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The Impact of Race and Diabetes on Mortality among Breast Cancer Patients

Jibril Alim

ABSTRACT

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By

Jibril Mubarak Ibn Abdu Alim

April 26, 2017

INTRODUCTION: Breast cancer and Type 2 diabetes Mellitus are two chronic conditions that impact the lifespan and quality of life of women. Both diabetes and breast cancer have a disproportionate impact on African-American/Black women and it is reasonable to believe that Biological mechanisms or treatments for this co-morbid condition may have an antagonistic effect and impact the individual's risk of mortality.

AIM: This study aims to address whether pre-existing diabetes occurs at different rates among African-American/Black women with breast cancer than White women, and if diabetes and race are associated with higher all-cause and breast cancer specific mortality among women.

METHODS: The US mortality linked data from the National Health Interview Survey (NHIS) 2006-2009, was used in the analysis. Cox proportional hazard regression was used to model and estimate the adjusted and unadjusted hazard ratios of the identified risk factors on mortality.

RESULTS: Diabetes and pre-existing diabetes (33.20% & 52.24%) were more prevalent among Black women with breast Cancer than Whites (13.87% & 39.82%). African-Americans experienced increased breast cancer specific mortality (HR: 1.564, 1.465-1.669 95%CI) than whites. Diabetes and Pre-diabetes were associated with increased risk of all-cause (HR: 1.60 & 1.329) and breast cancer specific mortality (HR: 1.37 & 1.177). Diabetes and pre-diabetes impacted all-cause mortality among Africans-Americans (HR: 15.757 & 13.658) differentially than Whites (HR: 1.377 & 1.079). Similarly, Diabetes and pre-diabetes impacted breast cancer-specific mortality among African-Americans (HR: 10.891 & 7.696) differentially than whites (HR: 1.125 & 0.850)

DISCUSSION: Diabetes and breast cancer was a more common comorbidity among Black women than Whites. Diabetes was associated with increased risk of all cause and breast cancer specific death. Race was found to have a significantly increase breast cancer specific mortality among diabetic individuals. Increased diabetes prevalence among Blacks may partially explain their higher breast cancer mortality rates.

The Impact of Race and Diabetes on Mortality among Breast Cancer Patients

by

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B.S., The Ohio State University

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APPROVAL PAGE

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Author’s Statement Page

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Chapter I

Introduction

Both breast cancer and type 2 diabetes mellitus (T2DM) are growing health concerns for aging women in the United States. Breast cancer is the second most common cancer among women with about 12.4% of women developing breast cancer during their lifetime (SEER, 2013). Breast cancer is the second leading cause of cancer death among women in the US with over 40,860 deaths each year (CDC, 2013). The risk of being diagnosed with breast cancer increases with age and the average age of diagnosis in the United States is 61 (CDC).

Per current data released by the CDC, 5.9% of adult women in the US had diabetes in 2014, this rate has more than doubled since 1980 when the rate for women was 2.9%. The risk of having diabetes increases with age; in 2014 the rate in the 0-44 age group was 1.5%, 12%in the 45-64 age group, 21.5% in the 65-74 age group, and 19.2% in the 75+ age group. The median age of diabetes diagnosis for women is 55.2 (CDC, 2011).

A growing trend in the United States is that of patients with multiple coexisting diseases termed comorbidities. According to the CDC, one in four Americans has multiple chronic conditions (DHHS 2014), and three in four Americans over the age of 65 have multiple chronic conditions (AHRQ 2014). Based on Medicare claims data, 42% of patients with breast cancer had one or more comorbidities at the time of diagnosis (Wu, et al., 2015). Comorbidities are associated with complex clinical management, increased health care costs, and poorer health outcomes including mortality and low quality of life. Comorbid conditions may make the diagnosis of another disease more difficult by obscuring, preventing, or delaying proper screening. The biological mechanisms for the coexisting conditions may interact to worsen the individual's health. The treatment for one disease also may have an antagonistic effect on a coexisting disease. These potential effects combine to impact the individual's risk for mortality.

Both diabetes and breast cancer have a disproportionate effect on black women in comparison to other ethnicities. Cancer is the second leading cause of death among African-Americans, accounting for 22.6% of deaths of all African-American women (CDC, 2013). Black women in the US suffer from higher breast cancer mortality rates than any other ethnicity and because of the high prevalence of diabetes within African-American women, it is reasonable to consider that this co-morbid condition may influence clinical outcomes. Furthermore, for a variety of socioeconomic, behavioral, and biological reasons, the comorbid condition of simultaneous diabetes and breast cancer may have different effects on clinical outcomes across racial ethnic groups.

To improve prevention and clinical management it is critical that researchers understand how multiple conditions may interact to affect the health of the patient and how this interaction may vary by demographic group.

Background

Diabetes

Type 2 diabetes mellitus, is a chronic disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine (ADA). Type 2 diabetes mellitus is caused by a combination of resistance to insulin action and an inadequate insulin secretory response (ADA).

The chronic hyperglycemia of diabetes can cause severe long-term damage, dysfunction, and failure of various organs; the eyes, kidneys, nerves, heart, and blood vessels. These complications include retinopathy with loss of vision, nephropathy leading to kidney failure, peripheral neuropathy leading to amputations in extremities, most commonly the foot, and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms (ADA). Diabetes is the seventh leading cause of death in the United states. Type 2 diabetes which was previously called non-insulin dependent diabetes mellitus, type II diabetes, or adult onset diabetes, is estimated to account for about 90% to 95% of all diagnosed cases of diabetes. Type 2 diabetes often goes undiagnosed for many years because hyperglycemia progresses gradually and at early stages is asymptomatic. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity.

Type 2 diabetes is often associated with a strong genetic predisposition however the genetics are complex and not clearly understood. Known risk factors that increase the likelihood of developing diabetes include being overweight or obese, family history of diabetes, genetic predisposition linked to race/ethnicity, prior history of gestational diabetes, hypertension, abnormal cholesterol levels, and being physically inactive (CDC 2015).

Among females, African-American women have notably high rates of diabetes with a prevalence of 9.9%. This is followed by women of Hispanic origin whose rates range from 8.1% to 9.6%. Black women are diagnosed at a younger age with diabetes than all other ethnicities at a median age of 49, compared to 55.4 for white women.

Breast Cancer

Breast cancer is a disease in which the cells in breast tissue grow out of control. Breast cancer is conceptually referred to as a single disease however it is distinguished by 21 distinct histological subtypes and 4 molecular subtypes that differ in presentation, response to treatment, and outcomes. Breast cancer is characterized both by the origin of the cancerous cells and the spread of the cells, termed in situ or invasive. There are three main tissues of breasts; the lobules, ducts, and connective tissue. The Most cancers begin in the ducts or lobules. Malingnancies termed as "in-situ" are carcinoma where the cancerous cells do not grow beyond the layer of cells in which they originated, whereas invasive carcinoma have spread into other tissues within the breast. The most common kinds of breast cancer are invasive ductal carcinoma where cancer cells grow outside the ducts into other parts of the breast tissue, and invasive lobular carcinoma where cancer cells spread from the lobules to nearby breast tissues.

An additional method of classification of breast cancers is the cancer cells' susceptibility to hormone treatment. In triple-negative breast cancer, breast cancer cells don't have estrogen or progesterone receptors and don't have significant levels of the HER2 protein. This results in a breast cancer subtype that is extremely resistant to treatment. Triple-negative breast cancer also grows and spreads faster than most other types of breast cancer.

Risk factors for breast cancer include getting older, genetic mutations, early menstrual period, late or no pregnancy, starting menopause after age 55, not being physically active, being overweight or obese after menopause, having dense breasts, using combination hormone therapy, taking oral contraceptives, personal or family history of breast cancer, previous treatment using radiation therapy, and drinking alcohol.

Black women have a breast cancer incidence rate of 124 per 100,000 which is slightly lower than that incidence rate of white women (128.1), but is higher than other minorities such as Hispanics, Asians/Pacific Islanders, and American Indians/Alaskan Natives. However, the death rate for black women with breast cancer at 31.0 per 100,000 is higher than the death rate for white women (21.9 per 100,000) and other ethnicities, 15.0 for AI/AN, 14.5 for Hispanic, and 11.4 for Asian/Pacific Islander (CDC 2015). The prevalence of more aggressive cancer subtypes such as triple negative breast cancers are more common among African-American women than other ethnicities, and nearly twice as common than in white women. The high prevalence of these aggressive sub-types contributes to mortality disparities.

Diabetes and Breast Cancer interaction

The current literature has reported mixed findings on the significance of diabetes on risk of breast cancer specific and all-cause mortality. Racial differences in the diabetes-breast cancer interaction have not been thoroughly explored. There have been few studies that have analyzed racial differences in the relationship between diabetes and breast cancer mortality; one focusing on the comparison of Hispanic women with non-Hispanic white women and one on African-American women.

Investigating the link between diabetes and mortality in breast cancer patients can elucidate whether the higher mortality observed in diabetic breast cancer patients is due to poor prognosis specific to breast cancer or due to competing risk. Investigating racial differences in the effect of pre-existing diabetes on all cause and breast cancer specific mortality may help explain disparities in breast cancer mortality. Additionally, findings from this study may help guide policy for prevention efforts and clinical management guidelines for women exhibiting this co-morbidity. Currently there are no clinical guidelines that focus on treating patients with cancer and other co-occurring diseases. Understanding the associations between diabetes and cancer mortality can contribute toward improving cancer screening and assessment practices.

Research Questions and Hypotheses

Using data from the National Health Interview Survey (NHIS), this study will address the following research questions:

1) Does diabetes and pre-existing diabetes occur at different rates among African-American women with breast cancer than White women in the US?

   H_a: African-American women have significantly higher prevalence of diabetes and pre-existing diabetes than white women.

2) Among women with both breast cancer and diabetes, Is diabetes and preexisting diabetes associated with higher all-cause mortality rates among African-American women with breast cancer than other ethnicities?

   H_a: African-American women with diabetes have higher all-cause mortality than white women.

3) Among women with both breast cancer and diabetes, Is diabetes and pre-existing diabetes associated with higher breast cancer specific mortality rates among African-American women with breast cancer than other ethnicities?

   H_a: African-American women who have breast cancer and diabetes have significantly different breast cancer specific mortality rates than white women.

4) Among women with both breast cancer and diabetes, is race associated with increased all-cause mortality?

   H_a: The racial classification of African-American/Black is associated with increased all-cause mortality.

5) Among women with both breast cancer and diabetes, is race associated with increased breast cancer specific mortality?

   H_a: The racial classification of African-American/Black is associated with increased breast cancer specific mortality.

6) Does the impact of diabetes and pre-existing diabetes on all-cause mortality differ among African-American and White breast cancer patients?

   H_a: Diabetes and pre-diabetes are associated with higher all-cause mortality among African-American women than White women.

7) Does the impact of diabetes and pre-existing diabetes on breast cancer specific mortality differ among African-American and White breast cancer patients?

   H_a: Diabetes and pre-diabetes are associated with higher breast cancer specific mortality among African-American women than White women.

Chapter II

Review of the Literature

Black women and breast cancer

Black women have 40% higher breast cancer mortality rates than white women. The disparity in breast cancer mortality between black women and white women has grown since 1979 when the mortality rate ratio between the groups was 1.39, compared to more recent mortality rate ratio estimates in 2010 of 2.00 (McCarthy, Yang, & Armstrong, 2015). Age is a well-established risk factor for the development of all cancers, however cancer has been shown to generally develop earlier in some racial/ethnic groups. The average age of breast cancer diagnosis for African American women is 57 compared to an average of 62 for white women (Newman, 2015). The impact of age is even more evident when cancer incidence and mortality is analyzed at the age-group level. Young black women in the 20-49 age group have higher breast cancer incidence rates than white women. Additionally, a study using data from the National Center for Health Statistics reported that among women aged 20-49 the breast cancer mortality rate was 2 times greater among black women when compared to white women (McCarthy, et al., 2015).

