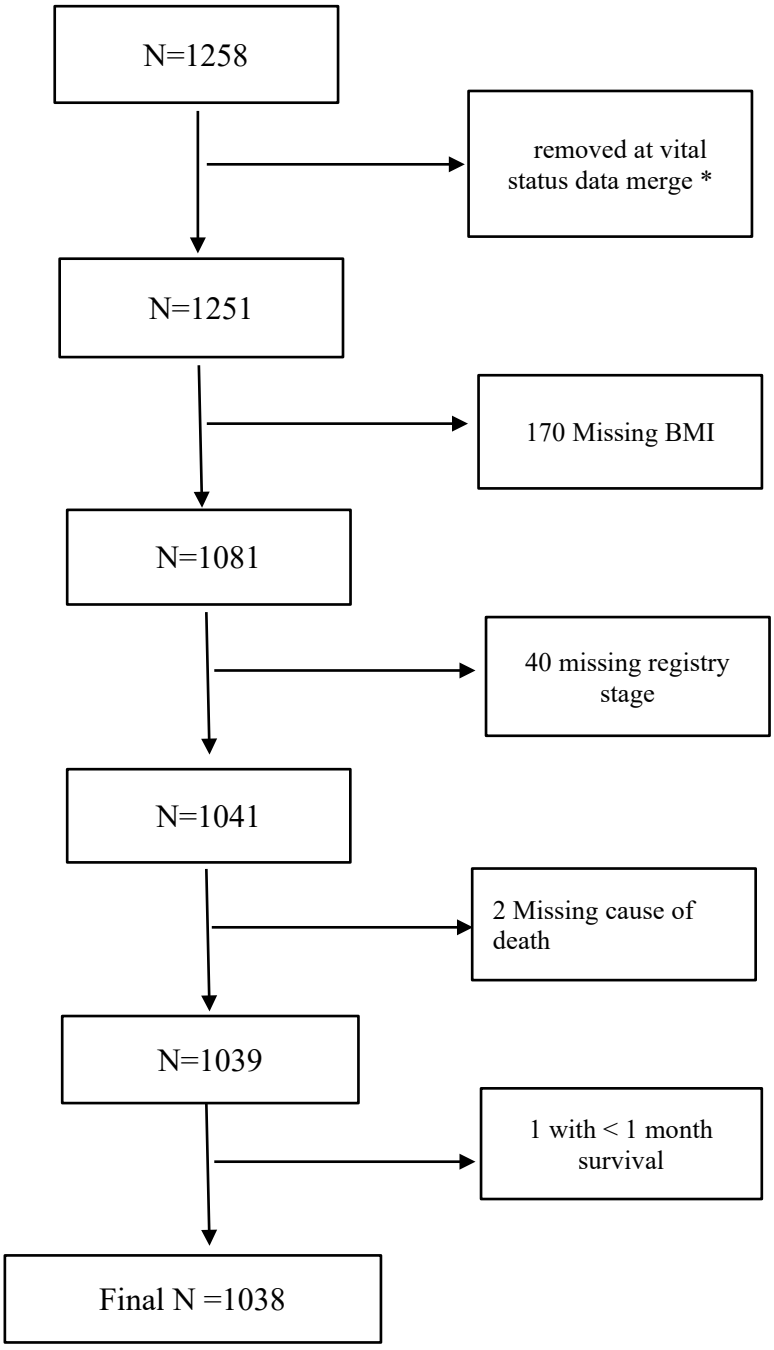


Figure 2: Age-adjusted Kaplan Meier Breast Cancer Survival Curves by Race and Body Mass Index Categories

