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The Impact of Autoimmune Disease on Breast Cancer Survival

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THE IMPACT OF AUTOIMMUNE DISEASE ON BREAST CANCER SURVIVAL

by

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Abstract

Background

Breast cancer is the second leading cause of cancer death for women in developed countries, while autoimmune disease effects approximately 10 million people in the United States, of which approximately 80% are female. Both diseases are associated with hormonal risk factors and are related to the divergent effects of the cellular and humoral immunity that is associated with the T-helper 1 and T-helper 2 immune response. To investigate the potential implications that autoimmune disease may have on breast cancer-specific mortality, we have conducted a population-based retrospective cohort study of women who were diagnosed with breast cancer between January 1, 1996 to December 31, 2010 in South Carolina.

Methods

This study included 3,286 female breast cancer patients. The participants were identified through administrative claims databases, the South Carolina Medicaid Program and the South Carolina State Employee Health Plan, and were linked by a unique identifier to the South Carolina Central Cancer Registry. The autoimmune disease (AD) cohort was identified as those that had at least one AD present (n = 629), while those without an AD diagnosis were placed into a second cohort (n = 2,657). A secondary analysis was performed identifying those with a T-helper 1 (Th1) dominant

AD and a T-helper 2 (Th2) dominant AD; these two groups were then compared to those without an AD present. Kaplan Meier and Cox regression was used to test for associations between AD and breast cancer-specific survival.

Results

Breast cancer-specific survival was not significantly different between the AD and no AD cohorts. However, the crude analysis showed a significant reduction in breast cancer mortality (54%) for those with a Th1 dominant AD compared to those without an AD. When controlling for chemotherapy and radiation therapy, the relationship remained significant with a 55% reduction in breast cancer mortality among those with a Th1 dominant AD compared to those without an AD (HR: 0.45, 95% CI: 0.23, 0.87).

Conclusion

Among women who are diagnosed with breast cancer, the presence of a Th1 dominant AD is significantly associated with a 54% reduced risk of breast cancer mortality.

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List of Abbreviations

AD……..Autoimmune disease

CD……Crohn's disease

CI……Confidence Interval

ER……Estrogen

ICD-9……International Classification of Disease, Ninth Revision

IL……..Interleukin

MS……..Multiple sclerosis

NK……..Natural killer

PR……Progesterone

RA……Rheumatoid arthritis

SCCR……South Carolina Central Cancer Registry

SIR……Standardized incidence ratio

SLE……Systemic lupus erythematosus

Th1……T-helper 1

Th2……T-helper 2

UC……Ulcerative colitis

Chapter 1
Introduction and Thesis Overview

1.1 Introduction

Breast cancer is the most common cancer among women in developed countries [1]. In 2017, an estimated 252,710 women in the United States will be diagnosed with invasive breast carcinoma, accounting for 30% of all female cancer cases [2]. While survival rates for breast cancer have improved significantly over time, breast remains the second leading cause of cancer mortality among American women. The American Cancer Society estimates that 282,500 women will die of cancer in 2017 with 40,610 of these deaths being attributed to breast cancer [2]. There are several known risk factors for breast cancer, however these only account for approximately 45% to 55% of the cases that occur [3].

Epidemiological studies have indicated that the overall risk for developing breast carcinoma may be partially attributed to the immune status of the individual [4]. The immune system consists of both the innate and adaptive immune response, which work together to protect the body against disease[5]. An autoimmune disease (AD) occurs when the adaptive immune system fails to recognize the difference between what is foreign and what is self, resulting in an attack of healthy tissues[5]. There are between 70 to 100 identified autoimmune diseases. It is estimated that approximately 10 million people in the United States, of which 80% are female, are effected by at least one AD [6].

There have been several hypotheses to why women are more likely to be affected by AD than men. One proposed theory is the difference and fluctuations of sex hormones, as several studies have presented an association between remission and flares that occur with AD and the hormonal fluctuations that occur in women, such as during pregnancy and the menstrual cycle [7].

Numerous studies have presented the associations between autoimmune disease and breast cancer risk, with conflicting results; however, little data exists regarding the association of AD with breast cancer survival. This is an important gap in the literature, given the potential hormonal implications that both these diseases share in common.

1.2 Significance of Research

The primary objective of this study was to investigate the association of AD with breast cancer specific survival among a cohort of female breast cancer patients in South Carolina. This research will provide insight into the relationship between AD prevalence and breast cancer survival. There have been many studies conducted looking at individual ADs in their relationship to breast cancer risk, however, few have looked at survival, and to date no population-based studies have analyzed the potential association that the T-helper 1 (Th1) and T-helper 2 (Th2) dominant ADs have on breast cancer survival. With over 70 identified ADs, the American Autoimmune Disease

Association states that only 24 ADs contain reputable epidemiological studies[8]. In conducting an analysis on all potential ADs and those with Th1 and Th2 dominance, this will help to fill a major gap that currently exists in the literature.

1.3 Thesis Overview

This thesis is comprised of five chapters. The first chapter provides a brief overview of the issues around AD and breast cancer, the primary purpose and objectives of this research, and a thesis overview. The second chapter includes a background of the current literature for both AD and breast cancer, discussing the studies that have been conducted to analyze the association between AD and cancer, with a specific focus on those studies that relate to breast cancer. This background information will provide information on the most relevant literature to help the reader in being able to critically evaluate the results and implications of this study. The third chapter provides information regarding the study design, methodological details, and the statistical methods that were used. The fourth chapter provides the results of the survival and multivariable analyses. The final chapter will include the discussion, highlighting the limitations of the study and providing an overall conclusion with suggestions regarding future directions for this research.

Chapter 2
Review of the Literature

2.1 Autoimmune Disease and the Immune System

The immune system is regulated by antigen presenting cells which are comprised of the innate and adaptive immunity[9]. The innate immune response, consists of phagocytes, which include your macrophages, granulocytes, dendritic cells, and natural killer cells[4]. The innate immune response communicates and activates the adaptive immune response in order to eliminate pathogens[5]. There are two types of adaptive immune responses, the humoral immunity, comprised the B lymphocytes, and the cellular immunity, made up of T lymphocytes. The B lymphocytes are programmed to create specific antibodies to target pathogens, while the T cells contribute to the immune defense by directing and regulating the immune response through the helper T cells, T-helper 1 (Th1) and T-helper 2 (Th2) cells[10]. Autoimmune diseases occur when the B cells develop antibodies to the organs and/or tissues and therefore misidentify normal body tissues as invaders[10].

The Th1 cytokines secrete IFN-□, IL-2, and TNF-α to promote cellular immunity, while the Th2 cytokines secrete IL-4 and IL-10 to promote humoral immunity[4,9]. Studies have shown that females tend to have stronger cellular and humoral immune response than that of men, therefore increasing their resistance to several infections but also

causing females to be more susceptible to developing an AD[8,11]. Collectively AD effects three times more women than men[8]. Approximately 80% of patients are women for Sjögren's syndrome, Systemic lupus erythematosus, Primary biliary cirrhosis, Autoimmune thyroid disease, and Scleroderma, while 60% to 75% of patients are women for multiple sclerosis, myasthenia gravis, and rheumatoid arthritis [6].

Table 2.1: Gender prevalence ratio for various autoimmune diseases.