A study based on the California Breast Cancer Survivorship Consortium (CBCSC) which included 2,060 black women, indicated there are racial/ethnic differences in some sociodemographic and lifestyle characteristics of breast cancer patients. Compared to non-Hispanic white women, African American women with breast cancer were less educated, more likely to be multiparous, younger at age of first birth, and have higher rates of first-degree family history of breast cancer (Wu, et al., 2013). Low neighborhood SES is more common in African American breast cancer patients compared to non-Hispanic white breast cancer patients. Additionally, tumor characteristics that are associated with poor survival such as Cancer stage, grade, ER-/PR status, nodal involvement, and tumor size were found to be worst in African-Americans compared to other racial/ethnic groups (Wu, et al., 2013).

Because few modifiable risk factors have been identified for breast cancer, persistent disparities suggest that there are differences breast cancer biology, prevention, and treatment. When racial disparities in mortality rates were first discovered racial differences in mammography screening were posited as the explanation for higher mortality rates among ethnic groups. However, estimates show that although screening rates for black women were lower in the 1980's and 90's, the gap has shrunk considerably since and currently Black women have comparable or higher screening rates across all age groups (McCarthy, et al., 2015). Studies have shown that breast cancer treatments display similar efficacy/effectiveness across different racial/ethnic groups however, treatment prevalence differs. Breast-conserving surgery rates in black women have been shown to lag behind the utilization rates of similarly staged white women (Shavers & Brown, 2002). Additionally, findings suggest that African-Americans less frequently receive radiation therapy after breast-conserving surgery (Shavers & Brown, 2002). Population based studies have revealed patterns of treatment failure on Ductal Carcinoma In Situ (DCIS) related to racial/ethnic identity. SEER based analyses report a 35%

higher mortality for African-American women compared to white women. As well as an increased risk of invasive and advanced recurrences among African-American women (Newman, 2015).

Evidence suggests that tumor biology may differ based on race/ethnicity. Disparities in mortality between African-American women and white women emerged when tamoxifen became a popular therapy for breast cancer. Tamoxifen has been shown to be very effective in women with hormone receptor positive forms of breast cancer, but ineffective in treating hormone receptor negative breast cancers. Hormone receptor negative breast cancers are more prevalent in black women, specifically, the triple negative breast cancer phenotype accounts for 15% of all breast cancers among white women, and 30% of all breast cancers among African-American women (Newman, 2015). Analysis of the California cancer registry shows that non-Hispanic white women have a higher proportion than African-American women of luminal cancers, being defined as ER-positive and/or PR positive (71.6% vs 53%) (Daly & Olopade, 2015). Similarly, a study using SEER registries found that 17.2% of African-American women had triple-negative breast tumors compared to 8.0% of non-Hispanic white women (Daly & Olopade, 2015). International studies have revealed that women from sub-Saharan African countries have higher rates of triple-negative breast cancer compared to other nations in the world (Newman, 2015).

Black women and diabetes

Diabetes mellitus is among the most common life and health threatening chronic diseases. There are established racial/ethnic disparities associated with inequities in diabetes control and rates of diabetes related complications. Many factors contribute to this including lifestyle and behaviors, biophysiological, psychosocial, sociodemographic, and environmental factors, as well as biogeographic ancestry.

The prevalence of type 2 diabetes among African-American women is double that of white women and approximately 40% greater than that of African-American men (Flegal, et al., 2012). Obesity is the strongest modifiable risk factor for diabetes and is more prevalent among African-American women than other ethnic groups (Zimmet, Alberti, & Shaw, 2001). Black women are less likely to report regular exercise than other racial/ethnic groups.

In addition to prevalence, there are also racial/ethnic disparities in long term complications that result from diabetes. Rates of end-stage kidney disease are 4 times higher among African-Americans compared to those of non-Hispanic whites. Rates of retinopathy are twice as high in African-Americans than in non-Hispanic whites (Osborn, Groot, & Wagner, 2013). This disparity in prevalence of diabetic retinopathy is associated with factors that influence diabetes severity (duration of diabetes, HbA1c levels, and treatment with insulin and oral agents). In a National Health and Nutrition Survey (NHANES) study, ethnic disparities of diabetes control were identified. A larger proportion of non-Hispanic black women with diabetes were treated with insulin alone (39.8%) than both non-Hispanic white women (31.4%) and Mexican-American women (26.6%) indicating more severe diabetes among non-Hispanic black women. This study revealed that non-Hispanic black women with diabetes had substantially higher HbA1c levels ($p<0.01$) than other diabetic groups. Logistic regression modeling fully adjusted for socioeconomic variables indicated that compared to white men, black women were twice as likely to have poor glycemic control (OR 2.01 95% CI 1.13, 3.58) which was the only significant OR identified and the highest point estimate of all groups analyzed (Harris, Eastman, Cowie, Flegal, & Eberhardt, 1999). Poor glycemic control is a risk factor for increased mortality among diabetic patients. The risk of death among people with diabetes mellitus is twice that of people of a similar age without diabetes mellitus (Yunhai, Xiang, Chen, & Jiazeng, 2015).

Pre-existing diabetes and Breast cancer

The interactions between breast cancer and diabetes are very complex. Diabetes may play a role in the development of breast cancer. People with diabetes have an estimated 27% higher risk of breast cancer incidence than non-diabetics (Boyle, et al., 2012). A study performed using longitudinal CMS linked data from the Women's Health Initiative (WHI) found that 10.6% of women diagnosed with invasive breast cancer had pre-existing diabetes (J. Luo, et al., 2015). A prospective cohort study of 8,108 women with invasive breast cancer found that 9% had pre-existing diabetes prior to breast cancer diagnosis (Juhua Luo, et al., 2014). This same study found that breast cancer patients with diabetes were significantly more likely to be older, heavier, less educated and of non-white racial/ethnic groups. Pre-diabetes was associated with an increased risk for the development of breast cancer in post-menopausal women but not premenopausal while diabetes increased the risk for breast cancer in both groups but showed a greater effect on post-menopausal women (adjusted OR 2.41 and 2.85 respectively) (Salinas-Martínez, et al., 2014). Women with diabetes are more likely to have HER2-negative tumors and advanced tumor stage than women without diabetes (J. Luo, et al., 2015). In a study focused on a racial/ethnic group with high rates of diabetes, A case-control study conducted among 646 Mexican women from 2011 to 2013 found that 42.1% of breast cancer patients reported having diabetes, compared to 28.6% of women without breast cancer (Salinas-Martínez, et al., 2014).

Diabetes may adversely affect cancer outcomes by influencing cancer screening, diagnosis, or treatment by patients and physicians. Underuse of breast cancer screening among diabetics, which may delay diagnosis and subsequently lead to more advanced tumors and poorer prognosis is a relevant factor to be considered (Lipscombe, Goodwin, Zinman, McLaughlin, & Hux, 2008). Among breast cancer patients, women with diabetes were more likely to have a longer interval from the last mammogram to breast cancer diagnosis than women without diabetes (J. Luo, et al., 2015). Diabetics may also receive different cancer treatments than non-diabetics which may adversely affect survival. In a SEER based cohort study of 70,781 men and women with breast cancer, diabetics had lower odds of receiving anthracyclines OR: 0.78 (95% CI 0.71, 0.87) and taxanes OR 0.86 (95% CI 0.75, 0.99) than non-diabetics (Srokowski, Fang, Hortobagyi, & Giordano, 2009). Comparisons of the odds of chemotherapy receipt for diabetic breast cancer patients have yielded mixed results in the literature, with some studies indicating lower odds and others indicating no difference (Gold, Makarem, Nicholson, & Parekh, 2014). A study on the WHI cohort shows that breast cancer patients with diabetes are less likely to receive radiation treatment than women without diabetes (J. Luo, et al., 2015). Overall, breast cancer patients with comorbidities are less likely to treated with radiotherapy and axillary node dissection (Lipscombe, et al., 2008). Breast cancer patients with diabetes have been shown to have higher rates of surgical site infection and hospitalization for chemotherapy complications (Gold, et al., 2014). Once receiving chemotherapy, patients with diabetes were more likely to be hospitalized for complications than patients without diabetes. Pre-clinical studies have suggested that the diabetes medication metformin may decrease breast cancer progression and aid in both overall survival (estimated HR: 0.53) as well as breast cancer specific survival (estimated HR: 0.89) (Xu, et al., 2015).

The potential link between diabetes mellitus and cancer development has been hypothesized to be related to hormonal, inflammatory, or metabolic characteristics of poorly controlled diabetes mellitus(Yunhai, et al., 2015). Hyperinsulemia and insulin resistance are two physiological manifestations of type 2 diabetes mellitus. Cancer cells overexpress insulin and the IGF-1 receptors. The Insulin/IGF axis is thought to be a critical interaction in diabetes associated risk and progression of cancer (Yunhai, et al., 2015). Hyperinsulemia could increase the levels of bioactive oestrogens by reducing the circulating sex hormone binding protein in diabetic women. Increased bioactive oestrogen stimulates the proliferation of breast cells and the inhibition of apoptosis to increase cancer risk (Yunhai, et al., 2015).

Hyperglycemia may also increase cancer risk. Indirectly, hyperglycemia induces the production of circulating growth factors and inflammatory cytokines. Hyperglycemia directly increases tumor cell proliferation, inducing mutations, augmenting invasion, and migration. High glucose can enhance Wnt/β-catenin signaling pathway which promotes cancer development and progression (Yunhai, et al., 2015). Uncontrolled diabetes can produce inflammatory conditions in the body. Chronic inflammation can promote genetic instability and is associated with increased cancer risk. Some studies have failed to observe a significant association between blood glucose control as indicated by Hba1c and tumor stage. In a cohort study conducted by Jousheghany et. Al, no significant difference was found in survival between groups of breast cancer patients with HbA1c < 6.5% and HbA1c > 6.5% (Jousheghany, Phelps, Crook, & Hakkak, 2016), however this study's conclusions are limited due to small sample size (n=88).

Diabetes and breast cancer share several risk factors in their development. Obesity is posited to be the primary shared risk factor between diabetes and breast cancer. However, it has been proposed that in obese women, diabetes is so frequent that it does not allow for discrimination of breast cancer risk (Salinas-Martínez, et al., 2014). In fact, in studies linking type 2 diabetes to breast cancer risk, obesity mitigates the magnitude of the association between diabetes and breast cancer(Maskarinec, et al., 2017). Obesity is a well established risk factor for breast cancer in postmenopausal women and is associated with development of diabetes as well. Obesity also is associated with poorer overall survival and increased risk of recurrence in women with breast cancer. A population based cohort study in China found that obesity before diagnosis with breast cancer was associated with a hazard ratio of 1.55 (95% CI 1.10, 2.17) compared to women at normal weight. Similarly, women who gained weight from pre- cancer diagnosis to post- cancer diagnosis had a hazard ratio of 1.71 (95% CI 1.12, 2.60) for total mortality and 1.90 (95% CI 1.23, 2.93) for breast cancer specific mortality (Chen, et al., 2010).