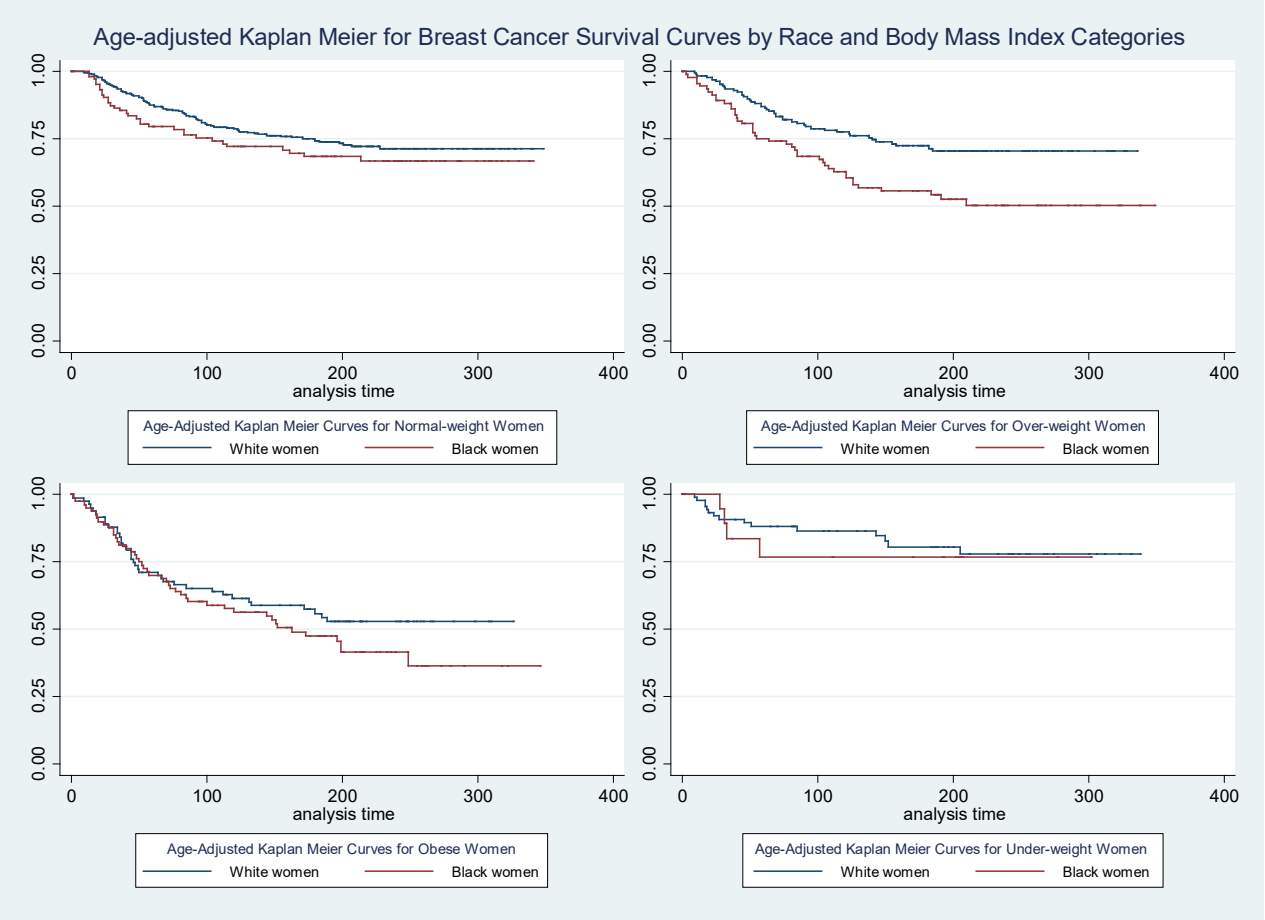


Figure 3: Age-adjusted Kaplan Meier All-Cause Survival Curves by Race and Body Mass Index Categories

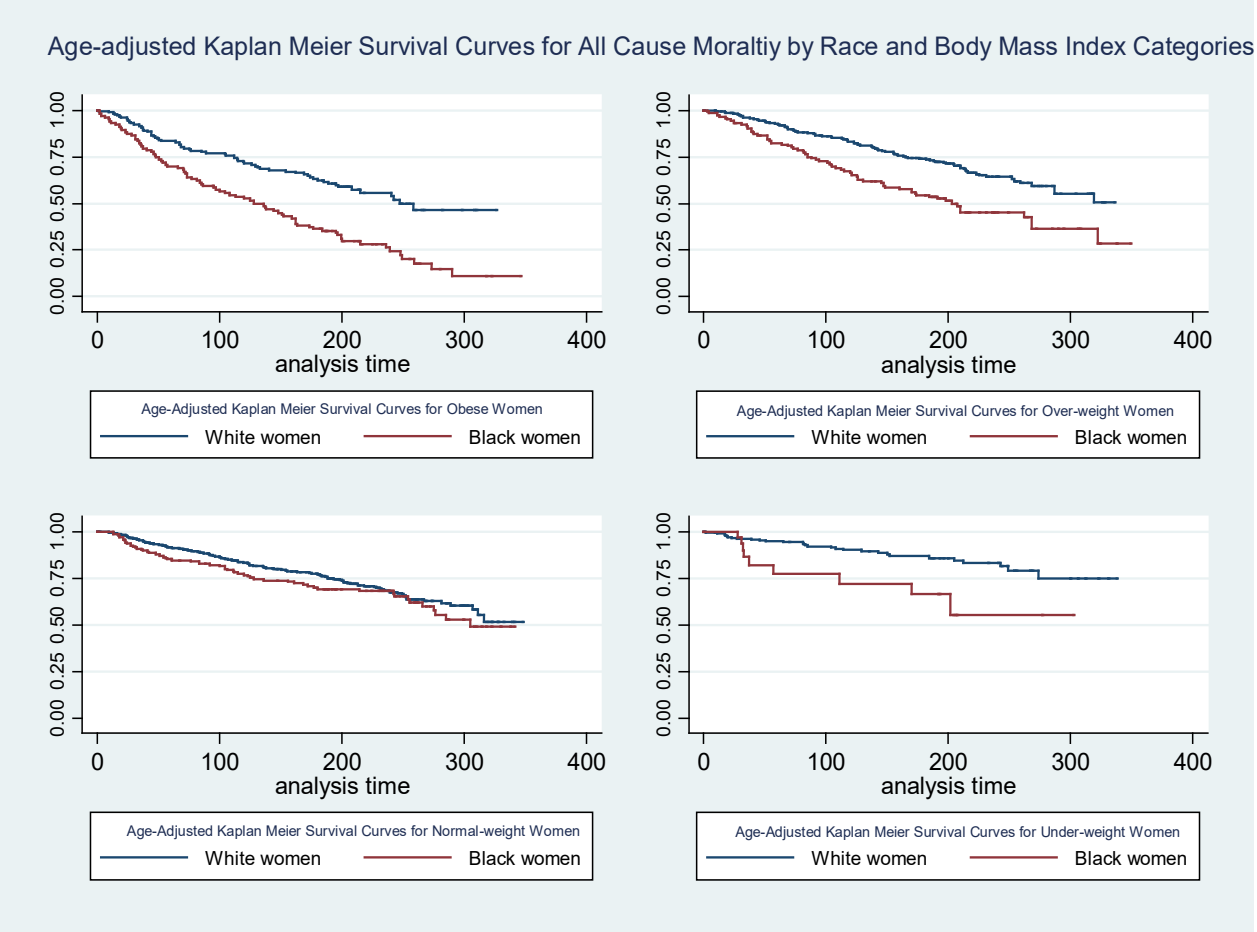
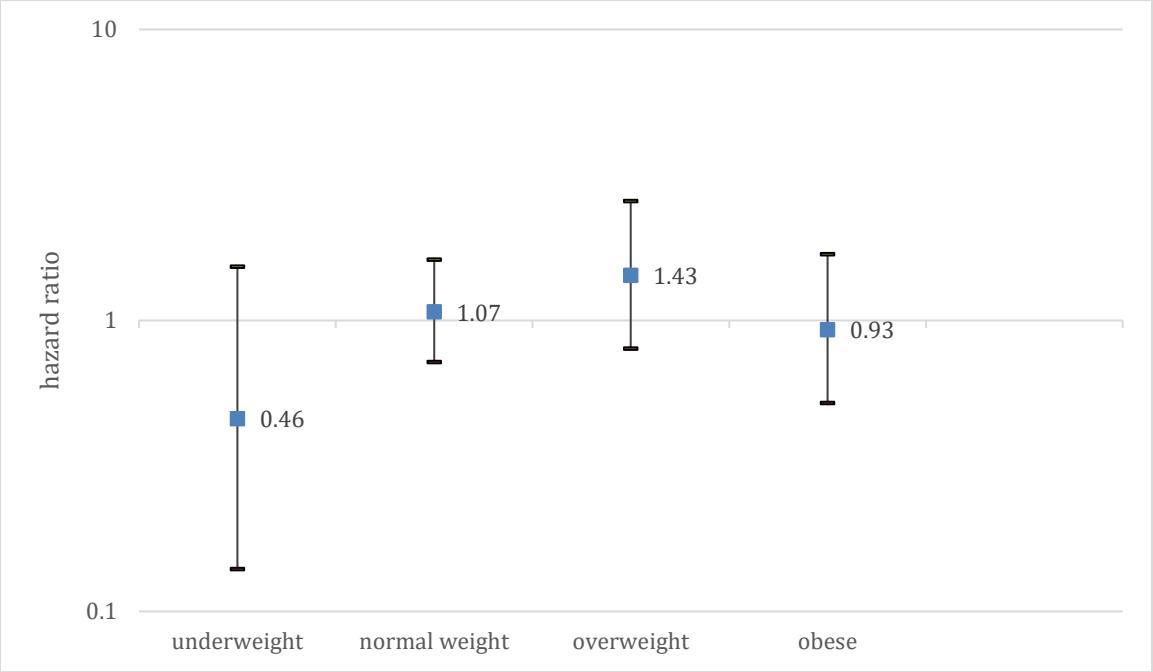