Autoimmune Disease	Ratio (female/male)	Reference
Addison's Disease	12.3:1	[11]
Antiphospholipid syndrome	9:1	[7,11,12]
Autoimmune hepatitis	7.5 – 8:1	[7,11–13]
Celiac disease	1.8 – 3.3:1	[11,14]
Crohn's disease	0.45 – 3:1	[11]
Dermatomyositis	2:1	[11,13]
Grave's disease	2.7 – 4:1	[11–13,15]
Hashimoto's thyroiditis/hypothyroidism	5.2 – 50:1	[7,11–13,15,16]
Mixed connective tissue disease	8:1	[11,12]
Multiple Sclerosis	2 – 3:1	[7,11,12]
Myasthenia gravis	1.6 – 3:1	[6,7,11,12]
Primary biliary cirrhosis	9:1	[8]
Rheumatoid arthritis	2.7 – 4:1	[7,11–13,15,16]
Scleroderma	3 – 11.8:1	[7,11–13,15]
Sjögren's syndrome	9 – 20:1	[7,11–13,15]
Systemic lupus erythematosus	7.4 – 9:1	[6,7,11–13,15,16]
Thrombocytopenic purpura	2:1	[8]
Vitiligo	1.1:1	[11]

2.2 Breast Cancer and the Immune System

Breast cancer is the result of malignant tumors developing in the breast [17]. Breast cancer is the most common cancer among women, with a lifetime risk of 12% and a 5% risk of mortality[18]. Studies have shown that fluctuations in the immune system may be associated with an increased risk of breast cancer. Women with estrogen receptor positive breast cancer typically have a better prognosis than those with estrogen receptor negative breast cancer, with a 10% difference in 5-year survival[19]. A study conducted on over 12,000 breast cancer patients in the United Kingdom and Canada found that among the women that had estrogen receptor negative tumors, the presence of CD8+ T cells within the tumor was associated with a significant reduction in breast cancer specific mortality reporting a hazard of 28% (95% CI: 16% - 38%)[20]. Additionally, studies have found that when T lymphocytes were present in malignant tumors the tumors were more likely to have negative auxiliary lymph nodes, have a smaller tumor diameter, a lower histological grade, and reoccurrence-free survival[4].

As mentioned previously, the T lymphocytes consists of the Th1 and Th2 cytokines. The Th1 cytokines enhance the antitumor immune response through the secretion of IFN-□, which causes the anti-tumor directed B cell factors and the CD8+ T cells to all work together to "favor tumor rejection"[4]. In contrast, the chronic activation of the Th2 cytokines secrete pro-growth factors which will decrease the CD8+ T lymphocytes, resulting in tumor promotion[4]. A study conducted by Campbell and colleagues analyzed the peripheral blood lymphocytes of 84 breast cancer patients and

26 healthy controls, finding that the Th1 cytokines were lower in the breast patients prior to therapy compared to healthy controls[21]. The CD8+ T cytokines, Th1 cytokines, and natural killer (NK) cells are the key players in protecting the body against tumor development and progression, while the B and Th2 cytokines that are involved in the humoral immune response promote both tumor development and progression[4].

2.3 Breast Cancer and Autoimmune Disease

The association that has been seen between the absence or decrease of T-helper cells and the increase risk of developing breast carcinoma suggests a possible beneficiary role that autoimmune diseases may implicate in potentially improving cancer prognosis, as studies have shown that there is an increase in T-helper cytokines for those with an AD. It is widely accepted now in the scientific community, that both the Th1 and Th2 cytokines play a major role in coordinating the immune system. The Th1/Th2 hypothesis began in the 1980s, when these two subgroups of T lymphocytes were recognized in mouse models[22]. This concept was later investigated and connected to the role that both these cytokine subgroups play in the development of disease. The Th1 pathways is considered the more aggressive of the two, and have been shown be the main coordinator in the attack against viruses, bacterial agents, and even cancer cells[22]. This subgroup of T cells has been referred to as the "antitumor immune response", which occurs when Th1 cytokines secrete IFN-□, resulting in an activation of macrophage cytotoxic activity[4]. However, when the Th1 cells become overactive the resulting consequence can be the development of an organ-specific AD[22]. The Th2 pathway promotes humoral immunity and consists of major anti-inflammatory

cytokines, IL-4 and IL-10[9]. This pathway is thought to be involved in downregulating the cell-mediated anti-tumor response and enhancing the "protumor humoral response"[4]. The overactivation of the Th2 cytokines has been associated with increasing the risk of developing allergies, IgE-related diseases, as well as systemic ADs[22].

2.3.1 Th1 Dominant Autoimmune Diseases and Breast Cancer

Table 2.2: T-helper 1 (Th1) dominant autoimmune diseases.

Autoimmune Disease	Reference
Crohn's disease (CD)	22,24,56,57
Hashimoto's thyroiditis/hypothyroidism	9,24,57,58
Multiple sclerosis (MS)	9,24,58
Psoriasis/Psoriatic arthritis	59
Sjögren's syndrome	58,60
Rheumatoid arthritis (RA)	9,24,57,58,61
Type I diabetes mellitus	9,22,24,58
Uveitis	62

Autoimmune diseases, such as Multiple sclerosis, Rheumatoid arthritis, and Type I diabetes mellitus, have been associated with a Th1 dominant immune response. Several studies have looked at the association between these Th1 dominant ADs and pregnancy, as pregnancy tends to enhance the Th2 cytokines and reduce the Th1 cytokines[23]. This shift from a Th1 to a Th2 immune response, often causes those with Th1 associated AD to undergo remission during pregnancy. However, during the postpartum period the Th1 related ADs will typically increase in severity[23]. The ADs, RA, MS, Type I diabetes mellitus, and Crohn's disease, have an excess of IL-12 and TNF-α, both of which are associated with the Th1 immune response. Women with these ADs, experienced remission during the third trimester of pregnancy due to the increased

levels of cortisol which suppresses the pro-inflammatory cytokines, IL-12 and TNF-α, while promoting the anti-inflammatory cytokines, IL-4 and IL-10[24].

As mention previously, the Th1 immune response has been seen to be associated with the downregulation of tumor growth[24]. Hemminki and colleagues conducted a study in Sweden, analyzing the risk and survival of female cancers among those women with an AD[25]. Of the 199,466 patients that were studied, 4,607 patients developed breast cancer. The standardized incidence ratio (SIR) was calculated as the ratio of what was observed in the Swedish Hospital Discharge Register to the ratio expected of that in the general population. The overall risk for breast cancer was significantly lower for those with an AD, with an SIR of 0.94 (95% CI: 0.91 to 0.97). Four of the six Th1 dominant ADs represented in this study had a significantly lower risk of developing breast cancer. There was a 15% reduced risk seen in Crohn's disease patients with an SIR of 0.85 (95% CI: 0.75 to 0.97). Hashimoto's thyroiditis patients had a significantly lower risk as well with an SIR of 0.78 (95% CI: 0.66 to 0.91)[25]. In addition, a cohort study conducted in Ontario, Canada identified 178,186 women with breast cancer and found that those with hypothyroidism had a significantly lower risk of dying compared to those that did not have hypothyroidism (HR: 0.87, 95% CI: 0.77 to 0.98)[1]. Hemminki and colleagues similarly found a significantly reduced risk for developing breast cancer among women with RA (SIR: 0.84, 95% CI: 0.79 to 0.89), results which were consistent with a study conducted through the Danish Cancer Registry[25,26]. However, Ji and colleagues found that those with RA compared to those without RA had a significantly worse prognosis, with HRs of 1.60 (95% CI: 1.40 to 1.84) for breast-cancer

specific survival and 1.55 (95% CI: 1.40 to 1.71) for overall survival[27]. In addition to Crohn's disease, Hashimoto's thyroiditis, and RA, those patients with Sögren's syndrome had a significantly reduced risk as well, with an SIR of 0.46 (95% CI: 0.26 to 0.75)[25].