Studies have demonstrated that diabetic breast cancer patients have an increased risk of all-cause mortality. Women with breast cancer who have diabetes have higher mortality (HR: 1.57, 95% CI 1.23, 2.01) than women with breast cancer without diabetes (J. Luo, et al., 2015). This study using the WHI cohort showed that women with diabetes had significantly increased risk of overall mortality after adjusting for demographic and traditional risk factors, factors related to delayed detection, cancer treatments, and tumor markers (J. Luo, et al., 2015). Similarly, this study shows that the distribution of cause of death differed between groups of diabetic and non-diabetic breast cancer patients. In the non-diabetic group 36.7% of the deaths were due to breast cancer, 17.8% were from other cancers, 18.4% from cardiovascular disease, 19.6% from other known causes, and 7.5% from unknown causes. In the diabetic group 26% of deaths were from breast cancer, 12.7% from other cancers, 23.2% from cardiovascular disease, 29.8% from other known causes and 8.3% from unknown causes. However, there was a noted difference in the proportion of deaths noted in each group, 20.3% of non-diabetics and 24.9% of diabetics (Juhua Luo, et al., 2014). This corresponded with an adjusted HR of 1.26 (95% CI 1.06, 1.48) for all-cause mortality comparing diabetics to non-diabetics. In a cohort study of women with breast cancer using population based health databases in Ontario, Canada, diabetes was associated with a significant decrease in survival. 30.9% of breast cancer patients with diabetes died during the study period, compared to 21.9% among women without diabetes. This corresponded with a HR of 1.39 (96% CI 1.22, 1.59).

Additionally, diabetic women may have lower breast cancer survival and greater breast cancer mortality. Few studies have examined the impact of diabetes on breast cancer specific mortality. Results have been inconsistent, and needs to be further investigated to elucidate whether the higher mortality is due to a poorer. WHI study showed insignificantly increased risk for breast cancer-specific mortality among women with diabetes (J. Luo, et al., 2015). In another WHI study an insignificant relationship between diabetes and mortality was observed, with an adjusted HR of 0.74 (95% CI 0.52, 1.02) which interestingly appears to suggest potential for diabetes decreasing the risk for death due to breast cancer (Juhua Luo, et al., 2014). In a population based cohort study in Ontario, Canada no significant interaction between diabetes and survival time was observed (Lipscombe, et al., 2008). These results may be due to the study having limited power to detect a significant association due to small number of breast cancer deaths. In a study using a SEER cohort of men and women with breast cancer, diabetes was found to impact breast cancer specific mortality based on treatment. Diabetic patients who did not receive chemotherapy had similar breast cancer specific mortality, however, diabetic patients who did receive chemotherapy had higher breast cancer specific mortality than non-diabetic patients with an associated OR of 1.20 (95% CI 1.07, 1.35) (Srokowski, et al., 2009).

Breast cancer, diabetes, and black women

Studies have found that breast cancer patients with diabetes are significantly more likely to be of non-white race/ethnicity groups (J. Luo, et al., 2015). In a study based off data from the California Breast Cancer Consortium, 5.5% of breast cancer patients were found to have diabetes, however comparatively 11.5% of all African-American breast cancer patients had diabetes which was the highest among the racial/ethnic groups (Wu, et al., 2015). A case control in the breast cancer health disparities study (BCHDS) consisting of NHW and Hispanic/Native American women aged 25-70 found that diabetes history was significantly associated with increased all-cause mortality risk among Hispanic women (HR 1.64 95% CI 1.08, 2.47) but not for NHW women (HR 1.53 95% CI 0.97, 2.40) (Connor, et al., 2016). Similarly, this same study found that the association between diabetes and breast cancer specific mortality was significant among Hispanic women (HR 1.85 95% CI 1.11, 3.09) but not for NHW (HR 1.33 95% CI 0.67, 2.62) (Connor, et al., 2016).

To date, one study has been conducted on the relationship between diabetes, breast cancer, and black women. The Black Women's Health Study is nationwide a prospective cohort study where 1,621 incident cases of invasive breast cancer from 1995 to 2013. This study found that 14% of black women with breast cancer had diabetes at the time of diagnosis. Women with breast cancer who had T2DM were older than women without T2DM, they were also more likely to be obese. A lower proportion of black women with T2DM underwent radiation therapy. The hazard ratio for black women with T2DM at the time of cancer diagnosis was found to be 1.28 (95% CI 0.88,1.86). However, after categorizing women according to number of years between diagnosis of diabetes and diagnosis of breast cancer, a significant association was found for women who had diabetes for at least 5 years prior to diagnosis of cancer with a HR of 1.86 (95% CI 1.05, 3.20). After adjusting for age and SEER stage, the relationship between T2DM and breast cancer mortality was 1.07 (95% CI 0.76, 1.50) and for T2DM ≥ 5 years was estimated at 1.32 (95% CI 0.91, 1.92). T2DM was significantly associated with al cause mortality with a hazard ratio of 1.54 (95% CI 1.15, 2.07) and for T2DM ≥ 5 years 2.26 (95% CI 1.62, 3.15) (Charlot, et al., 2017).

Chapter III

Methodology

Data Sources

NHIS

The National Health Interview Survey (NHIS) is a cross-sectional household interview survey conducted continuously throughout each year. The NHIS is one of the major data collection programs of the National Center for Health Statistics (NCHS) which is a part of the Center for Disease Control and Prevention (CDC).

The NHIS is one of several continuing studies enacted through the National Survey Act of 1956, and has been conducted continuously since July 1957.

The NHIS questionnaire has Core questions and supplements, which collect basic information on health status, health care services, and health behaviors. The Core contains four major components: Household, Family, Sample Adult, and Sample Child. This study utilized only the Sample Adult core. For the Sample Adult questionnaire, one civilian adult 18 years or older per family is randomly selected to self-report responses to questions.

The sampling plan is a multistage area probability design that permits representative sampling of households and non-institutional group quarters in the US. Examples of persons excluded from this study include patients in long-term care facilities, persons on active duty with the Armed Forces, persons incarcerated in the prison system, and US nationals living in foreign countries.

The years used in the analysis; 2006, 2007, 2008, and 2009 utilized the same sampling plan.

From 1987-2009 NHIS, Participants classified as eligible for mortality follow up had their sampling weight adjusted to account for those ineligible due to insufficient identifying data. This new weight is used to prevent biased mortality estimates. When pooling several survey years of LMF the sample weight should be adjusted by dividing each weight by the number of years being pooled.

NDI Mortality Files

The NCHS has linked various surveys with death certificate records from the national Death Index (NDI). The primary determination of mortality is based upon matching survey records to the NDI, however additional sources of information such as social security administration, the Centers for Medicare and Medicaid Services, and death certificates are used to determine the mortality status of a survey participants. Public use Linked Mortality Files (LMF) are available for 1986-2009 NHIS participants with mortality follow up available until December 31, 2011. The LMF were subjected to data perturbation techniques to reduce the risk of participant re-identification. For selected entries synthetic data were substituted for the actual date and underlying cause of death, however comparative analysis of cause specific mortality across both the altered and unaltered data set showed similar percentages of death attributed to leading causes of death.

Approval

This thesis utilized secondary public use data and did not require Institutional Review Board (IRB) approval. The NHIS is a preapproved data source with exempt status determined by the Georgia State University IRB (Institutional Review Board Policies).

Inclusion and Exclusion Criteria

Between the years of 2006 and 2009 the adult sample consisted of 83,708. Participants with missing responses to the primary questions of this study were excluded from analysis. The subpopulation of interest were white and African-American women with breast cancer, thus the sample was restricted to those who were listed as Female and responded yes to the questions of 1) Have you ever been told by a doctor that you had cancer? 2) What kind of cancer….Breast?. Respondents who answered no to either question were excluded from analysis in this study. The resulting sample size was of 216 adults.

Independent Variables

All of the independent variables were obtained through self-reported survey data from the 2006-2009 NHIS survey. History of diabetes is operationalized by the survey question "Have you ever been told you have diabetes?" and categorized into the answers, Yes, No, and Borderline. For the sample population, this is derived from the question "If female, other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?". Age first diagnosed with diagnosed with diabetes is a continuous variable. Body Mass Index (BMI) was determined from self-report and classified into 4 categories, ≤ 18.5 = underweight, <18.5 BMI ≤ 24.9 = normal weight, 24.9 < BMI ≤ 29.9 =

overweight, and overweight ≥ 30.0. Diabetic medications were assessed through two questions 1) "Are you now taking insulin?" and 2) "Are you now taking diabetic pills to lower your blood sugar? These are sometimes called oral agents or oral hypoglycemic agents.". Age was abstracted from the continuous variable Age_P in the NHIS questionnaire and subsequently classified into 3 categories, 18-34, 35-64, and 65+.

Pre-existing diabetes was derived from the two variables, "Age first diagnosed with breast cancer" and "Age first diagnosed with diabetes". Pre-existing diabetes was classified into two categories, Yes (where age first diagnosed with diabetes < age first diagnosed with breast cancer) and No (where age first diagnosed with diabetes ≥ age first diagnosed with breast cancer). Years of diabetes prior to cancer diagnosis was abstracted from two questions in the NHIS questionnaire; "Age first diagnosed with diabetes" and "Age first diagnosed with breast cancer. Age first diagnosed with diabetes was subtracted from age first diagnosed with breast cancer. The resulting integer was then classified into four categories; where the equation resulted in a negative integer the category was "Developed After", where the equation resulted in a positive integer, the results were classified into < 5 years, 5-10 years, and > 10 years.

Age first diagnosed with cancer is a continuous variable derived from the survey question "How old were you when cancer was first diagnosed?" among respondents who replied yes to having been diagnosed with breast cancer.

Dependent Variables

This study has two dependent variables. The first variable assessed is history of diabetes is operationalized by the survey question "Have you ever been told you have diabetes?" and categorized into the answers, Yes, No, and Borderline. For the sample population, this is derived from the question “If female, other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?”. (I think you defined it earlier, so consider removing the earlier one The second variable assessed is the time until the final mortality status, this is operationalized by the final mortality status obtained from the NDI mortality file. The final variable being assessed is the rate of death due to breast cancer specifically and all-causes in the sample. This is operationalized by the leading cause of death obtained from the NDI mortality file.

Data Analysis

All analyses for this study were conducted using Statistical Analysis Software System 9.4 (SAS 9.4). Analysis accounted for survey design by the incorporation of the mortality adjusted survey weight divided by 4 to account for pooled variance of the 4 years aggregated into the study population.

Descriptive statistics were used to illustrate characteristics that are risk factors for the development of breast cancer and the development of T2DM. Frequency distributions were used to identify the proportion of NHIS respondents from 2006, 2007, 2008, and 2009 who were of each race (African-American and White), who were diagnosed with diabetes and who were diagnosed with breast cancer. Additionally, frequency distributions for years of diabetes prior to cancer diagnosis and leading cause of death among breast cancer patients were reported. Chi-Square tests were conducted on the categorical variables and t-tests were conducted on the continuous variables for differences between the two racial/ethnic groups being analyzed.

Using the PHREG procedure in SAS 9.4, Cox proportional hazard regression analysis was used to produce two models that estimate the hazard ratio and respective 95% confidence intervals for both 1) all-cause mortality and 2) breast cancer specific mortality for each race adjusted for the independent variables of interest. In each model, age category, insulin medication, diabetic pill medication, years since diagnosed with cancer, BMI category, pre-existing diabetes, and years of diabetes prior to cancer diagnosis were the included variables. Risk factors were selected based on identification in the literatures as contributors towards mortality in breast cancer patients and availability in the NHIS questionnaire. Un-adjusted univariate and adjusted multivariate models were produced. P-values of 0.05 or less and appropriate 95% confidence intervals were considered statistically significant.