Figure 4: Adjusted Hazard Ratios of Black-White Differences in Breast Cancer Mortality by BMI Category



Model adjusts for age and stage;
p-value for interaction between race and BMI category=0.208

3.7 References

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Chapter 4 Hospital Context and Breast Cancer Mortality in a Managed Care Organization

4.1 Introduction

Breast cancer remains the most common type of cancer among women in the United States with 287,850 incident cases expected in 2022 and is the second leading cause of cancer death, despite a 42% mortality decline from 1989 to 2019.[1,2] Although the overall incidence of breast cancer among Black women remains lower than White women in the United States, significant disparities exist. Black women have a 41% higher breast cancer mortality rate compared to White women and the highest breast cancer mortality compared to all other racial/ethnic groups.[1] This racial disparity has persisted for the past 50 years.[3-7] While the exact causes of breast cancer and its disparities remain unknown, extensive research has documented a higher incidence among those with a family history or inherited genetic susceptibility, and reproductive and hormonal factors including delayed or not having children. In addition, modifiable factors that increase the risk of developing breast cancer include unhealthy dietary and sedentary lifestyles, hormone replacement therapy, and other factors.[7-9] Other research suggests that late stage at diagnosis, treatment delays, histologically aggressive tumors, comorbidity, and socially derived factors are major contributors to mortality.[7-10] However, less research has focused on how hospital context and quality may affect breast cancer outcomes in the United States.

Hospital factors may be important contextual drivers of breast cancer mortality. In recent years there has been increased research on the type and quality of care patients receive to improve cancer survivorship.[11-14] Improvements in the standardization of breast cancer treatment guidelines and the review and accreditation of breast cancer treatment centers have led to the improvement in breast cancer survival outcomes within hospitals. The number or volume of breast cancer treatments performed at a hospital may also improve survival and quality of life for women with breast cancer. In a systematic review of hospital volume and outcomes across a range of procedures and outcomes, Halm et al. reported that more than 70% of the studies included found statistically significant associations between hospital volume and better health outcomes.[15] They hypothesized that this association may be due to physicians and hospitals developing more effective skills and processes at higher-volume hospitals.[15] Despite these hypothesized pathways linking hospital factors and cancer outcomes in breast cancer outcomes, few studies have examined these factors.[16,17]

Limited research has shown that hospital size and volume are associated with breast cancer mortality. In a study of 53,192 records from the New York State hospital discharge records, Roohan et al. found that survival from breast cancer increased as hospital surgical volume increased.[18] In comparing 4 levels of hospital surgical volume, they also reported a 60% increase in 5-year mortality when comparing the lowest to highest volume hospitals in the study.[18] Another study by Stoltzfus et al. found that breast cancer patients treated at hospitals

with higher surgical volume consistently had a 20% increase in 5-year breast cancer survival compared to low surgical volume hospitals.[19] However, these studies are limited by heterogeneity in the measurement of hospital volume, with some studies assessing surgical volume and others using a crude proxy for surgical volume (e.g. the number of surgeons within the hospital).[15] There is also heterogeneity in the threshold used to establish low surgical volume which may be best informed by existing guidelines such as the American College of Surgeons Commission on Cancer.[13] Moreover, there is a need to investigate these associations within a managed care organization, which despite the use of protocols on standards of care, there may be important variability in quality and delivery of care.[20]

The neighborhood environment of the hospital may be another important indicator of hospital quality of care. A robust body of literature has shown that neighborhood environments are associated with cancer survivorship and outcomes.[21-23] Specifically, research has shown that poor neighborhood socioeconomic environments increase the risk of breast cancer recurrence and mortality.[22] However, there have been no studies to examine whether the area surrounding the hospital may confer a risk of adverse cancer-related outcomes. For example, hospital area-level poverty may be a proxy for hospital quality. A study by Nguyen et al. found that hospitals in low-income communities were more likely to have fewer physicians, especially specialty physicians.[24] Thus, there is a need to investigate whether hospital area-level poverty increases the risk of breast cancer mortality and other adverse outcomes.

To address these gaps in knowledge, we examined whether hospital factors (volume and hospital area-level poverty) are associated with breast cancer-specific and all-cause mortality. Additionally, we examined whether associations between hospital factors and mortality are modified by race/ethnicity. Racially marginalized groups often experience lower quality care as a function of larger forces such as structural racism.[25] As a result, they may be more sensitive to poor hospital environments and quality. We hypothesized that low hospital surgical volume and high area poverty level would be associated with breast cancer mortality and that the impact of these factors on mortality outcomes, would be most pronounced among Black individuals.