2.3.2 Th2 Dominant Autoimmune Diseases and Breast Cancer

Table 2.3: T-helper 2 (Th2) dominant autoimmune diseases.

Autoimmune Disease	Reference
Grave's disease/hyperthyroidism	[58]
Hemolytic anemia	[63]
Immune thrombocytopenic purpura	[63]
Scleroderma/Systemic Sclerosis	[57,58]
Systemic lupus erythematosus (SLE)	[22,24,57,63,64]
Ulcerative colitis (UC)	[56]

While, the Th1 dominant ADs that were represented in Hemminki and colleagues study were either not significant or provided results that showed a significant reduction in risk of developing breast cancer, two of the six Th2 dominant ADs represented in this study had a significantly higher risk of developing AD while the other Th2 ADs that were represented did not yield significant results. Grave's disease had a significant SIR of 1.13 (95% CI: 1.06 to 1.21), while ulcerative colitis had a significant SIR of 1.12 (95% CI: 1.01-1.24)[25]. While ulcerative colitis had a significant increase in risk for developing breast cancer, those patients with ulcerative colitis had a 25% reduced risk of dying compared to the general population (HR: 0.75, 95% CI: 0.58 to 0.98)[25]. While systemic lupus erythematosus (SLE), did not yield significant results in the previously mentioned study, a study conducted on the Chicago Lupus Cohort found that even after controlling for

hormone replacement therapy and oral contraceptive history, women with lupus had a higher risk of developing breast cancer[26].

2.3.3 Breast Cancer and Autoimmune Disease Risk Factors

Autoimmune diseases are estimated to effect approximately 3% of the population in the United States[28]. Prevalence rates very across the different ADs, with the more common ADs being grave's disease, RA, and hashimoto's thyroiditis with prevalence rates estimated at 500 per 100,000 people[28]. Risk factors vary across the wide range of ADs, but share some similarities with that of breast cancer, such as race, estrogen exposure, and taking certain medications such as hormone replacement therapy.

Among African Americans, the lifetimes risk of developing breast cancer for those 80 years of age and younger is 11%, while Caucasians have a 13% risk of developing breast cancer.[18] However, for those women younger than 45 years, African American women tend to have higher rates of breast cancer compared to Caucasian women, while the reverse association is true for those over the age of 60[18]. Within the United States, African Americans have a higher risk for developing SLE and scleroderma compared to Caucasians[28]. In addition, African Americans also tend to be diagnosed on average 7 years younger for both previously mentioned diseases compared to Caucasians. In contrast, the risk for type-I diabetes mellitus and MS is higher among Caucasians compared to African Americans, while similar rates are seen for RA[28].

As mentioned previously those with a Th2 dominant AD were more likely to develop breast cancer compared to those with a Th1 dominant AD. This could be because estrogen aids in regulating the Th2 immune response, therefore an increase in estrogen results in an increase in the Th2 response[11]. Lifetime exposure to estrogen is a known risk factor for developing breast cancer. Women who began their period at age 12 compared to those at age 14, had a 20% higher risk of developing breast cancer[29]. Lifetime estrogen exposure and breast cancer risk are linearly association, meaning that the younger a woman begins her menstrual cycle and the later a woman begins menopause the more at risk a woman is to developing breast cancer due to the lifetime exposure of estrogen[30].

It has been shown that within the first 2 to 3 years of taking combination hormone replacement therapy, breast cancer risk increases by approximately 75% and then goes back down 2 years after stopping the medication[31]. Hormone replacement therapy not only increases the risk of developing breast cancer, but has been shown to increase the risk of developing CD as well. A nested case-control conducted in the United Kingdom used frequency-matched controls to determine potential risk factors that may be associated with CD or UC. The results found that the longer-term use of hormone replacement therapy significantly increased the risk for developing CD (OR: 2.60, 95%CI: 1.04 to 6.49)[32].

2.3.4 Breast Cancer Survival Factors and Autoimmune Disease

While the breast cancer death rate among females has declined by 38% from 1989 to 2014, breast cancer still remains the second-leading cause of cancer death

among women[2]. The five-year survival rate for invasive breast carcinoma is 90%, while the ten-year survival rate decreases to 83%. Patient and tumor characteristics have all been shown to play a major role in determining survival.

Patient characteristics that effect breast cancer survival consist of characteristics such as age at diagnosis, time after diagnosis, socioeconomic status, and race. A retrospective cohort study conducted on 10,356 women breast cancer patients all under the age of 50, found that compared to those in the 45 to 49-year age group those who were less than 35 years old and those that were between 35 to 39 years of age had a significantly higher risk of dying, with an adjusted relative risk of 1.46 (95% CI: 1.27 to 1.70) and 1.26 (95% CI: 1.12 to 1.42), respectively[33]. These results are consistent with other studies, and can be attributed to the fact that younger women tend to be at higher risk for having a higher histopathologic grade and having tumors that are both larger in size and hormone-receptor-negative[18,33]. Race also plays a major factor for breast cancer survival. A study found that ten years following treatment 58% of African Americans survived compared to the 66% of Caucasian Americans that died, even after adjusting for additional prognostic factors there was still a 41% difference between the two racial groups[18].

Tumor size has been noted to be one of the strongest indicators of breast cancer survival. The cohort study mentioned previously, found that compared to those with a tumor size of 2cm or less, those patients with a tumor size of more than 2cm had a significant increase in risk of dying[33]. A case-control study assessed the association between Hashimoto's thyroiditis and invasive breast cancer, and found that those with

hypothyroidism were significantly more likely to have a smaller tumor size compared to those without the AD[34]. In addition, Cristofanilli and colleagues found that those with hypothyroidism were significantly more likely to be diagnosed with an earlier stage of breast cancer than those without the AD[34]. Stage, also known as histological grade, has been consistently shown to be associated with long-term breast cancer survival among those with the lowest score[18].

2.4 Introduction

Many studies have analyzed the associations between individual autoimmune diseases and breast cancer risk. However, few studies have looked at the association between AD and breast cancer survival and even fewer studies have looked at ADs collectively. There are also no known studies that have analyzed the potential implications that the Th1 and Th2 dominant ADs have on breast cancer survival. This study will provide an important gap in the literature and will include all ADs that have been identified by the American Autoimmune Diseases Association. In addition, a sub analysis will be included to address the potential implications that the Th1 and Th2 dominant ADs may have on breast cancer survival.

Chapter 3
Methods

3.1 Purpose and Objectives

The primary objective of this study was to investigate the association of AD presence with breast cancer mortality in a cohort of 3,286 female breast cancer patients. To explore the possible associations between breast cancer survival and AD, the following specific aims were proposed:

1. Assess and compare the baseline patient, tumor, and treatment characteristics for those with and without AD among this cohort of female breast cancer patients.
2. Conduct multivariable analyses on the differences in breast cancer specific survival among those with and without an AD.
3. Conduct multivariable analyses on the differences in breast cancer specific survival among those that have a T-helper 1 dominant AD, T-helper 2 dominant AD, and those without an AD.

3.2 Hypothesis

Women with AD will experience an increase in breast cancer survival compared to those women without AD.