Chapter IV
Results

Inclusion of Cases for analysis

Table 4.1: Included Cases

Female Breast Cancer Cases Abstracted from NHIS 2006-2009 **(n=47,046)**		
	Unweighted	Weighted
NHIS Total Adult Population	83,708	92,702,566
NHIS Population of Adult Women	47,046	51,063,587
NHIS Population of Adult Women with Diabetes	4,289	4,444,373
NHIS Population of Adult Women with Breast Cancer	1,318	1,508,231
NHIS Population of Adult Women with Breast Cancer and Diabetes	216	234,165
NHIS Population of Adult Women with Breast Cancer and Diabetes who are deceased	30	39,185

Table 4.2: Missing Responses

Female Breast Cancer Cases Abstracted from NHIS 2006-2009		
	Frequency Missing	
	Unweighted	Weighted
NHIS Total Adult Population	13,472	9,485,622
NHIS Population of Adult Women	7,269	4,909,590
NHIS Population of Adult Women with Diabetes	630	422,686
NHIS Population of Adult Women with Breast Cancer	113	85,935
NHIS Population of Adult Women with Breast Cancer and Diabetes	21	15,181
NHIS Population of Adult Women with Breast Cancer and Diabetes who are deceased	2	1,749

Descriptive Statistics

Table 4.3 Adult Women in the U.S. (2006-2009)

	White (n=43,420,000)	African-American/Black (n=7,643,674)	p-value
Age			
	50.07	44.86	<0.0001
Age Category			
18-34	10,900,000 (25.11%)	2,651,621 (34.67%)	<0.0001
35-65	21,780,000 (50.17%)	3,733,633 (48.82%)	
65+	10,730,000 (24.72%)	1,263,017 (16.51%)	
BMI			
	26.86	29.67	<0.0001
BMI Category			
Underweight	1,059,133 (2.44%)	20,198 (1.57%)	<0.0001
Normal	18,020,000 (41.50%)	1,990,378 (26.02%)	
Overweight	11,550,000 (26.61%)	2,127,757 (27.82%)	
Obese	12,790,000(29.45%)	3,409,939 (44.58%)	
Diabetes			
Yes	3,475,210 (8.10%)	969,163 (12.68%)	<0.0001
Borderline	465,577 (1.07%)	99,517 (1.30%)	
No	39,450,000 (90.92%)	6,574,994 (86.02%)	
Cancer			
Yes	4,865,083 (11.21%)	357,537 (4.67%)	<0.0001
No	38,510,000e7 (88.69%)	7,286,716 (95.27%)	
Breast Cancer			
Yes	1,378,918 (3.18%)	129,312 (1.69%)	<0.0001
No	42,040,000 (96.82%)	7,518,958 (98.31%)	

Table 4.3 displays the characteristics of the study population categorized by the two racial/ethnic groups of interest.

The mean age of white women was 50.07 years, compared to 44.86 for African-American/Black women. The breakdown of the age categories reflected this trend of a younger African-American/Black population. The white population was composed of 25.11% 18-34 year olds, 50.17% 35-64 year olds, and 24.72% aged 65+, compared to 34.67%, 48.82%, and 16.51% respectively for the black population. The mean BMI for white women was 26.86 compared to 29.67for African-American/Black women. 2.44% of white women were classified as underweight, 41.50% as normal weight, 26.62% as overweight, and 29.4% as obese.

Comparatively, 1.57% of African-American/Black women were classified as underweight, 26.02% as normal weight, 27.82% as overweight, and 44.58% as obese. 8.10% of white women reported having diabetes, 1.07% as borderline diabetic, and 90.92% as not having diabetes. Comparatively, 12.68% of African-America/Black women reported having diabetes, 1.30% as borderline diabetic, and 86.02% as not having diabetes. 11.21% of white women reported having cancer while 88.69% reported not having cancer. 4.67% of African-American/Black women reported having cancer while 95.27% reported not having any type of cancer. 3.18% of White women reporting having breast cancer and 96.82% reported not having breast cancer. 1.69% of black women reported having breast cancer while 98.31% did not report having breast cancer. Differences between all characteristics were significant across the two racial/ethnic groups at the p=0.05 level.

Table 4.4 Diabetic Adult Women in the U.S. (2006-2009)

	White (n=3475210)	African-America/Black (n=969163)	P-value
Age			
	62.35	59.57	<0.0001
Age Category			
18-34	144250 (4.15%)	76564 (7.90%)	<0.0001
35-64	1714693 (49.34%)	491739 (50.74%)	
65+	1616268 (46.51%)	400861 (41.36%)	
Age Diagnosed with Diabetes			
	49.79	46.08	<0.0001
BMI			
	32.00	33.13	<0.0001
BMI Category			
Underweight	21930 (0.63%)	7386 (0.76%)	<0.0001
Normal	566530 (16.30%)	119206 (12.30%)	
Overweight	916071 (26.36%)	230992 (23.83%)	
Obese	1970679 (56.71%)	611579 (63.10%)	
Taking Insulin			
Yes	916434 (26.40%)	298111 (30.81%)	<0.0001
No	2555270 (73.60%)	669401 (69.19%)	
Taking Diabetic Pills			
Yes	2434499 (70.10%)	715931 (74.00%)	<0.0001
No	1038383 (29.90%)	251581 (26.00%)	
Cancer			
Yes	638387 (18.37%)	91796 (9.47%)	<0.0001
No	2833496 (81.53%)	877367 (90.53%)	
Breast Cancer			
Yes	191231 (5.50%)	42934 (4.43%)	<0.0001
No	3283979 (94.50%)	926230 (95.57%)	

Table 4.4 displays the prevalence of characteristics of the population of US women with diabetes categorized by the two racial/ethnic groups of interest.

The mean age of white women in this group was 62.35 while the mean age of African-American/Black women was 59.57. 4.15% of Adult white women with diabetes in the US were estimated to be in the 18-34 years of age group, 49.34% in the 35-64 years of age group, and 46.51% in the 65+ years of age group. 7.90% of Adult African-American/Black women with diabetes in the US were estimated to be in the 18-34 years of age group, 50.74% in the 35-64 years of age group, and 41.36% in the 65+ years of age group. The mean age for diagnosis with diabetes for white women was estimated to be 49.79. Comparatively, the mean age of diagnosis with diabetes for African-American/Black women was 46.08. The mean BMI of white women with diabetes was 32.00 compared to 33.13 for African-American/Black women with diabetes. 0.63% of white women with diabetes were classified as underweight, 16.30% as normal weight, 26.36% as overweight, and 56.71% as obese. Comparatively, 0.76% of African-American/Black women were classified as underweight, 12.30% as normal weight, 23.83% as overweight, and 63.10% as obese. 26.40% of white women with diabetes reported taking insulin while 73.60% reported not taking insulin. Comparatively, 30.81% of African-American/Black women reported taking insulin while 69.19% reported not taking insulin. 70.10% of white women with diabetes reported taking diabetic pills while 29.90% reported not taking diabetic pills. Comparatively, 74% of African-American/Black women with diabetes reported taking diabetic pills and 26% reported not taking diabetic pills. 18.37% of white women with diabetes reported having cancer of some type, while 9.47% of black women with diabetes reported having cancer. 5.50% of white women with diabetes reported having breast cancer, while 4.43% of African-American/Black women with diabetes reported having breast cancer. Differences between all characteristics were significant across the two racial/ethnic groups at the $p=0.05$ level.

Table 4.5 Adult Women with Breast Cancer in the U.S. (2006-2009)

	White (n= 1378918)	African-America/Black (n=129312)	P-Value
Age			
	67.73	62.53	<0.0001
Age Category			
18-34	6222 (0.45%)	3062 (2.37%)	<0.0001
35-64	539121 (39.10%)	65143 (50.38%)	
65+	833575 (55.27%)	61107 (47.26%)	
Age Diagnosed with Breast Cancer			
	56.36	50.42	<0.0001
BMI			
	26.96	29.83	<0.0001
BMI Category			
Underweight	27353 (1.98%)	1361 (1.05%)	<0.0001
Normal	540715 (39.21%)	33029 (25.54%)	
Overweight	415554 (30.14%)	38399 (29.69%)	
Obese	726214 (28.67%)	56523 (43.71%)	
Diabetes			
Yes	191231 (13.87%)	42934 (33.20%)	<0.0001
Borderline	17309 (1.26%)	1707 (1.32%)	
No	1170378 (84.88%)	84672 (65.48%)	

Table 4.5 displays the prevalence of selected characteristics of the US population of women with breast cancer categorized by the two racial/ethnic groups of interest.

The mean age of white women with breast cancer was estimated to be 67.73 compared to a mean age of 62.53 for African-American/Black women with breast cancer. 0.45% of Adult white women with breast cancer in the US were estimated to be in the 18-34 years of age group, 39.10% in the 35-64 years of age group, and 55.27% in the 65+ years of age group. 2.37% of Adult African-American/Black women with breast cancer in the US were estimated to be in the 18-34 years of age group, 50.38% in the 35-64 years of age group, and 47.26% in the 65+ years of age group. The mean BMI of white women with breast cancer was 26.96 compared to 29.83 for African-American/Black women with breast cancer. 1.98% of white women with breast cancer were classified as underweight, 39.21% as normal weight, 30.14% as overweight, and 28.67% as obese. Comparatively, 1.05% of African-American/Black women with breast cancer were classified as underweight, 25.54% as normal weight, 29.69% as overweight, and 43.71% as obese. 13.87% of white women with breast cancer reported having diabetes, 1.26% as borderline diabetic, and 84.88% as not having diabetes. Comparatively, 33.20% of African-American/Black women with breast cancer reported having diabetes, 1.32% as borderline diabetic, and 65.48% as not having diabetes. Differences between all characteristics were significant across the two racial/ethnic groups at the p=0.05 level.

Table 4.6 Non-Diabetic Adult Women with Breast Cancer in the U.S. (2006-2009)

	White	African-American/Black	P-Value
Age			
	67.36	60.71	<0.0001
Age Category			
18-34	15777 (0.75%)	6370 (4.22%)	<0.0001
35-65	975603 (46.13%)	82708 (54.85%)	
65+	1123342 (53.12%)	61708 (40.92%)	
Age First Diagnosed with Breast Cancer			
	55.99	50.60	0.0024
BMI			
	26.23	28.91	<0.0001
BMI Category			
Underweight	44312 (2.10%)	0	<0.0001
Normal	897590 (42.44%)	44854 (29.75%)	
Overweight	627357 (29.67%)	46930 (31.12%)	
Obese	545463 (25.79%)	59001 (39.13%)	
Leading Underlying Cause of Death			
Heart Disease	12919 (9.30%)	1516 (17.05%)	<0.0001
Malignant Neoplasms	62902 (45.26%)	5433 (61.09%)	
Chronic Lower-Respiratory Diseases	6894 (4.96%)	0	
Accidents	5537 (3.98%)	0	
Cerebrovascular Diseases	6493 (4.67%)	0	
Diabetes	0	0	
Alzheimer's	4300 (3.09%)	0	
Influenza and pneumonia	2714 (1.95%)	0	
Kidney Disease	1201 (0.86%)	0	
All other Causes	36019 (25.92%)	1945 (21.86%)	

Table 4.6 displays the prevalence of selected characteristics of US women with breast cancer who do not have diabetes categorized by the two racial/ethnic groups of interest.