4.2 Methods

Data Sources. Data were obtained from a hospital subset of the historical Kaiser Permanente Northern California Medical Care Program (KPMCP) Co-morbidity Study cohort.[26] The purpose of the KPMCP Co-morbidity study was to examine whether Black patients seen at Kaiser Hospitals had a higher prevalence of concurrent health conditions (co-morbidities than White patients, which may contribute to their risk of breast cancer death. White and Black women with histologically confirmed invasive breast cancer were eligible for inclusion in the original study. All cases were diagnosed between January 1, 1973, and December 31, 1986, and were enrolled members of the KPMCP of Northern California at the time of diagnosis. Patient data were abstracted by medical record review at KPMCP Northern California, linked to the Northern California Cancer Center (NCCC), Surveillance, Epidemiology and End Results (SEER) Program data, and vital status records updated in October 2002.

Hospital discharge data from the California Department of Health Care Access and Information, HCAI (formerly known as the California Office of Statewide Health Planning and Development) was used to collect the number of breast cancer surgeries performed for each of the Kaiser Northern California hospitals including those in the original KPMCP study.

This work was approved by the human subject review boards of the NCCC[27] and the University of California Berkeley (OPHS # 2003-8-43 before data access was granted.

Study Population. Case selection for this historical cohort was based on the original KPMCP criteria: 1) non-Hispanic Black or non-Hispanic White race; 2) diagnosed with histologically confirmed invasive breast cancer between January 1, 1978, and December 31, 1985; 3) diagnosed at one of the seven KPMCP Hospitals in Northern California; 4) resident of either Alameda, Contra Costa, Marin, San Francisco, or San Mateo Counties at diagnosis; 5) and alive at the time of diagnosis. A total of 1258 breast cancer cases, 417 Black and 841 White women, met the specified eligibility criteria.

Exclusion Criteria. Thirty-seven patients were excluded based on the criteria of this study. Seven patients were removed for missing vital status data, two patients were missing the cause of death, and two patients were recorded as in situ cancer instead of invasive breast cancer. The remaining 26 of the 37 cases were missing the site of treatment/surgical hospital leaving a final study sample of 1221 women, 398 Black and 823 White (Figure 1). There were no significant differences in age, stage, or percent of Black and White women between the full sample and the sample used for this study.

Study Variables

Outcome Measures. Breast cancer-specific mortality and all-cause mortality were the outcome measures for the study. California vital records data were used to collect information on the vital status of patients in the study. Death information, including the cause of death, was abstracted and matched to the patient records. Deaths were categorized as breast cancer (International Classification of Diseases codes ICD-9-174-175, ICD10-C50) and non-breast cancer deaths. Breast cancer deaths are considered any deaths where breast cancer was recorded as the primary or underlying cause of death. Overall mortality was considered death from any cause during the follow-up period. Patients in the historical cohort were followed from the time of diagnosis to the final vital status update in October 2002 for an average of 13 years of follow-up.

Demographic and Clinical Variables. Race and age were abstracted from the KPMCP medical records. Self-identified race (Black, White) was abstracted from the KPMCP medical records of each patient. Women of other races were not included in the study as the purpose of the original KPMCP study was to investigate disparities in breast cancer mortality between Black and White women. Age at the time of diagnosis was calculated using the patient's date of birth. Tumor stage at diagnosis was abstracted from the original medical records and was classified as local, regional, or remote. Due to the small sample size, we collapsed the tumor stage categories to local or regional/remote. Body Mass Index (BMI) was calculated using the

patient's height at the time of diagnosis, recorded in feet and inches, and the patient's weight at diagnosis recorded in pounds and categorized based on the World Health Organization cut points for weight categories. [28]

Hospital Characteristics. The total number of breast cancer surgeries, according to ICD-9 procedure codes, performed at each KPMCP hospital from 1983 to 1986 was used to calculate hospital surgical volume. Surgical records were obtained from the HCAI hospital discharge data and surgical volume was calculated using the number of breast cancer surgeries performed at each hospital. This method for calculating volume was based on the *OSHPD Technical Note for Calculating Volume of Cancer Surgeries in California Hospitals*.[29] Hospitals were categorized as high volume if an average of 40 or more breast cancer surgeries were performed per year and low volume if 39 or less were performed per year based on prior research. [30,31]

Zip code-based income data for each KPMCP hospital was used as a proxy for hospital area poverty levels and calculated based on the 1990 US Census five-year income estimates. [32] Although zip codes are large geographical areas, research has shown that they remain useful for detecting health outcome differences. [22,33,34] In a study comparing the use of zip code, census tract, and block group, Berkowitz et al. found zip code data provided comparable area-based socioeconomic estimates to the more granular indicators, census tract, and block group. [34] Zipcode poverty thresholds were based on previous research [35] and calculated based on the percentage of households with income below the federal poverty level. Low area poverty was considered 0-12% of households with income below the federal poverty level and high area poverty was considered 13% or more households with income below the federal poverty level.[35]

Statistical Analysis

Our primary analysis examined associations between the hospital volume and hospital area poverty level and the mortality outcomes. Descriptive analyses were performed to calculate the means, proportions, and univariate distributions of study variables by breast cancer-specific and all-cause mortality. Bivariate associations between the study covariates and hospital characteristics were performed using the Chi-squared test. Kaplan Meier survival curves and the log-rank test were used to compare the age-adjusted survival times for overall mortality and breast cancer-specific mortality by hospital volume category and hospital area poverty level.