3.3 Study Design

3.3.1 Study Population

This retrospective cohort study includes 3,286 female breast cancer patients in South Carolina that were diagnosed with primary breast cancer between the dates January 1, 1996 to December 31, 2010 and are 65 years of age or younger.

3.3.2 Database

To create a cohort of diverse women, we linked individual data contained within the South Carolina Employee Health Plan, the South Carolina Medicaid Program, South Carolina's National Breast and Cervical Cancer Early Detection Program (Best Chance Network), and the South Carolina Central Cancer Registry (SCCR). This provided us with complete data on screening, treatment, mortality, medical procedures, co-morbid condition, prescriptions, and corresponding-dates of cancer treatment/services.

The two administrative claims databases that were used in this study were the South Carolina Medicaid Program and the South Carolina Employee State Health Plan. Medicaid is considered one of South Carolina's largest insurance providers and covers approximately one-quarter of the state's population. The South Carolina Employee State Health Plan covers 600 different employer groups in South Carolina, consisting of 422,000 spouses and dependents, 178,000 active employees, and 63,000 retirees. The Best Chance Network began in 1992, and provides screening services (i.e., mammograms, diagnostic procedures, community education, etc.) to underserved women that are between the ages of 47 to 64 years. All women diagnosed in this program are subsequently insured through Medicaid for the duration of their breast

cancer treatment. The SCCCR is a population-based data system collecting cancer incidence in South Carolina, and has achieved and maintained gold certification awarded by the NAACCR since its' first evaluation in 1997.

3.3.3 Inclusion and Exclusion Criteria

To be included in this study, each patient had to be diagnosed with breast cancer between the dates January 1, 1996 to December 31, 2010 and have information regarding co-morbid conditions and vital status. This information was provided by the SCCCR. In addition, the patient had to be either African American or European American and could have no prior cancer diagnosis to this initial breast cancer diagnosis. Since Medicare was not included in this analysis, all women had to be less than 65 years of age.

3.4 Measurements

3.4.1 Exposure Variable

Autoimmune disease was defined by the American Autoimmune Disease Association. This association provided a comprehensive list of ADs that was used to identify any patients in the cohort that had an AD. The International Classification of Disease, Ninth Revision (ICD-9), was used to identify the AD. The ICD-9 codes that were used in this study were identified through previous literature and the Find-A-Code database, an online database of medical billing codes and information, the codes that were used can be seen in table 4.1.

In addition, there were two categories of AD, Th1 and Th2 dominant ADs. These were identified through the literature and can be seen in table 2.2 and table 2.3. The

Th1 dominant ADs were defined as patients that had at least one of the following: Crohn's disease, Hashimoto's thyroiditis/hypothyroidism, Multiple sclerosis, Psoriasis/Psoriatic arthritis, Sjögren's syndrome, Rheumatoid arthritis, Type I diabetes mellitus, and Uveitis. The Th2 dominant ADs were defined as patients that had at least one of the following: Grave's disease/hypothyroidism, Hemolytic anemia, Immune thrombocytopenic purpura, Scleroderma/Systemic Sclerosis, Systemic lupus erythematosus, Ulcerative colitis.

3.4.2 Outcome Variable

The outcome of interest was breast cancer specific mortality, which was ascertained from the SCCCR. Each year the records in the SCCCR are linked to the National Death Index to capture information regarding the date and primary cause of death. The time frame for breast cancer-specific mortality was initiated on the date of diagnosis and ended on the date of death. All non-deceased participants were censored December 31, 2013.

3.4.3 Patient and Clinical Variables

Variables were collected regarding the patient, tumor, and treatment characteristics. Patient characteristics included age at diagnosis, race, insurance type, and year of diagnosis. Age at diagnosis was analyzed as a continuous variable in this study, and race was dichotomized as Caucasian or African American. Insurance type was also dichotomized as type I and type II since due to payor stipulations for data use, insurance type was encrypted in our dataset. Year of diagnosis was grouped into categories (2002-2004, 2004-2006, 2008-2010).

Tumor characteristics were identified through the SCCCR database and included histological grade, estrogen receptor status, progesterone receptor status, hormone receptor status, stage, tumor size, and lymph node status. Both tumor size and lymph node status were identified using the TNM classification. T describes the size of the primary tumor, N provides information regarding the extent that the tumor has spread to nearby lymph nodes, and M indicates if the cancer has metastasized[27]. For tumor size, T was used to identify those that were less than or equal to 2cm, those tumors that were larger than 2cm but less than 5cm, and those that were over 5cm in diameter. Additionally, N captured the number of positive lymph nodes.

The treatment characteristics of hormone therapy, radiation therapy, and chemotherapy were also identified by the SCCCR. These variables were dichotomized as yes/no variables.

3.5 Statistical Analyses

Statistical analyses were run using the Statistical Analysis Software (SAS version 9.2, SAS Institute, Cary, NC). All statistical tests had an alpha level of 0.05.

3.5.1 Baseline Data

Baseline data was stratified by those patients that have at least one AD and those that do not have an AD. Age at diagnosis was treated as a continuous variable and analyzed though a t-test, means, standard deviations, and p-values were reported. Patient, tumor, and treatment characteristics were categorized, as mentioned in the previous section. Chi-square test were run to determine possible associations between

these variables and AD status; corresponding frequencies, row percentages, and p-values were reported.

3.5.2 Survival Analysis

The primary analysis for this study consisted of comparing breast cancer specific survival for those with at least one AD and those without an AD, while our secondary analysis consisted of comparing those with a Th1 or Th2 dominant AD to those that did not have an AD diagnosis. Survival time was calculated as the date of diagnosis to the date of death or date of censoring. Since breast cancer-specific survival was our primary outcome of interest, death due to other causes was censored at the date of death. Kaplan Meier, a non-parametric method, along with the Log-rank test was used to analyze the difference between the comparison groups for both the primary and secondary analysis. Survival probabilities and corresponding p-values were reported at year 3, 5, and 10.

The Cox proportion hazard regression model was used to estimate the hazard ratios (HR) and the corresponding 95% confidence intervals (CI) for breast-cancer specific mortality. Based on previous literature the following variables were considered for the final fully-adjusted model: race, insurance type, year of diagnosis, stage, radiation therapy, chemotherapy, and hormone therapy. Hormone receptor status was not considered for the model, due to the collinearity that exists between both hormone receptor status and hormone therapy. A collinear pattern also exists for stage, grade, and lymph node status; since there were more participants with information regarding stage compared to the other two variables, stage was considered for the model. The

proportional hazard assumption for the covariates was assessed using Schoenfeld residuals. Covariates were stratified in the models if they failed to meet the proportionality assumption. Unadjusted models were analyzed along with models that included the covariates that were shown to be significant.

Chapter 4
Results

Among the 3,286 women diagnosed with breast cancer between 1996 to 2010, there were 513 breast cancer-specific deaths and 639 total deaths were reported. 19.14% of participants had at least one AD prior to the initial breast cancer diagnosis. The most common ADs within this study were rheumatoid arthritis, type I diabetes mellitus, and antiphospholipid syndrome (Table 4.1).

The average age of breast cancer diagnosis for a participant with an AD was significantly different from that of a participant without an AD, at 52 years versus 50 years, respectively. Those with an AD were more likely to have Type I insurance compared to those participants without an AD. However, no additional differences were observed between the two groups (Table 4.2).