The mean age of white women with breast cancer and no diabetes was estimated to be 67.37 compared to a mean age of 60.71 for African-American/Black women with breast cancer and diabetes. 0.75% of Adult white women with breast cancer and no diabetes in the US were estimated to be in the 18-34 years of age group, 46.13% in the 35-64 years of age group, and 53.12% in the 65+ years of age group. 4.22% of Adult African-American/Black women with breast cancer and no diabetes in the US were estimated to be in the 18-34 years of age group, 54.85% in the 35-64 years of age group, and 40.92% in the 65+ years of age group. The mean BMI of white women with breast cancer and no diabetes was 26.23 compared to 28.91 for African-American/Black women with breast cancer and no diabetes. 2.10% of white women with breast cancer and no diabetes were classified as underweight, 42.44% as normal weight, 26.67% as overweight, and 25.79% as obese. Comparatively, 0% of African-American/Black women with breast cancer and no diabetes were classified as underweight, 29.75% as normal weight, 31.12% as overweight, and 39.13% as obese. Of White women with breast cancer and no diabetes who died during the study period, heart disease was the leading cause of death for 9.30%, malignant neoplasms was the leading cause of death for 45.26%, chronic respiratory disease was the leading cause of death for 4.96%, accidents were the leading cause for 3.98%, cerebrovascular disease was the leading cause for 4.67%, diabetes was the leading cause for 0%, Alzheimer's was the leading cause for 3.09%, influenza and pneumonia was the leading cause for 1.95%, kidney disease was the leading cause for 0.86%, and all other causes accounted for 25.92%. Comparatively, of African-American/Black women with breast cancer and no diabetes who died during the study period, heart disease was the leading cause of death for 17.05%, malignant neoplasms was the leading cause of death for 61.09%, chronic respiratory disease was the leading cause of death for 0%, accidents were the leading cause for 0%, cerebrovascular disease was the leading cause for 0%, diabetes was the leading cause for 0%, Alzheimer's was the leading cause for 0%, influenza and pneumonia was the leading cause for 0%, kidney disease was the leading cause for 0%, and all other causes accounted for 21.86%. Differences between all characteristics were significant across the two racial/ethnic groups at the p=0.05 level.

Table 4.7 Diabetic Adult Women with Breast Cancer in the U.S. (2006-2009)

	White (n=331070)	African-American/Black (n=63786)	P-Value
Mean Age			
	70.16	66.46	0.0543
Age Category			
18-34	477(0.25%)	0	<0.0001
35-65	52051 (27.22%)	18227 (42.45%)	
65+	138704 (72.53%)	24707 (57.55%)	
Age First Diagnosed with Breast Cancer			
	58.77	50.41	0.0019
BMI			
	30.92	31.54	0.6717
BMI Category			
Underweight	2174 (1.14%)	1361 (3.17%)	<0.0001
Normal	41277 (21.58%)	7016 (16.34%)	
Overweight	58127 (30.40%)	12604 (29.36%)	
Obese	89654 (46.88%)	21953 (51.13%)	
Preexisting Diabetes			
Yes	76140 (39.82%)	22428 (52.24%)	<0.0001
No	115091 (60.18%)	20505 (47.76%)	
Age First Diagnosed with Diabetes			
	57.90	47.95	0.0009
Years of Diabetes Prior to Cancer Diagnosis			
	-0.7681	3.1687	0.4500
Years of Diabetes Prior to Cancer Diagnosis			
Developed After	100286 (52.44%)	16629 (38.73%)	<0.0001
< 5 years	41327 (21.61%)	18227 (21.61%)	
5-10 Years	16071 (8.40%)	6559 (15.28%)	
> 10 Years	33547 (17.54%)	11518 (26.83%)	
Taking Insulin			
Yes	42802 (22.51%)	10901 (25.39%)	<0.0001
No	147338 (77.49%)	32032 (74.61%)	
Taking Diabetic Pills			
Yes	140388 (73.41%)	34328 (79.96%)	<0.0001
No	50843 (26.59%)	8606 (20.04%)	
Leading Underlying Cause of Death			
Heart Disease	1089 (3.35%)	0	<0.0001
Malignant Neoplasms	12302 (37.81%)	4062 (61.10%)	
Chronic Lower- Respiratory Diseases	1916 (5.89%)	621 (9.34%)	
Accidents	1971 (6.06%)	0	
Cerebrovascular Diseases	1859 (5.71%)	0	
Diabetes	3825 (11.76%)	667 (10.03%)	
Influenza and pneumonia	1509 (4.64%)	0	
Kidney Disease	2104 (6.47%)	669 (10.07%)	
All other Causes	5963 (18.33%)	629 (9.46%)	

Table 4.7 displays the prevalence of selected characteristics of US women with both diabetes and breast cancer categorized by the two racial/ethnic groups of interest.

The mean age of white women with breast cancer and diabetes was estimated to be 70.16 compared to a mean age of 66.46 for African-American/Black women with breast cancer and diabetes. 0.25% of Adult white women with breast cancer and diabetes in the US were estimated to be in the 18-34 years of age group, 27.22% in the 35-64 years of age group, and 72.53% in the 65+ years of age group. 0% of Adult African-American/Black women with breast cancer and diabetes in the US were estimated to be in the 18-34 years of age group, 42.55% in the 35-64 years of age group, and 57.55% in the 65+ years of age group. The mean BMI of white women with breast cancer and diabetes was 30.92 compared to 31.54for African-American/Black women with breast cancer and diabetes. 1.14% of white women with breast cancer and diabetes were classified as underweight, 21.58% as normal weight, 30.40% as overweight, and 46.88% as obese. Comparatively, 3.17% of African-American/Black women with breast cancer and diabetes were classified as underweight, 16.34% as normal weight, 29.36% as overweight, and 51.13% as obese. 39.82% of white women with breast cancer and diabetes had pre-existing diabetes, compared to 52.24% of African-American/Black women. The mean age for diagnosis with diabetes for white women with breast cancer was estimated to be 57.90, compared to 47.95 for African-American/Black women. White women with breast cancer and diabetes developed diabetes on average 0.7861 years after being diagnosed with breast cancer. Comparatively, African-America/Black women with breast cancer and diabetes developed diabetes 3.1687 years prior to being diagnosed with breast cancer. 52.44% of white women with diabetes were diagnosed with diabetes after breast cancer diagnosis, 21.61 developed diabetes less than 5 years before breast cancer diagnosis, 8.40% developed diabetes between 5 and 10 years before breast cancer diagnosis, and 17.54% more than 10 years before breast cancer diagnosis. Comparatively, 38.73% of white women with diabetes were diagnosed with diabetes after breast cancer diagnosis, 21.61 developed diabetes less than 5 years before breast cancer diagnosis, 15.28% developed diabetes between 5 and 10 years before breast cancer diagnosis, and 26.83% more than 10 years before breast cancer diagnosis. 22.51% of white women with breast cancer and diabetes reported taking insulin while 77.49% reported not taking insulin. Comparatively, 25.39% of African-American/Black women with breast cancer and diabetes reported taking insulin while 74.61% reported not taking insulin. 73.41% of white women with breast cancer and diabetes reported taking diabetic pills while 26.59% reported not taking diabetic pills. Comparatively, 79.96% of African-American/Black women with breast cancer and diabetes reported taking diabetic pills and 20.04% reported not taking diabetic pills. Of White women with breast cancer and diabetes who died during the study period, heart disease was the leading cause of death for 3.35%, malignant neoplasms was the leading cause of death for 37.81%, chronic respiratory disease was the leading cause of death for 5.89%, accidents were the leading cause for 6.06%, cerebrovascular disease was the leading cause for 5.71%, diabetes was the leading cause for 11.76%, influenza and pneumonia was the lead cause for 4.64%, kidney disease was the leading cause for 6.47%, and all other causes accounted for 18.33%. Comparatively, of African-American/Black women with breast cancer and diabetes who died during the study period, heart disease was the leading cause of death for 0%, malignant neoplasms was the leading cause of death for 61.10%, chronic respiratory disease was the leading cause of death for 9.34%, accidents were the leading cause for 0%, cerebrovascular disease was the leading cause for 0%, diabetes was the leading cause for 10.03%, influenza and pneumonia was the leading cause for 0%, kidney disease was the leading cause for 10.07%, and all other causes accounted for 9.46%. With the exception of mean age, mean BMI, and mean years of diabetes prior to breast cancer diagnosis, differences between all characteristics were significant across the two racial/ethnic groups at the p=0.05 level.

Cox Proportional Hazard Models

Table 4.8: Unadjusted Univariate All-Cause Mortality

Model	Variable	Hazard Ratio	95% Confidence Interval
Model 1: Women with Breast Cancer			
	Age Category		
	18-34	-----	----
	35-64	2.741	(2.544-2.954)
	65+	2.357	(2.190-2.536)
	Race		
	White	----	----
	African-American/Black	1.217	(1.191-1.243)
	BMI Category		
	Underweight	0.944	(0.909-0.979)
	Normal	----	---
	Overweight	0.761	(0.749-0.773)
	Obese	1.094	(1.077-1.111)
	Ever Been Diagnosed with Diabetes		
	Yes	1.504	(1.485-1.524)
	Borderline	1.354	(1.274-1.438)
	No	---	---
	Years of Diabetes Prior to Cancer Diagnosis		
	Developed After		
	< 5 years	---	---
	5-10 years	1.551	(1.511-1.591)
	10+ years	1.808	(1.756-1.862)
		1.922	(1.883-1.961)
	Pre-existing Diabetes		
	Yes	0.908	(0.893-0.923)
	No	---	
Model 2: Women with Breast Cancer and Diabetes			
	Age Category		
	18-34	--	---
	35-64	1.215	(1.184-1.247)
	65+	.	.
	Race		
	White	---	---
	African-American/Black	1.226	(1.194-1.259)
	BMI Category		
	Underweight	7.299	(6.934-7.682)
	Normal	---	---
	Overweight	1.097	(1.066-1.128)
	Obese	1.346	(1.314-1.379)
	Pre-existing Diabetes		
	Yes	1.309	(1.282-1.336)
	No	---	----
	Years of Diabetes Prior to Cancer Diagnosis		
	Developed After		
	< 5 years	---	---
	5-10 years	1.257	(1.221-1.294)
	10+ years	1.398	(1.353-1.445)
		1.543	(1.504-1.582)
	Taking Insulin		
	Yes	1.220	(1.193-1.247)
	No	---	---
	Taking Diabetic Pills		
	Yes	0.756	(0.740-0.772)
	No	---	---

Table 4.8 displays the unadjusted hazard ratios of all-cause mortality and accompanying 95% confidence intervals for specified covariates of two cox proportional hazards models, one conducted using all women with breast cancer, and the other using only women with both breast cancer and diabetes.

Model 1 was conducted using all women with breast cancer. The age category of 35-64 was associated with a 2.741 (2.544-2.954 95% CI) times higher hazard of mortality than the 18-34 age group. Similarly, the age category of 65+ was associated with a 2.357 (2.190-2.536 95% CI) times higher hazard of mortality than the 18-34 age group. The racial classification of African-American/Black was associated with a 1.217 (1.191-1.243 95% CI) times higher hazard of mortality than the racial classification of White. The BMI categories of underweight, overweight, and obese, were associated with a 0.944(0.909-0.979 95% CI) times lower, 0.761 (0.749-0.773 95% CI) times lower, and 1.094(1.077-1.111 95% CI) times higher hazard of mortality than the BMI category of normal weight respectively. Those who reported being diagnosed with diabetes and those who reported being diagnosed with borderline diabetes were associated with a 1.504 (1.485-1.524 95% CI) and 1.354 (1.274-1.438 95% CI) respectively, times higher hazard of mortality than those without diabetes. Having diabetes for up to 5 years prior to cancer diagnosis was associated with a 1.551 (1.511-1.591 95% CI) times higher hazard of mortality than developing diabetes after breast cancer diagnosis. Having diabetes for 5-10 years, and 10+ years prior to diagnosis with breast cancer were associated with 1.808 (1.756-1.862 95% CI) and 1.922 (1.883-1.961 95% CI) respectively times higher hazard of mortality than diabetes developed after breast cancer diagnosis. Pre-existing diabetes was associated with a

0.908 (0.893-0.923 95% CI) times lower hazard of mortality than diabetes developed after cancer diagnosis.