Multivariable Cox proportional hazard regression models were used to estimate hazard ratios and 95% confidence intervals for the association between hospital exposures (hospital surgical volume and area-level poverty) and mortality outcomes (breast cancer, all-cause) before and after adjustment for confounders. Covariates in the models included age, race, stage at diagnosis, and BMI. Cross product terms between race and hospital factors were created to determine if associations between hospital factors and mortality outcomes were modified by race. Interaction terms were considered statistically significant if $p<0.05$. All models were examined to verify model assumptions and there were no violations of proportional hazards. All statistical analyses were performed using STATA version 12.0 software. [36]

4.3 Results

One thousand two hundred twenty-one women diagnosed with primary invasive breast cancer met the inclusion criteria of the study. The mean age was 56 years of age (SD=13.3), 67% White and 33% Black. Over an average of 13 years of follow-up (186,888 months of person-time), of the study population who died, 62% died from all causes and 31 % died from breast cancer (Table 1).

Breast cancer mortality varied by age, BMI, and stage at diagnosis. Breast cancer mortality was highest among women who were 65 and older, obese, or had a regional/remote stage tumor at diagnosis (Table 1). Total mortality varied by age, BMI, stage at diagnosis, and hospital area poverty level and was highest among women who were 65 and older, obese, or had a regional/remote stage tumor at diagnosis. Breast cancer and all-cause mortality varied across the 8 hospitals in KPNC. (Figure 2). Breast cancer-specific mortality was highest at the Martinez site and lowest at the Walnut Creek site. Figure 2 also illustrates some variation in all-cause mortality by hospital. However, all-cause mortality was highest at the San Rafael site and lowest at the Walnut Creek site. Of the 8 hospitals included, there were 3 low surgical volume and 5 high surgical volume hospitals. There were no significant differences in the characteristics of patients who received care at high versus low surgical volume hospitals for, stage, and BMI. However, White women were more likely to receive care in hospitals with low surgical volume as they made up 67.4% of the population but 85.1% of the patients in low volume hospitals.

Hospital area-level poverty also varied by race. Black women made up 32.6% of patients in the sample but 55.1% of patients of hospitals located in high poverty areas. However, there were no significant differences in breast cancer survival by area-level poverty. (Table 2)

In Cox proportional hazard models (Table 3), adjusted for confounders, patients from hospitals with low surgical volume had an 8% higher rate of breast cancer mortality and a 1% higher rate of all-cause mortality, although estimates lacked precision (HR 1.08 95% CI 0.82-1.43 for breast cancer mortality; HR 1.01 95% CI 0.83-1.23 for all-cause mortality). Similarly, in adjusted models women from hospitals with high area-level poverty, had a 2% higher rate of breast cancer-specific mortality, and a 5% higher rate of all-cause mortality (HR 1.02 95% CI0.79-1.33 for breast cancer-specific mortality; HR 1.05 95% CI 0.88-1.26) but estimates included the null hypothesis value of 1 (Table 4). There was no evidence of effect modification by race for either hospital surgical volume or areal-level poverty, independent of confounders (all p-values>0.20).

4.4 Discussion

We evaluated the association between hospital factors and mortality outcomes in a retrospective cohort of 1221 women diagnosed and treated for invasive breast cancer across hospitals in the Kaiser Permanente Northern California Medical system. We found no indication that low breast cancer surgical volume or high hospital area- level poverty were associated with an increased risk of breast cancer-specific or overall mortality among women treated.

In previous studies of the association between hospital volume, higher surgical volume hospitals were associated with better breast cancer patient outcomes and lower mortality rates. [15,18,19,37,38] However, these studies used large cohorts of breast cancer patients that included patients cared for at non-health maintenance organization hospitals. Greenup et al. demonstrated that low breast cancer surgical volume was associated with an 11% lower breast cancer survival rate overall, and this increased to 20% in Black patients regardless of hospital volume, suggesting the association was modified by race.[37]

The results of this study are consistent with those of Greenup et al. in that there were no significant interactions between hospital volume and race/ethnicity.[37] Although our results showed more variability in deaths across hospitals based on Kaplan Meier curves with breast cancer mortality rates ranging from 4.2% to 34.3%, our results were not statistically significant. These results may be due to the use of historical data, limited variability due to having a standard of care "template" used regardless of location in the Kaiser Permanente hospitals studied because experienced Kaiser doctors may work in low volume hospitals. Clarke et al. found that in California, approximately 60% of surgeries are performed in top-quintile volume hospitals. [29] Seventy-two percent of Californians who received surgeries in low-volume hospitals lived within 50 miles of a top-quintile volume hospital. [29] As such, hospital volume may not be a good proxy for hospital quality in the state of California. Future studies should investigate other, more direct indicators of quality such as time to treatment and adherence to national treatment guidelines. [12,39]

We were also one of the first studies to examine hospital area-level poverty and mortality outcomes, but we did not find any associations. While there are no studies that have examined hospital area poverty, breast cancer, and total mortality using historical data, there is emerging research on hospital-level effects and cancer outcomes. We considered hospital area-level poverty as a proxy for overall hospital quality Lawson and colleagues investigated the association of hospital-level quality indicators including location, teaching status, and volume on prostate cancer outcomes in 1245 hospitals.[16] Results of this study show that the quality of prostate cancer care varied by all three hospital-level indicators after controlling for patient characteristics with non-teaching, low volume, and western hospitals performing the worst.[16] Future research should consider larger data sets with the use of census tracts or more granular geographic areas. Moreover, continued research on more direct measures of hospital quality will help provide a more nuanced understanding of how hospital quality affects breast cancer outcomes.