4.1 Primary Outcome

No associations were observed between those with an AD and those without an AD for both breast cancer-specific survival or all-cause survival (Figure 4.1 and 4.2). For breast cancer-specific survival, the probability of survival was slightly lower for those with an AD at 3, 5, and 10 years post-diagnosis (Table 4.4). For all-cause survival, those with an AD had a slightly higher probability of survival (0.89) compared to those without

an AD (0.87) 3 years post-diagnosis.

Cox models were initially run with the following covariates: race, insurance type, stage, hormone medication, chemotherapy, and radiation. When the proportional hazard assumption was tested with the variables mentioned previously, race, insurance type, stage, hormone medication, and radiation therapy violated the assumption. Both adjusted and unadjusted models were run and stratified by the variables that failed to meet the proportional hazard assumption (Table 4.6). Models were adjusted for by chemotherapy. Among African Americans, those with an AD had a 5% reduction in breast cancer mortality compared to those without an AD, while the inverse occurred for European Americans with a 11% increase in breast cancer mortality among those with an AD. This inverse association remained when controlling for chemotherapy. An inverse relationship occurred for stage as well. Compared to those without an AD, those with an AD had a reduction in breast cancer mortality when they had a carcinoma that was in-situ or local (HR: 0.89, 95% CI: 0.55, 1.44) and an increase in mortality for those with a carcinoma that was regional or distant (HR: 1.16, 95% CI: 0.91, 1.49). There was a 51% increase in breast cancer mortality among patients that did not receive radiation therapy and had an AD compared to those that did not have an AD. However, when controlling for chemotherapy there was a 17% increase in breast cancer mortality among AD patients compared to non-AD patients. There was a 9% reduction in breast cancer mortality among the AD patients that received radiation therapy compared to those non-AD patients. The bivariate adjusted and unadjusted Cox models for both insurance type and hormone medication showed an overall increase in breast cancer

mortality among patients with an AD. There was a 6% increase in breast cancer mortality among patients with an AD compared to those without an AD, and a 9% increase when controlling for chemotherapy.

Table 4.1: Autoimmune disease frequencies and ICD-9 codes.

Autoimmune Disease	ICD-9 Code[4]	Number of Patients	ICD-9 Code Reference
Addison's disease	255.4, 255.41	11 (1.39)	[35,36]
Agammaglobulinemia/ Hypogammaglobulinemia[1]	279.00, 279.06	3 (0.38)	[36,37]
Alopecia areata	704.01	12 (1.51)	[38]
Antiphospholipid syndrome	286.5, 286.9, 289.81, 795.79	110 (13.87)	[39,40]
Autoimmune hepatitis	571.42, 571.49	10 (1.26)	[35]
Behcet's disease	136.1	1 (0.13)	[41]
Bullous pemphigoid	694.5	1 (0.13)	[36]
Celiac disease	579.0	2 (0.25)	[42,43]
Chagas disease	086.0	1 (0.13)	[36]
Chronic inflammatory demyelinating polyneuropathy	357.81	1 (0.13)	[36]
Crohn's disease	555.0, 555.1, 555.2, 555.9	23 (2.90)	[42–45]
Dermatomyositis and Polymyositis	710.3	1 (0.13)	[41,46]
Discoid lupus	695.4	10 (1.26)	[43,47]
Erythema nodosum	695.2	2 (0.25)	[48]
Evan's syndrome	287.32	1 (0.13)	[36]
Fibrosing alveolitis	516.3	5 (0.63)	[49]
Giant cell arteritis	446.5	8 (1.01)	[45]
Glomerulonephritis	580.9, 581.0, 581.1, 581.9, 582.9	5 (0.63)	[35,44,50]
Grave's disease/Hyperthyroidism	242.00, 242.01	24 (3.03)	[35,41,43]
Guillain-Barre syndrome	357.81		[36]
Hashimoto's thyroiditis/Hypothyroidism	245.2	21 (2.65)	[35,41,51,43]
Hemolytic anemia	283.0		[35,36]
Henoch-Schonlein pupura	287.0	2 (0.25)	[36]
Immune thrombocytopenic purpura	287.31, 287.3, 287.30, 287.31, 287.32, 287.39	11 (1.39)	[43,47]

Interstitial cystitis	595.1	20 (2.52)	[36]
Lichens planus	697.0	10 (1.26)	[52]
Lichen sclerosus	701.0	16 (2.02)	[36]
Meniere's disease	386.0, 386.00, 386.01	9 (1.14)	[36]
Mucha-Habermann disease	696.2	1 (0.13)	[36]
Multiple sclerosis	340	13 (1.64)	[35,43–45]
Myasthenia gravis	358.00	1 (0.13)	[35,41,44]
Neutropenia	288.09	9 (1.14)	[36]
Optic neuritis	377.30	5 (0.63)	[36]
Palindromic rheumatism	719.33, 719.34, 719.35, 719.37	3 (0.38)	[48]
Pernicious anemia	281.0	36 (4.55)	[35,43,47]
Polyarteritis nodosa	446.0	2 (0.25)	[43,47]
Polymyaglia rheumatica	725	11 (1.39)	[43,46,47]
Primary biliary cirrhosis	571.6	1 (0.13)	[35,43,47]
Primary sclerosing cholangitis	576.1	1 (0.13)	[36]
Psoriasis/Psoriatic arthritis[2]	696.0, 696.1, 696.8	46 (5.82)	[37,45,53]
Raynaud's phenomenon	443.0	9 (1.14)	[48]
Retroperitoneal fibrosis	593.4	4 (0.51)	[36]
Rheumatoid arthritis	714.0, 714.1, 714.2, 714.30	82 (10.37)	[35,41,43,44,53,54]
Rheumatic fever	390, 391.0	3 (0.38)	[35,43,47]
Sarcoidosis	135	24 (3.03)	[43,47]
Scleroderma[3]	710.1, 701.0	4 (0.51	[35,41,46,43]
Sjögren's syndrome	710.2	12 (1.52)	[35,41,43,46,52]
Subacute bacterial endocarditis	421.0	1 (0.13)	[36]
Systemic lupus erythematosus	710.0	22 (2.78)	[35,41,43,46]
Type I diabetes mellitus	250.01, 250.03	126 (15.93)	[35,45]
Ulcerative colitis	556.0, 556.2, 556.3, 556.5, 556.6, 556.9	21 (2.65)	[42–45,47]
Uveitis	364.00, 364.01, 364.3, 360.11	23 (2.91)	[35,36,41]
Vitiligo	709.01	4 (0.51)	[35]
Wegner's granulomatosis	446.4	1 (0.13)	[50,47]

[1]Agammaglobulinemia and hypogammaglobulinemia were placed in the same category since the same ICD-9 code is used for both diseases

[2]Psoriasis and Psoriatic arthritis were placed in the same category since the same ICD-9 code is used for both diseases

[3]This includes both systemic sclerosis and localized scleroderma

[4]All ICD-9 codes that were included in this table were only the codes that were present in this study, the other codes not included in this table that were present in the study were for those ADs that were not yet classified (ICD-9 Codes: 710.8, 710.9)

Table 4.2: Baseline patient, tumor, and treatment characteristics of breast cancer patients with and without an AD.