Model 2 was conducted using only women with both breast cancer and diabetes. The age category of 35-64 was associated with a 1.215 (1.184-1.247 95% CI) times higher hazard of mortality than the 18-34 age group. Due to a lack of sufficient data, no hazard ratio was produced for the 65+ age group. The racial classification of African-American/Black was associated with a 1.215 (1.184-1.247 95% CI) times higher hazard of mortality than the racial classification of White. The BMI categories of underweight, overweight, and obese, were associated with a 7.299 (6.934-7.682 95% CI) times higher, 1.097 (1.066-1.128 95% CI) times lower, and 1.346 (1.314-1.379 95% CI) times higher hazard of mortality than the BMI category of normal weight respectively. Pre-existing diabetes was associated with a 1.309 (1.282-1.336 95% CI) times higher hazard of mortality than diabetes developed after cancer diagnosis. Having diabetes for up to 5 years prior to cancer diagnosis was associated with a 1.257 (1.221-1.294 95% CI) times higher hazard of mortality than developing diabetes after breast cancer diagnosis. Having diabetes for 5-10 years, and 10+ years prior to diagnosis with breast cancer were associated with 1.398 (1.353-1.445 95% CI) and 1.543 (1.504-1.582 95% CI) respectively times higher hazard of mortality than diabetes developed after breast cancer diagnosis. Taking Insulin was associated with a 1.220 (1.193-1.247 95% CI) times increased hazard of mortality than not taking insulin. Taking diabetic pills was associated with a 0.756 (0.740-0.772 95% CI) times lower hazard of mortality than not taking diabetic pills.

Table 4.9: Adjusted Multivariate All-Cause Mortality

Model	Variable	Hazard Ratio	95% Confidence Interval
Model 1: Women with Breast Cancer			
	Age Category		
	18-34	------	-------
	35-64	2.530	(2.895-3.384)
	65+	2.297	(2.279-2.644)
	Race		
	White	-------	------
	African-American/Black	1.102	(1.076-1.130)
	BMI Category		
	Underweight	1.025	(0.987-1.065)
	Normal	--------	------------------
	Overweight	0.800	(0.787-0.813)
	Obese	0.989	(0.972-1.006)
	Ever Been Diagnosed With Diabetes		
	Yes	1.603	(1.577-1.630)
	Borderline	1.154	(1.083-1.230)
	No	--------	
	Pre-existing Diabetes		
	Yes	1.329	(1.301-1.358)
	No	--------	
Model 2: Women with Diabetes and Breast Cancer			
	Age Category		
	18-34	----------	---
	35-64	1.645	(1.551-1.744)
	65+	What happened here?	.
	Race		
	White	-------	---
	African-American/Black	0.741	(0.711-0.773)
	BMI Category		
	Underweight	12.281	(11.506-13.107)
	Normal	-------	---
	Overweight	1.410	(1.361-1.461)
	Obese	1.353	(1.302-1.406)
	Pre-existing Diabetes		
	Yes	1.157	(1.109-1.206)
	No	------	
	Years of Diabetes Prior to Cancer Diagnosis		
	Developed After	----	---
	< 5 years	0.895	(0.848-0.945)
	5-10 years	1.378	(1.305-1.455)
	10+ years	1.184	(1.128-1.242)
	Taking Insulin		
	Yes	1.140	(1.094-1.188)
	No	---	---
	Taking Diabetic Pills		
	Yes	0.889	(0.860-0.919)
	No	---	---

Table 4.9 displays the adjusted hazard ratios of all-cause mortality and accompanying 95% confidence intervals for specified covariates of two cox proportional hazards models, one

conducted using all women with breast cancer, and the other using only women with both breast cancer and diabetes.

Model 1 was conducted using all women with breast cancer. Controlling for all other co-variates, the age category of 35-64 was associated with a 2.530 (2.344-2.731 95% CI) times higher hazard of mortality than the 18-34 age group. Similarly, the age category of 65+ was associated with a 2.297 (2.133-2.474 95% CI) times higher hazard of mortality than the 18-34 age group. Controlling for all other co-variates, the racial classification of African-American/Black was associated with a 1.102 (1.017-1.172 95% CI) times higher hazard of mortality than the racial classification of White. Controlling for all other co-variates, the BMI categories of underweight, overweight, and obese, were associated with a 1.025 (0.987-1.065 95% CI) times higher, 0.800 (0.787-0.813 95% CI) times lower, and 0.989(0.972-1.006 95% CI) times lower hazard of mortality than the BMI category of normal weight respectively. Controlling for all other co-variates, those who reported being diagnosed with diabetes and those who reported being diagnosed with borderline diabetes were associated with a 1.603 (1.577-1.630 95% CI) and 1.154 (1.083-1.230 95% CI) respectively, times higher hazard of mortality than those without diabetes. Controlling for all other co-variates, pre-existing diabetes was associated with a 1.329 (1.301-1.358 95% CI) times higher hazard of mortality than diabetes developed after cancer diagnosis.

Model 2 was conducted using only women with both breast cancer and diabetes. Controlling for all other covariates, the age category of 35-64 was associated with a 1.215 (1.184-1.247 95% CI) times higher hazard of mortality than the 18-34 age group. Due to a lack of sufficient data, no hazard ratio was produced for the 65+ age group. Controlling for all other co-variates, the racial classification of African-American/Black was associated with a 0.741 (0.711-0.773 95% CI) times lower hazard of mortality than the racial classification of White. Controlling for all other co-variates, the BMI categories of underweight, overweight, and obese, were associated with a 12.281 (11.56-13.107 95% CI) times higher, 1.410 (1.361-1.461 95% CI) times higher, and 1.353 (1.301-1.406 95% CI) times higher hazard of mortality than the BMI category of normal weight respectively. Controlling for all other co-variates, pre-existing diabetes was associated with a 1.157 (1.09-1.206 95% CI) times higher hazard of mortality than diabetes developed after cancer diagnosis. Controlling for all other co-variates, having diabetes for up to 5 years prior to cancer diagnosis was associated with a 0.895(0.848-0.945 95% CI) times lower hazard of mortality than developing diabetes after breast cancer diagnosis. Having diabetes for 5-10 years, and 10+ years prior to diagnosis with breast cancer were associated with 1.378 (1.305-1.455 95% CI) and 1.184 (1.128-1.242 95% CI) respectively times higher hazard of mortality than diabetes developed after breast cancer diagnosis. Controlling for all other co-variates, taking Insulin was associated with a 1.140 (1.084-1.188 95% CI) times higher hazard of mortality than not taking insulin. Controlling for all other co-variates, taking diabetic pills was associated with a 0.889 (0.860-0.919 95% CI) times lower hazard of mortality than not taking diabetic pills.

Table 4.10: Unadjusted Univariate Breast Cancer Specific Mortality

Model	Variable	Hazard Ratio	95% Confidence Interval
Model 1: Women with Breast Cancer			
	Age Category		
	18-34	---	--
	35-64	1.728	(1.602-1.864)
	65+	0.678	(0.630-0.731)
	Race		
	White	---	---
	African-American/Black	1.990	(1.935-2.046)
	BMI Category		
	Underweight	0	(0-7.934e11)
	Normal	---	---
	Overweight	0.788	(0.769-0.87)
	Obese	1.180	(1.152-1.209)
	Ever Been Diagnosed With Diabetes		
	Yes	1.475	(1.445-1.505)
	Borderline	0	(0-1.88e11)
	No	--------	
	Pre-existing Diabetes		
	Yes	0.935	(0.910-0.961)
	No	--------	
Model 2: Women with Diabetes and Breast Cancer			
	Age Category		
	18-34	------	-------
	35-64	2.326	(2.251-2.404)
	65+	.	.
	Race		
	White	-------	------
	African-American/Black	1.879	(1.813-1.947)
	BMI Category		
	Underweight	0	(0-2.162e20)
	Normal	--------	-----------------
	Overweight	0.630	(0.602-0.658)
	Obese	0.913	(0.882-0.945)
	Years of Diabetes Prior to Cancer Diagnosis		
	Developed After	----	---
	< 5 years	1.307	(1.251-1.367)
	5-10 years	2.652	(2.545-2.763)
	10+ years	0.972	(0.929-1.017)
	Taking Insulin		
	Yes	0.578	(0.554-0.603)
	No	---	---
	Taking Diabetic Pills		
	Yes	0.706	(0.684-0.730)
	No	---	---

Table 4.10 displays the unadjusted hazard ratios of breast cancer specific mortality and accompanying 95% confidence intervals for specified covariates of two cox proportional hazards models, one conducted using all women with breast cancer, and the other using only women with both breast cancer and diabetes.

Model 1 was conducted using all women with breast cancer. The age category of 35-64 was associated with a 1.728 (1.602-1.864 95% CI) times higher hazard of breast cancer specific mortality than the 18-34 age group. The age category of 65+ was associated with a 0.678 (0.630-0.731 95% CI) times lower hazard of breast cancer specific mortality than the 18-34 age group. The racial classification of African-American/Black was associated with a 1.990 (1.935-2.046 95% CI) times higher hazard of breast cancer specific mortality than the racial classification of White. The BMI categories of underweight, overweight, and obese, were associated with a 0 (0-7.934e11 95% CI) times, 0.788 (0.769-0.870 95% CI) times lower, and 1.180 (1.152-1.209 95% CI) times higher hazard of breast cancer specific mortality than the BMI category of normal weight respectively. Those who reported being diagnosed with diabetes and those who reported being diagnosed with borderline diabetes were associated with a 1.475 (1.445-1.505 95% CI) and 0 (0-1.88e1195% CI) respectively, times higher hazard of breast cancer specific mortality than those without diabetes. Pre-existing diabetes was associated with a 0.935 (0.910-0.961 95% CI) time lower hazard of breast cancer specific mortality than diabetes developed after breast cancer diagnosis.

Model 2 was conducted using only women with both breast cancer and diabetes. The age category of 35-64 was associated with a 2.326 (2.251-2.404 95% CI) times higher hazard of breast cancer specific mortality than the 18-34 age group. Due to a lack of sufficient data, no hazard ratio was produced for the 65+ age group. The racial classification of African-American/Black was associated with a 1.879 (1.813-1.947 95% CI) times higher hazard of breast cancer specific mortality than the racial classification of White. The BMI categories of underweight, overweight, and obese, were associated with a 0 (0-2.162e20 95% CI) times, 0.630 (0.602-0.658 95% CI) times lower, and 0.913 (0.882-0.945 95% CI) times higher hazard of breast cancer specific mortality than the BMI category of normal weight respectively. Having diabetes for up to 5 years prior to cancer diagnosis was associated with a 1.307(1.251-1.367 95% CI) times lower hazard of mortality than developing diabetes after breast cancer diagnosis. Having diabetes for 5-10 years, and 10+ years prior to diagnosis with breast cancer were associated with 2.652 (2.545-2.763 95% CI) times higher and 0.972 (1.128-1.242 95% CI) times lower hazard of breast cancer specific mortality than diabetes developed after breast cancer diagnosis. Taking Insulin was associated with a 0.578 (0.554-0.603 95% CI) times higher hazard of breast cancer specific mortality than not taking insulin. Taking diabetic pills was associated with a 0.706 (0.684-0.730 95% CI) times lower hazard of breast cancer specific mortality than not taking diabetic pills.