This study has several limitations. The use of historical data limited our ability to extrapolate findings to current day patterns of hospital quality and links with cancer-related outcomes, which may have changed over time. Moreover, this historical data came from a managed-care organization which limits the generalizability of our study findings. We used hospital breast cancer surgical volume as a proxy for hospital quality.[19,37] However, other quality indicators or indices, may provide a more accurate measure of hospital quality. [29] Breast cancer surgeries are more likely to be performed at high volume hospitals compared to esophageal, pancreatic,

stomach, liver, and bladder cancer procedures. As such, it may be important to examine whether low-volume hospitals that perform more of these procedures have access to multidisciplinary teams, which may point to increased numbers of experienced doctors who work in low-volume hospitals.[29] Gort and colleagues found that access to multidisciplinary teams was the most robust predictor of increased breast cancer survival. [14] Additionally, the lack of standardization around what represents a "low" versus "high" breast cancer volume in assessing mortality creates challenges in the interpretation of findings. [15,18,30,37,40] Since this study was restricted to Kaiser hospitals that have a "template" of care, other factors such as non-health maintenance organization hospital status should be examined in future studies. It is possible that high risk and medically complex patients are referred to higher volume specialty centers, which can correlate hospital volume with low mortality.[38] Future studies should examine whether Black patients who are high risk and have medically complex conditions are referred to higher volume specialty centers at the same rate as White patients to disentangle this correlation. [41 42] It is also important to define hospital volume groups based on their relationship to survival rather than arbitrary cut-points. [37]

We also used zip-code level poverty concentration of diagnosis facility as a proxy for hospital quality which may not be the most salient for mortality outcomes. There is no consensus as to whether the location of hospitals in low-income areas translates to poorer quality care received at these hospitals.[34] However, teaching hospitals are often located in low-income communities and there is a body of research evidence that supports better cancer outcomes in teaching hospitals compared to non-teaching hospitals. [24,43-46] This and similar findings may indicate that the geographic location is less important than the training and adherence to the most current cancer treatment protocols.[13]

Finally, there are a series of methodological limitations to our study. Given the low number of hospital factors, we were unable to account for within-hospital correlation between patients and this small number limited our statistical power to detect associations, especially for tests of effect modification by race. We also cannot rule out residual confounding due to the unavailability of key variables that are potential confounders such as breast cancer treatment, or due to measurement error of the variables included in analyses.

4.5 Conclusion

In conclusion, we did not find evidence that breast cancer survivorship is associated with hospital quality and area-level deprivation, in this health maintenance hospital setting. However, more robust hospital quality indicators, a wider sample of hospitals, and an updated breast cancer cohort with complete individual-level data may provide a more complete assessment of the role of hospital context in mortality disparities between Black and White women with breast cancer.

4.6 Tables and Figures

Tables

Table 1: Distribution of Selected Characteristics at Diagnosis of Patients with Breast Cancer by Race

	Overall		Breast Cancer Mortality		All-Cause Mortality	
	(N=1,221)		Yes (N= 379)	No (N=842)	Yes=756	No=465
	N	%	(%)	(%)	(%)	%
Race						
White participants	823	67.4	61.7	69.9	65.6	70.3
Black participants	398	32.6	38.3	30.1	34.4	29.7
Age at diagnosis, years						
<45	284	23.3	25.9	22.1	17.0	33.6
45-54	254	20.8	24.3	19.3	18.9	23.9
55-64	351	28.7	28.7	28.7	26.8	31.8
65 and older	332	27.2	21.1	29.9	37.3	10.7
Stage						
Local	677	55.5	32.7	65.7	47.2	68.8
Regional/Remote	493	40.4	63.3	30.1	48.2	27.5
missing	51	4.2	4.0	4.3	4.6	3.7
BMI (kg/m^2)						
<20	69	5.7	5.3	5.8	5.4	6.0
20-24.9	453	37.0	32.2	39.3	32.9	43.9
25-29.9	313	25.6	22.9	26.8	25.6	25.6
≥30	219	18.0	21.9	16.2	20.2	14.2
missing	167	13.7	17.7	11.9	15.7	10.3
Breast Cancer Surgical Volume						
High (≥40)	973	79.7	79.4	79.8	80.8	77.85
Low (<40)	248	20.3	20.6	20.2	19.2	22.15
Hospital Area-Level Level						
High	619	50.7	53.0	50.4	53.3	46.5
Low	602	49.3	47.0	49.6	46.7	53.5

Table 2: Study variables by Hospital Volume and Hospital Area-level poverty

	Overall	Breast Cancer Surgical Volume		Hospital Area Poverty Level	
	(N=1,221)	High (N=973)	Low (N=248)	High (N=619)	Low (N=602)
	N	**%**	**%**	**%**	**%**
Race					
White participants	823	63.0	85.1	44.9	90.5
Black participants	398	37.0	14.9	55.1	9.5
Age at diagnosis, years					
<45	284	23.5	22.2	25.4	21.1
45-54	254	20.0	24.2	18.6	23.1
55-64	351	28.5	29.4	27.8	29.7
≥65	332	28.0	24.2	28.2	26.1
Stage					
Local	677	55.6	54.8	52.7	58.3
Regional/Remote	493	40.4	40.3	42.5	38.2
missing	51	4.0	4.8	48.8	3.5
BMI (kg/m^2)					
<20	69	5.6	6.1	5.7	5.7
20-24.9	453	36.9	37.9	35.5	38.7
25-29.9	313	24.9	28.2	27.0	24.2
≥30	219	17.9	18.1	20.2	15.6
missing	167	14.7	9.7	11.6	15.8

Table 3: Cox-proportional hazards for hospital volume and breast cancer specific and all-cause mortality

N=1,221	Breast Cancer Mortality				All-Cause Mortality			
	Model 1		Model 2		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% C.I.
Hospital Volume								
High	ref		ref		ref		ref	
Low	0.99	0.77 to 1.29	1.08	0.82 to 1.43	0.93	0.77 to 1.11	1.01	0.83 to 1.23
Age at diagnosis								
<45	0.96	0.72 to1.27	0.86	0.62 to 1.18	0.78	0.61 to 0.99	0.69	0.53 to 0.90
45-54	ref		ref		ref		ref	
55-64	0.83	0.63 to 1.10	0.84	0.62 to 1.14	1.03	0.84 to 1.29	1.00	0.79 to 1.27
65+	0.76	0.56 to 1.02	0.85	0.61 to1.19	2.05	1.67 to 2.52	2.26	1.81 to 2.83
Race								
White participants			ref				ref	
Black participants			1.13	0.88 to 1.44			1.13	0.95 to 1.34
Stage								
local			ref				ref	
Regional/Remote			3.58	2.81 to 4.56			2.27	1.93 to 2.67
missing			2.18	1.16 to 4.08			1.59	1.06 to 2.39
BMI (kg/m^2)								
<20			1.42	0.88 to 2.30			1.52	1.09 to 2.13
20-24.9			ref				ref	
25-29.9			1.09	0.83 to 1.44			1.15	0.95 to 1.39
≥30			1.47	1.09 to 1.97			1.32	1.07 to 1.63