	Patients with AD (n=629)	Patients without AD (n=2657)	p-value[1]
Patient Characteristics			
Age at diagnosis	52.05 ± 6.55	50.14 ± 7.83	**<.0001**
Race			
African American	228 (20.73)	872 (79.27)	0.1013
Caucasian	401 (18.34)	1785 (81.66)	
Geographic location			
Urban	479 (19.38)	1992 (80.62)	0.5375
Rural	150 (18.40)	665 (81.60)	
Insurance			
Type I	417 (20.41)	1626 (79.59)	**0.0177**
Type II	212 (17.06)	1031 (82.94)	
Year of Diagnosis			
2002-2004	175 (17.61)	819 (82.39)	0.3357
2005-2007	203 (19.90)	817 (80.10)	
2008-2010	251 (19.73)	1021 (80.27)	
Tumor Characteristics			
Histological Grade			
I	93 (19.02)	396 (80.98)	0.3975
II and III	471 (19.42)	1954 (80.58)	
IV	7 (12.28)	50 (87.72)	
Missing	58	257	
Estrogen Receptor Status			
ER+	236 (18.88)	1014 (81.12)	0.2265
ER-	119 (21.33)	439 (78.67)	
Missing	274	1204	
Progesterone Receptor Status			
PR+	196 (18.33)	873 (81.67)	0.1111
PR-	156 (21.37)	574 (78.63)	
Missing	277	1210	
Hormone Receptor Status			
ER+/PR+	183 (17.91)	839 (82.09)	0.1022
ER+/PR-	49 (22.90)	165 (77.10)	
ER-/PR+	13 (28.89)	32 (71.11)	
ER-/PR-	106 (20.70)	406 (79.30)	
Missing	278	1215	
Stage			
In-situ	101 (18.20)	454 (81.80)	0.4744
Local	275 (19.70)	1121 (80.30)	
Regional	220 (19.75)	894 (80.25)	

Distant	28 (15.38)	154 (84.62)	
Missing	5	34	
Tumor Size			
≤2cm	212 (19.78)	860 (80.22)	0.8498
>2cm-5cm	143 (20.40)	558 (79.60)	
>5cm	36 (21.56)	131 (78.44)	
Missing	238	1108	
Lymph Node Status			
Positive	316 (19.73)	1286 (80.27)	0.8364
Negative	188 (20.06)	749 (79.94)	
Missing	125	662	
Treatment Characteristics			
Hormone Therapy			
Yes	386 (19.36)	1608 (80.64)	0.6955
No	243 (18.81)	1049 (81.19)	
Chemotherapy			
Yes	301 (19.16)	1270 (80.84)	0.9759
No	308 (19.20)	1296 (80.80)	
Missing	20	91	
Radiation Therapy			
Yes	268 (18.95)	1146 (81.05)	0.7698
No	352 (19.36)	1466 (80.64)	
Missing	9	45	

[1]P-values were calculated using a t-test for continuous variables (the corresponding mean and standard errors were reported), and a chi-square test for categorical variables (the corresponding frequencies and row percentages were reported)
Abbreviations used: ER (estrogen), PR (progesterone), AD (autoimmune disease)

Table 4.3: Cause of death among those with and without an AD.

Cause of death	Patients with AD (n=629)	Patients without AD (n=2657)	p-value[1]
Alive	493 (18.62)	2154 (81.38)	**0.0209**
Breast	100 (19.49)	413 (80.51)	
Other	36 (28.57)	90 (71.43)	

[1]P-values were calculated using chi-square test (the corresponding frequencies and row percentages were reported)
Abbreviations used: AD (autoimmune disease)

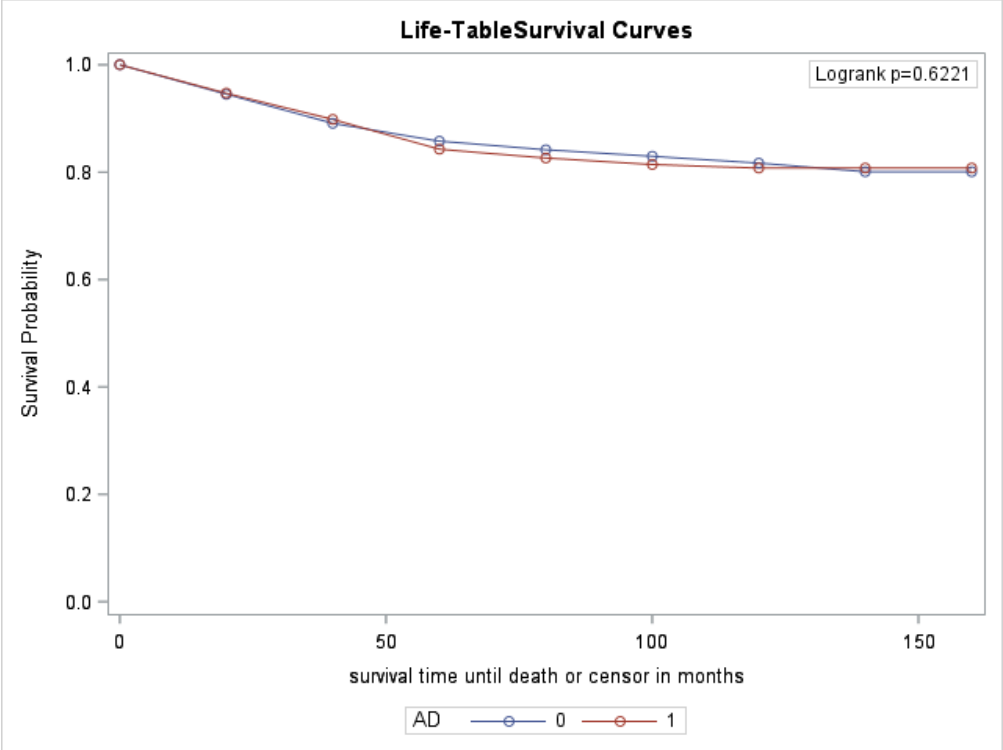

Figure 4.1: Breast cancer specific survival for those diagnosed with at least one AD (indicated by the red line) and those without an AD (indicated by the blue line).

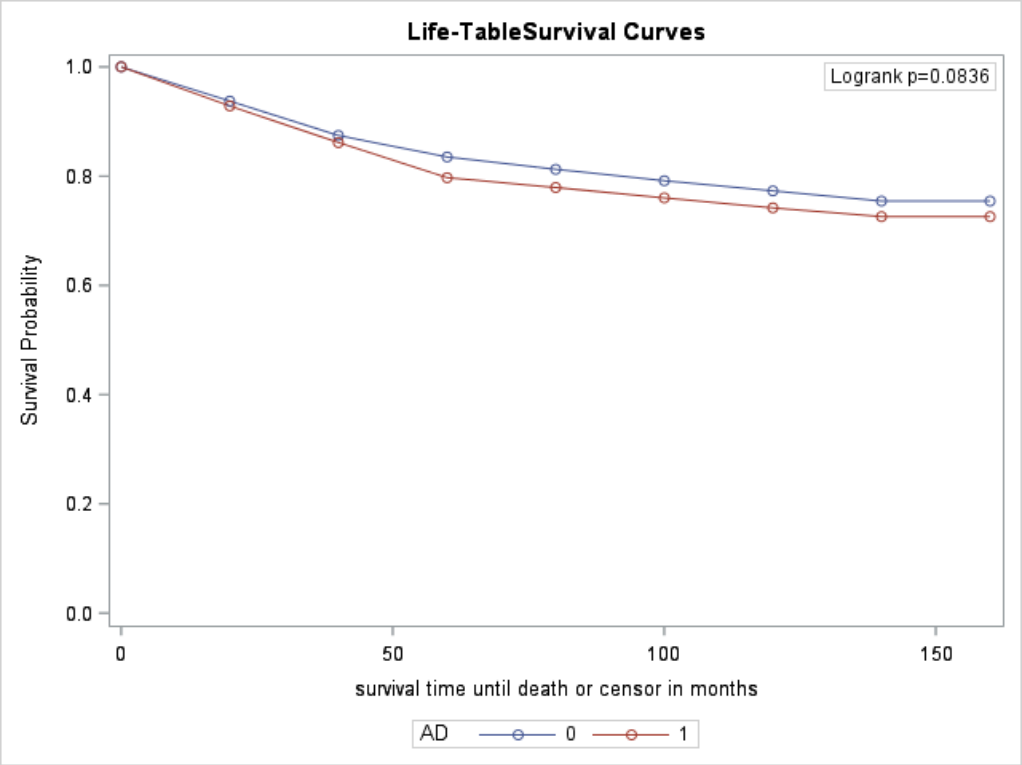

Figure 4.2: All cause survival for those with at least one AD (indicated by the red line) and those without an AD (indicated by the blue line).