Table 4.11: Adjusted Multivariate Breast Cancer Specific Mortality

Model	Variable	Hazard Ratio	95% Confidence Interval
Model 1: Women with Breast Cancer			
	Age Category		
	18-34	---	--
	35-64	1.827	(1.688-1.978)
	65+	0.738	(0.684-0.797)
	Race		
	White	---	---
	African-American/Black	1.269	(1.228-1.312)
	BMI Category		
	Underweight	0	(0-1.17e8)
	Normal	---	---
	Overweight	0.740	(0.662-0.697)
	Obese	0.929	(0.904-0.954)
	Ever Been Diagnosed With Diabetes		
	Yes	1.375	(1.577-1.630)
	Borderline	0	0-1.131e24)
	No	--------	
	Pre-existing Diabetes		
	Yes	1.177	(1.138-1.217)
	No	--------	
Model 2: Women with Diabetes and Breast Cancer			
	Age Category		
	18-34	------	-------
	35-64	5.289	(4.762-5.874)
	65+	.	.
	Race		
	White	-------	------
	African-American/Black	1.564	(1.465-1.669
	BMI Category		
	Underweight	0	(0-8.00e7)
	Normal	--------	------------------
	Overweight	0.857	(0.814-0.902)
	Obese	1.021	(0.971-1.075)
	Years of Diabetes Prior to Cancer Diagnosis		
	Developed After		
	< 5 years	----	---
	5-10 years	0.102	(0.090-0.116
	10+ years	0.507	(0.469-0.549)
		0.599	(0.565-0.634)
	Taking Insulin		
	Yes	0.274	(0.257-0.292)
	No	---	---
	Taking Diabetic Pills		
	Yes	0.344	(0.314-0.373)
	No	---	---

Table 4.11 displays the adjusted hazard ratios of breast cancer specific mortality and accompanying 95% confidence intervals for specified covariates of two cox proportional hazards models, one conducted using all women with breast cancer, and the other using only women with both breast cancer and diabetes.

Model 1 was conducted using all women with breast cancer. Controlling for all other co-variates, the age category of 35-64 was associated with a 1.827 (1.688-1.978 95% CI) times higher hazard of breast cancer specific mortality than the 18-34 age group. Similarly, the age category of 65+ was associated with a 0.738 (0.684-0.797 95% CI) times lower hazard of breast cancer specific mortality than the 18-34 age group. Controlling for all other co-variates, the racial classification of African-American/Black was associated with a 1.269 (1.228-1.312 95% CI) times higher hazard of breast cancer specific mortality than the racial classification of White. Controlling for all other co-variates, the BMI categories of underweight, overweight, and obese, were associated with a 0 (0-1.17e8 95% CI) times, 0.740 (0.662-0.697 95% CI) times lower, and 0.929 (0.904-0.954 95% CI) times lower hazard of breast cancer specific mortality than the BMI category of normal weight respectively. Controlling for all other co-variates, those who reported being diagnosed with diabetes and those who reported being diagnosed with borderline diabetes were associated with a 1.340 (1.305-1.375 95% CI) and 0 (0-1.131e24 95% CI) respectively, times higher hazard of breast cancer specific mortality than those without diabetes. Controlling for all other co-variates, pre-existing diabetes was associated with a 1.177 (1.138-1.217 95% CI) times higher hazard of breast cancer specific mortality than diabetes developed after cancer diagnosis.

Model 2 was conducted using only women with both breast cancer and diabetes. Controlling for all other covariates, the age category of 35-64 was associated with a 5.289 (4.762-5.874 95% CI) times higher hazard of breast cancer specific mortality than the 18-34 age group. Due to a lack of sufficient data, no hazard ratio was produced for the 65+ age group. Controlling for all other co-variates, the racial classification of African-American/Black was associated with a 1.564 (1.465-1.669 95% CI) times higher hazard of breast cancer specific mortality than the racial classification of White. Controlling for all other co-variates, the BMI categories of underweight, overweight, and obese, were associated with a 0 (0-8.00e7 95% CI) times, 0.857 (0.814-0.902 95% CI) times lower, and 1.021 (0.971-1.075 95% CI) times higher hazard of breast cancer specific mortality than the BMI category of normal weight respectively. Controlling for all other co-variates, having diabetes for up to 5 years prior to cancer diagnosis was associated with a 0.102 (0.090-0.116 95% CI) times lower hazard of breast cancer specific mortality than developing diabetes after breast cancer diagnosis. Having diabetes for 5-10 years, and 10+ years prior to diagnosis with breast cancer were associated with 0.507 (0.469-0.549 95% CI) and 0.599 (0.565-0.634 95% CI) respectively times lower hazard of breast cancer specific mortality than diabetes developed after breast cancer diagnosis. . Controlling for all other co-variates, taking Insulin was associated with a 0.274 (0.257-0.292 95% CI) times lower hazard of breast cancer specific mortality than not taking insulin. Controlling for all other co-variates, taking diabetic pills was associated with a 0.344 (0.314-0.373 95% CI) times lower hazard of breast cancer specific mortality than not taking diabetic pills.

Table 4.12: Adjusted Multivariate Racially Stratified Mortality

Model	Variable	White Hazard Ratio (95% CI)	African-American/Black Hazard Ratio (95% CI)
Model 1: All-Cause Mortality			
	Age Category		
	18-34	---	.
	35-64	2.853 (2.641-3.081)	---
	65+	2.397 (2.226-2.581)	1.050 (0.999-1.104)
	BMI Category		
	Underweight	0.838 (0.803-0.874)	0.877 (0.764-1.006)
	Normal	---	---
	Overweight	0.759 (0.747-0.772)	0.046 (0.040-0.053)
	Obese	1.041 (1.023-1.059)	0.047 (0.041-0.054)
	Ever Been Diagnosed With Diabetes		
	Yes	1.377 (1.353-1.402)	15.575 (14.156-17.136)
	Borderline	1.001 (0.939-1.067)	.
	No	--------	----
	Pre-existing Diabetes		
	Yes	1.079 (1.055-1.105)	13.658 (12.443-14.992)
	No	--------	---
Model 2: Breast Cancer Specific Mortality			
	Age Category		
	18-34	---	.
	35-64	1.845 (1.703-2.000)	---
	65+	0.753 (0.698-0.813)	0.190 (0.175-0.206)
	BMI Category		
	Underweight	0 (0-2.365e14)	0 (0-3.664e35)
	Normal	---	---
	Overweight	0.698 (0.679-0.718)	0.020 (0.017-0.023)
	Obese	1.024 (0.996-1.052)	0.010 (0.009-0.012)
	Ever Been Diagnosed With Diabetes		
	Yes	1.125 (1.093-1.158)	10.891 (9.763-12.150)
	Borderline	0 (0-4.9e23)	.
	No	---	---
	Pre-existing Diabetes		
	Yes	0.850 (0.818-0.884)	7.696 (6.936-8.540)
	No	---	---

Table 4.12 displays the racially stratified adjusted hazard ratios of breast cancer specific mortality and all-cause mortality with accompanying 95% confidence intervals for the specified

covariates in models conducted using all women with breast cancer. Model 1 assesses all-cause mortality as an endpoint. Controlling for BMI, diabetes diagnosis, and pre-existing diabetes the age category of 35-64 was associated with a 2.853 (2.641-3.081 95% CI) times higher and the 65+ age category was associated with a 2.397 (2.226-2.581 95% CI) times higher hazard of mortality from any cause than the 18-34 age group, among white women. Controlling for all other covariates, the BMI category of underweight was associated with a 0.838 (0.803-0.874 95% CI) time lower and the BMI category of overweight was associated with a 0.759 (0.747-0.772 95% CI) times lower hazard of mortality from any cause than the BMI category of normal weight among white women. The BMI category of Obese was associated with a 1.041 (1.023-1.059 95% CI) times higher hazard of mortality from any cause than the BMI category of normal weight among white women. Controlling for all other co-variates, diabetes diagnosis was associated with 1.377 (1.353-1.402 95% CI) times higher hazard of mortality from any cause than not having a diabetes diagnosis, among white women. Controlling for all other co-variates, pre-existing diabetes was associated with a 1.079 (1.055-1.105 95% CI) times higher hazard of mortality from any cause than not having pre-existing diabetes, among white women.

Due to a lack of sufficient data, the 18-34 age group was not used as the referent group among black women. Controlling for BMI, diabetes diagnosis, and pre-existing diabetes the age category of 65+ was associated with a 1.050 (1.703-2.000 95% CI) times higher hazard of mortality from any cause than the 35-64 age group, among African-American/Black women. Controlling for all other covariates, the BMI categories of underweight, overweight, and obese were associated with a 0.877 (0.764-1.006 95% CI), 0.046 (0.040-0.053 95% CI), and 0.047 (0.041-0.054 95% CI) respectively, times lower hazard of mortality from any cause that the BMI category of normal, among African-American/Black women. Controlling for all other co-variates, diabetes diagnosis was associated with a 15.575 (14.156-17.136 95% CI) times higher hazard of mortality from any cause than not having a diabetes diagnosis, among black women. Controlling for all other co-variates, pre-existing diabetes was associated with a 13.658 (12.443-14.992 95% CI) times higher hazard of mortality from any cause than not having pre-existing diabetes, among African-American/Black women.

Model 2 assesses breast cancer specific mortality as an endpoint. Controlling for BMI, diabetes diagnosis, and pre-existing diabetes the age category of 35-64 was associated with a 1.845 (1.703-2.000 95% CI) times higher and the 65+ age category was associated with a 0.753 (0.698-0.813 95% CI) times lower hazard of mortality from breast cancer than the 18-34 age group, among white women. Controlling for all other covariates, the BMI category of underweight was associated with a 0 (0-2.365e14 95% CI) time lower and the BMI category of overweight was associated with a 0.698 (0.679-0.718 95% CI) times lower hazard of mortality from breast cancer than the BMI category of normal weight among white women. The BMI category of Obese was associated with a 1.024 (0.996-1.052 95% CI) times higher hazard of mortality from breast cancer than the BMI category of normal weight among white women. Controlling for all other co-variates, diabetes diagnosis was associated with 1.125 (1.093-1.158 95% CI) times higher hazard of mortality from breast cancer than not having a diabetes diagnosis, among white women. Controlling for all other co-variates, pre-existing diabetes was associated with a 0.850 (0.818-0.884 95% CI) times lower hazard of mortality from breast cancer than not having pre-existing diabetes, among white women.

Due to a lack of sufficient data, the 18-34 age group was not used as the referent group among black women. Controlling for BMI, diabetes diagnosis, and pre-existing diabetes the age category of 65+ was associated with a 0.190 (0.175-0.206 95% CI) times lower hazard of mortality from breast cancer than the 35-64 age group, among African-American/Black women. Controlling for all other covariates, the BMI categories of underweight, overweight, and obese were associated with a 0 (0-3.664e35 95% CI), 0.020 (0.017-0.023 95% CI), and 0.010 (0.009-0.01295% CI) respectively, times lower hazard of mortality from breast cancer that the BMI category of normal, among African-American/Black women. Controlling for all other co-variates, diabetes diagnosis was associated with a 10.891 (9.763-12.150 95% CI) times higher hazard of mortality from breast cancer than not having a diabetes diagnosis, among black women. Controlling for all other co-variates, pre-existing diabetes was associated with a 7.696 (6.936-8.540 95% CI) times higher hazard of mortality from breast cancer than not having pre-existing diabetes, among African-American/Black women.