Model 1: age-adjusted; Model 2: adjusted for age, race, stage, BMI;

ref= Reference category

Table 4: Cox-proportional hazards for hospital area poverty level and breast cancer and all-cause mortality

N=1,221	Breast Cancer-Specific Mortality				All-Cause Mortality			
	Model 1		Model 2		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% C.I.
Hospital area-level poverty								
High	1.14	0.93 to 1.40	1.02	0.79 to 1.33	1.15	0.99 to 1.33	1.05	0.88 to 1.26
Low	ref		ref		ref		ref	
Age at diagnosis								
<45	0.94	0.71 to1.26	0.85	0.62 to1.18	0.77	0.61 to 0.98	0.69	0.53 to 0.90
45-54	ref		ref		ref		ref	
55-64	0.83	0.63 to 1.10	0.83	0.61 to 1.13	1.03	0.83 to 1.28	0.99	0.79 to 1.26
65+	0.75	0.55 to 1.02	0.84	0.60 to 1.18	2.04	1.66 to 2.49	2.24	1.79 to 2.80
Race								
White participants			ref				ref	
Black participants			1.09	0.83 to 1.45			1.09	0.90 to 1.33
Stage								
local			ref				ref	
Regional/Remote			3.58	2.81 to 4.56			2.27	1.93 to 2.67
missing			2.18	1.17 to 4.08			1.60	1.06 to 2.40
BMI (kg/m^2)								
<20			1.42	0.88 to 2.30			1.51	1.08 to 2.12
20-24.9			ref				ref	
25-29.9			1.09	0.83 to 1.44			1.15	0.95 to 1.39
≥30			1.48	1.10 to1.98			1.33	1.07 to 1.63

Model 1: age-adjusted; Model 2: adjusted for age, race, stage, BMI

ref= Reference category

Figures

Figure1: Study sample flow chart

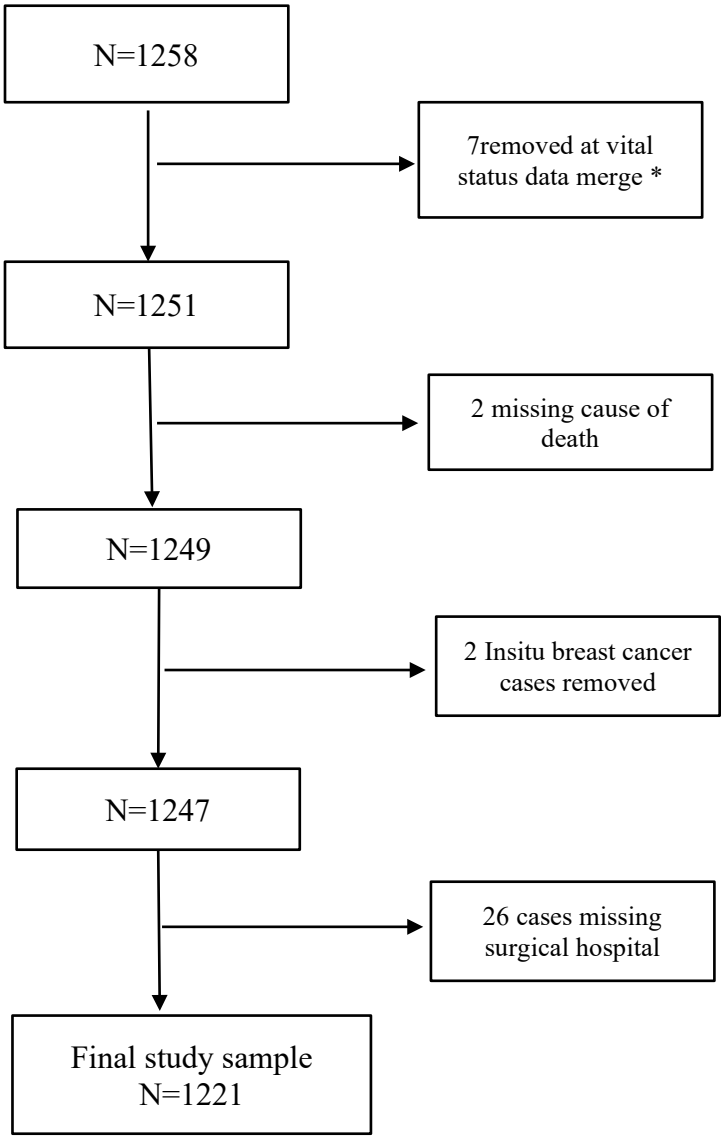
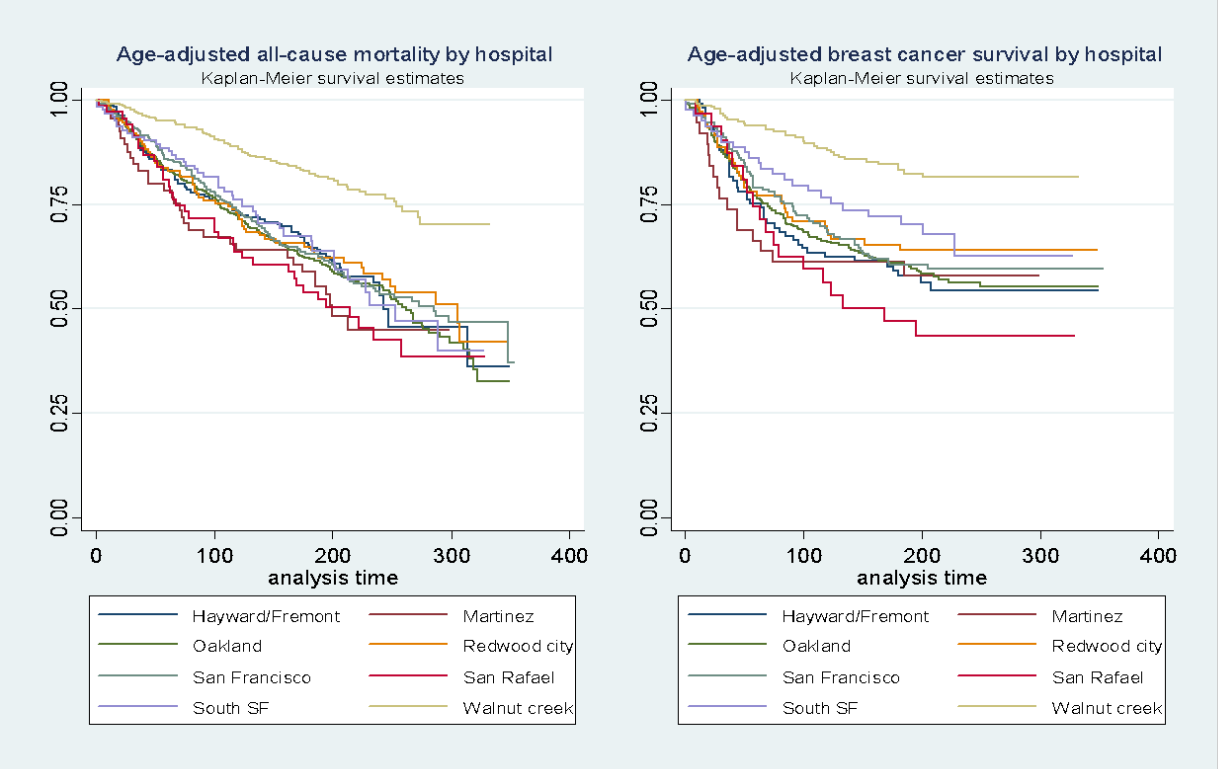