Table 4.4: Three, five, and ten-year survival comparison among those with and without an AD.

	All Cause Survival		Breast Cancer Specific Survival	
AD Status by Timepoint	Probability of Survival	p-value[1]	Probability of Survival	p-value[1]
Year 3				
AD	0.8855	0.2811	0.9011	0.8763
No AD	0.8712		0.9009	
Year 5				
AD	0.7998	**0.0391**	0.8449	0.4728
No AD	0.8371		0.8594	
Year 10				
AD	0.7442	0.0825	0.8108	0.5677
No AD	0.7742		0.8190	

[1] P-values were calculated using the log rank test
Abbreviations used: AD (autoimmune disease)

Table 4.5: Cox model for breast cancer specific mortality among those with and without an AD.

AD status (sample size)	Number of deaths	Unadjusted analysis		Multivariable analysis[1]	
		HR	95% CI	HR	95% CI
No AD (2657)	503	1.0 (referent)		1.0 (referent)	
AD (629)	136	1.06	0.85, 1.32	1.09	0.88, 1.36

[1]Adjusted for chemotherapy

Abbreviations used: AD (autoimmune disease), HR (hazard ratio), CI (confidence interval)

Table 4.6: Bivariate Cox model for breast cancer specific mortality among those with and without an AD.

Stratum variables by AD status (sample size)	Number of deaths	Unadjusted analysis		Multivariable analysis[1]	
		HR	95% CI	HR	95% CI
Race					
African American					
No AD (872)	238	1.0 (referent)		1.0 (referent)	
AD (228)	63	0.949	0.69, 1.30	0.99	0.72, 1.35
European American					
No AD (1785)	265	1.0 (referent)		1.0 (referent)	
AD (401)	73	1.11	0.82, 1.50	1.14	0.83, 1.55
Insurance					
Type I					
No AD (1626)	158	1.0 (referent)		1.0 (referent)	
AD (417)	50	1.22	0.85, 1.74	1.27	0.89, 1.82
Type II					
No AD (1031)	345	1.0 (referent)		1.0 (referent)	
AD (212)	86	1.12	0.85, 1.47	1.14	0.86, 1.51
Stage					
In-situ and local					
No AD (1626)	140	1.0 (referent)		1.0 (referent)	
AD (389)	42	0.89	0.55, 1.44	0.90	0.55, 1.47
Regional and distant					
No AD (997)	349	1.0 (referent)		1.0 (referent)	
AD (235)	93	1.16	0.91, 1.49	1.19	0.93, 1.53

Hormone medication					
Yes					
No AD (1608)	220	1.0 (referent)		1.0 (referent)	
AD (386)	63	1.11	0.80, 1.54	1.14	0.82, 1.59
No					
No AD (1049)	283	1.0 (referent)		1.0 (referent)	
AD (243)	73	1.03	0.77, 1.39	1.09	0.81, 1.48
Radiation therapy					
Yes					
No AD (1146)	186	1.0 (referent)		1.0 (referent)	
AD (268)	43	0.91	0.62, 1.33	0.97	0.67, 1.42
No					
No AD (1466)	311	1.0 (referent)		1.0 (referent)	
AD (352)	91	1.51	0.88, 1.51	1.17	0.89, 1.54

[1]Adjusted for chemotherapy
Abbreviations used: AD (autoimmune disease), HR (hazard ratio), CI (confidence interval)

4.2 Secondary outcome

Among the Th1, Th2 dominant AD, and no AD cohorts breast cancer-specific survival was statistically significant (Figure 4.7). The probability of survival was greater among the Th1 group compared to the other two groups at all three-time points (Table 4.8). Compared to those without an AD those with a Th2 dominant AD also had a higher probability of breast cancer-specific survival. All-cause survival was not statistically significant (Figure 4.3), but at 3-years post-diagnosis that was a significant difference between the cohorts, with the same pattern that was seen for breast cancer-specific survival. However, at year 10 those that were in the Th2 cohort had a lower probability survival than those that did not have an AD.

Cox models were used to determine the risk of breast cancer mortality among the three groups. Models were stratified by race, insurance, stage, and hormone medication due to the time dependence that is associated with these variables. Adjusted models controlled for both chemotherapy and radiation therapy. There was a significant reduction in breast cancer mortality for both for those with a Th1 AD compared to those without an AD (HR: 0.46, 95% CI: 0.25, 0.87). This relationship remained significant when controlling for both chemotherapy and radiation therapy with a 55% reduction in breast cancer mortality. A reduction in breast cancer mortality was also seen for both the adjusted and unadjusted Cox models for those patients with a Th2 dominant AD, however results were not significant. Among those with breast carcinoma that was either regional or distant, there was a significant reduction in breast cancer mortality in both the unadjusted and adjusted Cox models when comparing those patients with a Th1 AD to those without an AD with a HR of 0.46 (95% CI: 0.23, 0.92) and 0.44 (95% CI: 0.21, 0.93), respectively. However, those with a Th2 AD had an increase in breast cancer mortality for both the unadjusted and adjusted Cox models among patients with a breast carcinoma that was either regional or distant.

Table 4.7: Cause of death among those with a Th1 dominant and Th2 dominant AD

and those without an AD.				
Cause of death	Patients with a Th1 AD (n = 136)	Patients with a Th2 AD (n = 53)	Patients without an AD (n = 2657)	p-value[1]
Alive	121 (5.22)	42 (1.81)	2154 (92.97)	**0.0128**
Breast	10 (2.33)	6 (1.40)	413 (96.27)	
Other	5 (5.00)	5 (5.00)	90 (90.00)	

[1]P-values were calculated using chi-square test (the corresponding frequencies and row percentages were reported)
Abbreviations used: AD (autoimmune disease), Th1 (T-helper 1), Th2 (T-helper 2)