Chapter V

Discussion

The Data abstracted from the 2006-2009 NHIS adult surveys showed that generally, African-American/Black women and White women differ in their prevalence of characteristics of interest regarding diabetes and cancer. White women are older, have lower BMIs and smaller proportions that can be considered overweight (26.61%) or obese (29.45%), and a lower prevalence of diabetes (8.10%) than African-American/Black women (27.82%overweight, 44.58% obese, 12.68% diabetic). However, White women had a higher prevalence of general cancer (11.21%) as well as breast cancer (3.18%) than African-American/Black women (4.67% and 1.69%) respectively. This data closely resembles the general trend of current CDC estimates of obesity prevalence among adult White women (35.5%) and black women (56.9%) and diabetes prevalence among adult White (5.3%) and African-American/Black women (9.9%) (CDC 2014).

Among women with diabetes, across both racial/ethnic groups, individuals were older, had higher BMIs, and higher rates of both cancer and breast cancer than the general female population. However, among women with diabetes, African-American/Black women showed trends of being of a younger age, being diagnosed with diabetes earlier, and higher proportions being considered obese. Additionally, African-American/Black women had higher proportions of women taking medication to treat their diabetes in the form of Insulin or diabetic pills than their white counterparts.

Women with breast cancer were older than the general population, with similar distributions of BMI categories and higher prevalence of diabetes. The prevalence of diabetes in the general population of women was 8.10% for white women and 12.68% for African-American/Black women, compared to 13.87% and 33.20% for White and African-American/Black women with breast cancer. This indicates that diabetes is a much larger concern for cancer patients than the general population, especially among African-American/Black women. Among women with breast cancer, African-American/Black women were younger, diagnosed with breast cancer younger, had higher BMIs, and several times magnitude higher prevalence of diabetes than White women.

Diabetes and Pre-existing Diabetes Rates

The first research question assessed in this study was "Does Diabetes and pre-existing diabetes occurs at a different rate among African-American women with breast cancer than White women?". Statistical analysis showed that African-American/Black women with did, in fact, have a higher prevalence of diabetes than White women (33.20% v 13.87%, $p < 0.0001$). This would appear to be intuitive given diabetes higher background prevalence in the general population of African-American women in this study (12.68%), however the prevalence among women with breast cancer is nearly 3 times higher than the prevalence of diabetes in the general population of African-American women in this study and most recent CDC estimates (9.9%). Comparatively, among White women, the prevalence of diabetes also increased from the general population (8.10%) to the population of White women with breast cancer (13.87%), but not to the same magnitude.

Among women with breast cancer and diabetes, the rate of pre-existing diabetes was higher among African-American/Black women than in White women (52.24% v 39.82%, p <0.0001). There was no significant difference in mean years of diabetes prior to breast cancer diagnosis, however higher proportions of African-American women reported having diabetes for 5-10 years (15.28%) and >10 years (26.83%) prior to breast cancer diagnosis than White women (8.40% and 17.54% respectively). Because breast cancer develops over an extended period of time, pre-existing diabetes for significant lengths of time suggests a biological interaction between the diabetic state and the formation of breast cancer. Although the presence of diabetes 5+ years prior to breast cancer diagnosis may suggest that diabetes played a role in the incipiency, diabetes at any stage prior to diagnosis may still impact the malignancy by accelerating the growth of the tumor. This study's findings that a higher proportion of African-American/Black women with breast have diabetes (33.20%) than White women with breast cancer (13.87%) supports previous studies in the literature that suggest that breast cancer patients with diabetes are more likely to be of non-white racial/ethnic groups (J. Luo, et al., 2015) although the magnitude differs significantly from what has been put forth, 5.5% of White women with breast cancer having diabetes and 11.3% of African-American/Black (Wu, et al., 2015).

<u>Diabetes and All-Cause/Breast Cancer Specific Mortality</u>

The next set of research questions addressed whether diabetes and pre-existing diabetes is associated with increased all-cause and breast cancer-specific mortality. In the adjusted Cox proportional hazard model for all-cause mortality among all women with breast cancer, diabetes was associated with an increased hazard of death from any cause (HR: 1.603, 1.577-1.630 95% CI). Among diabetic women with breast cancer, pre-existing diabetes was associated with an increased hazard of death from any cause (HR: 1.157, 1.109-1.206 95% CI).

Overall, diabetes increases the risk of all-cause mortality. This study identified a hazard ratio of 1.603. Studies by (J. Luo, et al., 2015) also identified similar increased risks of all-cause mortality (HR: 1.57), another study identified an adjusted HR of 1.26(need to find citation). BMI is associated with increased mortality at all categories. Interestingly, underweight has the highest hazard ratio compared to normal weight. Although higher BMI could indicate additional health problems that are associated with obesity, including more severe diabetes, weight loss is also a result of both cancer progression and cancer treatment.

In the adjusted Cox proportional hazard model for breast cancer specific mortality among all women with breast cancer, diabetes was associated with an increased hazard of death from any cause (HR: 1.340, 1.305-1.375 95% CI). Among diabetic women with breast cancer, pre-existing diabetes did not meet stepwise model selection criteria. However, among all women with breast cancer, pre-existing diabetes was associated with an increased risk of breast cancer-specific mortality as well (HR: 1.177, 1.138-1.217 95% CI).

Few studies have been conducted on the relationship between breast cancer-specific mortality and diabetes. A recently conducted study using the WHI identified an insignificant relationship between diabetes and breast cancer-specific mortality, HR: .74 (0.52-1.02 95% CI) (J. Luo, et al., 2014). Conversely, this study identified a significant relationship between diabetes and breast cancer-specific mortality, HR: 1.375. Studies have found that women with diabetes are more likely to have hormone negative tumors and advanced tumor stage, which is a plausible explanation the increase in breast cancer specific mortality. However, the significance of race as a factor even among diabetic breast cancer patients may indicate that other factors in the environment, behaviors, or genetic biology of African-American women lead to more aggressive malignancies.

<u>Race and All-Cause/Breast Cancer Specific Mortality</u>

The next set of research questions addressed the impact of race on all-cause and breast cancer-specific mortality. In the adjusted Cox proportional hazard model for all-cause mortality among all women with breast cancer, the racial classification of African-American/Black was associated with an increased hazard of death from any cause. African-American/Black women were 10% more likely (HR: 1.102, 1.076-1.130 95% CI) to die from any cause when compared to White women. Among diabetic women with breast cancer, African-American women were less likely to die from any cause (HR: 0.741, 0.711-0.773 95% CI).

In the adjusted Cox proportional hazard model for breast cancer specific mortality among all women with breast cancer, African-American/Black women were 27% more likely (HR: 1.269, 1.228-1.312 95% CI) to die from breast cancer than White women. Among diabetic women with breast cancer, African-American/Black women were 56% more likely (HR: 1.564, 1.465-1.669 95% CI) to die from breast cancer than White women.

Throughout the literature, an increase in mortality has been shown for African-American women compared to White women. However, this study showed a differential effect of race, increasing the risk of death from all-causes in African-American women compared to White women, yet decreasing that risk among diabetic patients. However, the hazard ratio of mortality from breast cancer increased from 1.269 (all breast cancer patients) to 1.564 (diabetic breast cancer patients) indicating that diabetes impacts the progression of cancer, and furthermore that impact has a greater impact on African-American women. This may be due to many factors including differences in treatment and differences in cancer biology.

Impact of Diabetes on All-Cause and Breast Cancer Specific Mortality among White Women v Black Women

<u>Diabetes, Race, and All-Cause/Breast Cancer Specific Mortality</u>

The final set of research questions assessed how the impact of diabetes differed on the all-cause and breast cancer-specific mortality between African-American and White women. The models run by stratifying breast cancer specific and all-cause mortality by racial classification (Table 4.12) showed that diabetes diagnosis does significantly raise the risk of mortality for both African-American and White women. However, diabetes and pre-existing diabetes show differential effects across each race. Both diabetes and pre-existing diabetes increase the risk of all-cause mortality in each race. However, the magnitude is several times larger for African

American women (adjusted Diabetes HR: 15.575, adjusted Pre-existing HR: 13.658) than for White women (adjusted Diabetes HR: 1.377, adjusted Pre-existing HR: 1.079).

In the modeling of breast cancer-specific mortality stratified by race, diabetes was shown to increase the risk of mortality for both races; however, pre-existing diabetes conferred a protective effect on white breast cancer patients while increasing mortality risk for African-American breast cancer patients. Similar to the model of all-cause mortality, the association of diabetes and pre-existing diabetes with breast cancer-specific mortality was several times larger for African American women (adjusted Diabetes HR: 1.891, adjusted Pre-existing HR:7.696) than it was for White women (adjusted Diabetes HR: 1.125, adjusted Pre-existing HR: 0.850).

<u>Strengths and Limitations</u>

Weaknesses in this study: This study is based on the NHIS which is a self-report survey and is subject to recall bias as well as classification error. Studies using cancer registries would be more accurate and verifiable as well as more comprehensive in reporting of cancer characteristics. This study was unable to control for characteristics of breast cancer that may impact mortality, such as histology, stage, and hormone receptor status. This study was unable to assess breast cancer treatments and how these may impact survival. Because the NHIS is meant to provide estimates on the prevalence of health-related characteristics in the US, this data could not adequately assess the incidence of breast cancer among diabetics. Additionally, this study was unable to abstract information such as education, income, and health insurance status that may impact treatment and diagnosis of both breast cancer and diabetes.

BMI in this study is at the time of survey not at the time of diagnosis with cancer, so BMI may be influenced by cancer progression and /or lifestyle changes made by the individual.

Strengths in this study: At the time the analysis was done, this was one of 2 studies to assess how diabetes affects mortality in African-American/Black women. The NHIS is designed to be nationally representative, so this study provides robust estimates of the prevalence of the selected characteristics and statistical significance of the associations identified.

Implications

Diabetes is highly prevalent among African-American/Black breast cancer patients. Moreover, African-American/Black women are more likely to have pre-existing diabetes upon breast cancer diagnosis than White women. Diabetes increases both all-cause and breast cancer-specific mortality among both African-American/Black and White breast cancer patients. However, it appears to increase the disparity in hazard of death between the two racial groups. Diabetes may develop in individuals who already have breast cancer. However, Pre-existing diabetes is a significant contributor to mortality from all causes as well as breast cancer specifically. Thus, prevention and control of diabetes may help slow the progression of breast cancer and decrease the likelihood of mortality, particularly among African-American women.

Additionally, specified treatment guidelines may be needed for diabetic breast cancer patients to aid in mitigating the increased mortality among this group.

Future studies

Case-Control studies could be conducted to ascertain if diabetes associated with the development of more aggressive sub-types of breast cancer. This study and others showed that diabetes is associated with an increase in cancer mortality; however, the exact mechanism remains unclear. Additionally, longitudinal studies on black women's health can be used to assess the incidence of breast cancer among both diabetics and non-diabetics. Studies that link to SEER registries for better accuracy. Future studies would also include clinical follow-ups to assess how controlled and uncontrolled diabetes impact mortality, and BMI at the time of cancer diagnosis. Future studies could also analyze the impact of diabetes on treatment selection and treatment outcomes.

Conclusion

This study contributes significantly to the literature by providing additional data on the co-morbidity of diabetes and breast cancer. Specifically, this study assessed the impact this co-morbidity has on African-American/Black women. African-American/Black women have disproportionately high breast cancer mortality rates, and by identifying the role that a common co-morbidity may have on that mortality rate, this study contributes to the body of literature aimed at decreasing this disparity. Interventions aimed at decreasing the prevalence of diabetes among breast cancer patients and emphasis on controlling diabetic severity among breast cancer patients, specifically African-Americans may lead to improvements in prognosis. Additionally, this study added to the literature indicating that diabetic medication may have a protective effect on all-cause and breast cancer-specific mortality among cancer patients.

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