Figure 2: Kaplan Meir Curves of Breast Cancer and All-Cause Mortality by Hospital within KPNC (N=-1221)



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Chapter 5 Conclusion

5.1 Summary

The presence of comorbid conditions such as obesity and related comorbid conditions that are associated with the progression of breast cancer and are also more prevalent among Black women may contribute to adverse breast cancer outcomes. Comorbidity and hospital quality are both risk factors for poor breast cancer outcomes that can be modified to improve breast cancer survival among black women. This dissertation contributes to a body of knowledge that explores the causal and mediating factors of adverse breast cancer outcomes in Black women

In Chapter 2, we conducted a systematic review to determine if breast cancer survival disparities are reduced or no longer significant after adjustment for comorbid conditions. Based on the review of the twelve studies included in the review, we did not find that comorbidity accounted for the disparities in breast cancer survival among Black women. However, the variation in sample populations, measures of confounders, and comorbidity limit the interpretation of these studies. Three of the 12 studies that used a sum total of comorbid conditions did not find an association with an increased risk of breast cancer death but did report an increased risk of death from all causes. The seven studies that used the Charlson Comorbidity index reported comorbidity accounted for a small amount of the survival disparity between Black and White women before the addition of covariates to the model. Two studies investigated the association of specific comorbid conditions to breast cancer outcomes. Of these studies, one reported that hypertension accounts for 20% of the breast cancer survival disparity between Black and White women, and the other reported no significant findings that the presence of diabetes accounts for survival disparities. Future studies of the contributions of comorbidity to breast cancer survival outcomes should focus on specific comorbid conditions or combinations of conditions.

In Chapter 3, we used data on 1038 Black and White women with primary breast cancer from a historical cohort to examine the role of body mass index in explaining the breast cancer-specific mortality disparities between Black and White women. We found some evidence that breast cancer mortality was most pronounced among women in the overweight and obese categories. Cox proportional hazards ratios varied by BMI category for Black and White women. Black women who were overweight had a 54% higher rate of breast cancer mortality compared to overweight White women. The Black-White differences in breast cancer survival were less pronounced among obese women than expected. Moreover, we did not find any evidence that Black-White differences in all-cause mortality were modified by obesity status. However, current literature suggests that body mass index may not be the best measure of adiposity. This limitation and the moderate associations we found suggest that further research should be done using better measures of adiposity to determine the contributions of overweight and obesity to breast cancer mortality disparities. Taken together these findings suggest an opportunity for intervention and to narrow the gap in Black White breast cancer mortality outcomes.

In Chapter 4, we examined the effect of hospital volume and hospital area-level poverty on breast cancer mortality. Using data on 1221 women from the historical Kaiser Permanente Comorbidity Study cohort, surgical volume data from the California Department of Health Care Access and Information, and the US Census, we assessed the association between these hospital characteristics, breast cancer, and all-cause mortality outcomes. We found no association between hospital breast cancer surgical volume or area level deprivation with breast cancer or all-cause mortality outcomes. These results are encouraging in that a template of care like that in a managed care organization setting, may be a solution for quality variation in other hospital settings. However, these results may also be a result of the hospital quality indicators studied. More comprehensive hospital quality indicators may provide a more complete assessment of the role of hospital context and mortality disparities.

5.2 Conclusion and Future Direction

Understanding and addressing the widening gap in breast cancer-specific mortality is important to the health and longevity of Black women with breast cancer. More than 40 years of research has not yielded enough actionable research to significantly narrow the mortality gap. Therefore, breast cancer mortality disparity research should focus on modifiable and preventable risk factors. Comorbidity and specifically obesity are risk factors that can be prevented, or the effects of these factors interrupted to slow or halt the progression of disease and mortality. Hospital quality is another factor that can be improved to ensure a standard of care that is equitable.

Current research on individual risk factors and exposure does not account for the persistent and widening mortality gap. Therefore, future research on adverse breast cancer outcomes among Black women should consider the complex inter-relationship of biological and societal exposures. The societal context in which specific risk factors occur should also be assessed. For example, research to examine the obesogenic environment in which many Black women live or the inclusion of measures of structural and perceived racism may provide more insight into the factors that contribute to mortality disparities. It is our opinion that this broadening field of research will lead to a more complete picture of the factors that contribute to breast cancer mortality disparities among Black women.