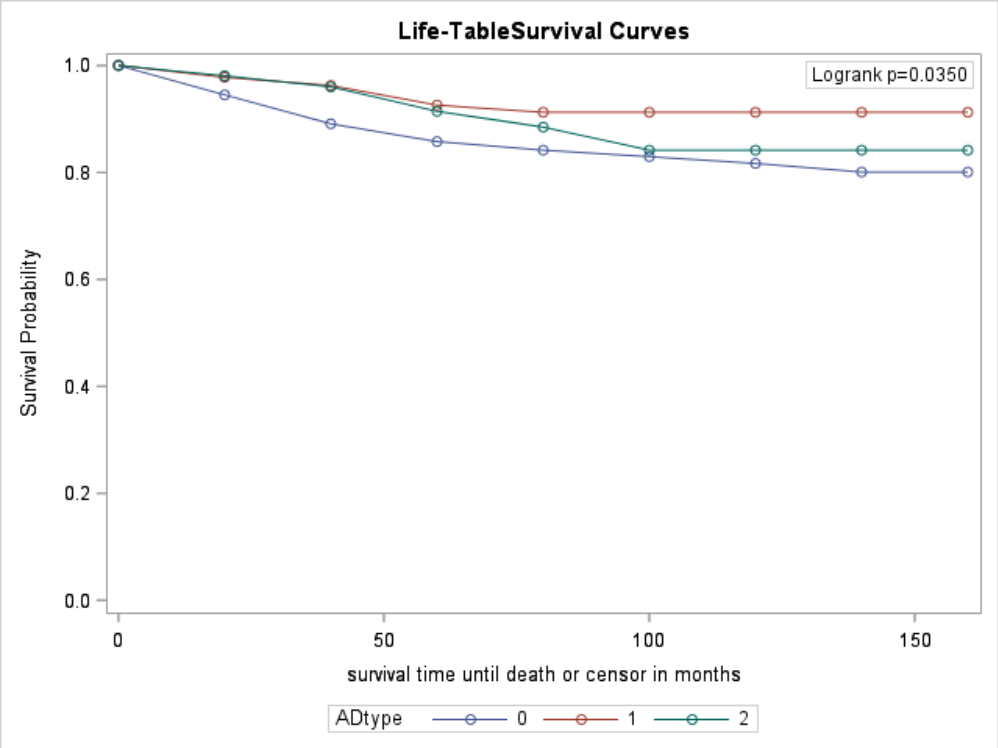

Figure 4.3: Breast cancer specific survival for those diagnosed with Th1 dominant AD (indicated by the red line), Th2 dominant AD (indicated by the green line), and no AD (indicated by the blue line).

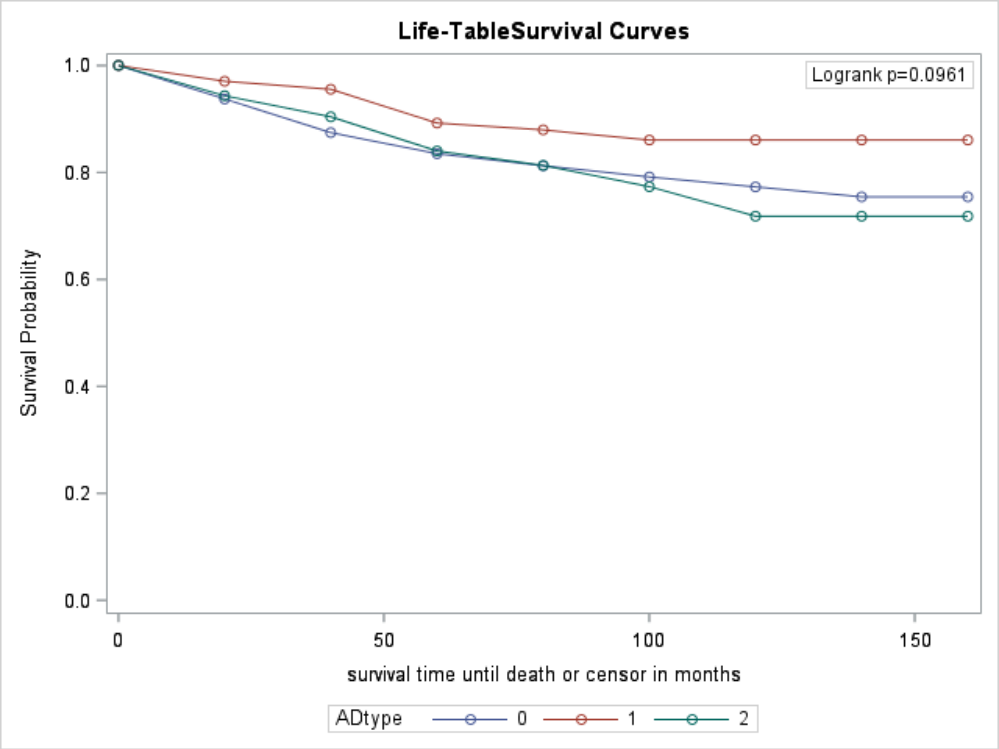

Figure 4.4: All cause survival for those diagnosed with Th1 dominant AD (indicated by the red line), Th2 dominant AD (indicated by the green line), and no AD (indicated by the blue line).

Table 4.8: Three, five, and ten-year survival comparison among those with a Th1 dominant and Th2 dominant AD and those without an AD.

	All Cause Survival		Breast Cancer Specific Survival	
AD Status by Timepoint	Probability of Survival	p-value[1]	Probability of Survival	p-value[1]
Year 3				
Th1 AD	0.9559	**0.0344**	0.9630	**0.0197**
Th2 AD	0.9245		0.9612	
No AD	0.8855		0.9009	
Year 5				
Th1 AD	0.8946	0.1466	0.9260	**0.0358**
Th2 AD	0.8417		0.9170	
No AD	0.8371		0.8594	
Year 10				
Th1 AD	0.8593	0.0999	0.9142	**0.0378**
Th2 AD	0.7156		0.8420	
No AD	0.7742		0.8190	

[1] All p-values were determined by the log rank test

Abbreviations used: AD (autoimmune disease), Th1 (T-helper 1), Th2 (T-helper 2)

Table 4.9: Cox model breast cancer specific mortality among those with a Th1 dominant and Th2 dominant AD and those without an AD.

AD status (sample size)	Number of deaths	Unadjusted analysis		Multivariable analysis[1]	
		HR	95% CI	HR	95% CI
No AD (2657)	503	1.0 (referent)		1.0 (referent)	
Th1 AD (136)	15	0.46	**0.25, 0.87**	0.45	**0.23, 0.87**
Th2 AD (53)	11	0.70	0.31, 1.58	0.71	0.32, 1.60

[1]Adjusted for chemotherapy and radiation therapy
Abbreviations used: AD (autoimmune disease), Th1 (T-helper 1), Th2 (T-helper 2), HR (hazard ratio), CI (confidence interval)

Table 4.10: Bivariate Cox model for breast cancer specific mortality among those with a Th1 dominant and Th2 dominant AD and those without an AD.

Stratum variables by AD status (sample size)	Number of deaths	Unadjusted analysis		Multivariable analysis[1]	
		HR	95% CI	HR	95% CI
Race					
African American					
No AD (872)	238	1.0 (referent)		1.0 (referent)	
Th1 AD (47)	6	0.45	0.19, 1.09	0.48	0.20, 1.17
Th2 AD (20)	4	0.39	0.10, 1.58	0.34	0.08, 1.37
European American					
No AD (1785)	265	1.0 (referent)		1.0 (referent)	
AD (89)	9	0.46	0.19, 1.12	0.40	0.15, 1.08
Th2 AD (33)	7	1.02	0.38, 2.75	1.18	0.44, 3.18
Insurance					
Type I					
No AD (1626)	158	1.0 (referent)		1.0 (referent)	
Th1 AD (97)	7	0.66	0.27, 1.61	0.70	0.29, 1.71
Th2 AD (34)	3	0.70	0.17, 2.83	0.70	0.17, 2.83
Type II					
No AD (1031)	345	1.0 (referent)		1.0 (referent)	
Th1 AD (39)	8	0.45	0.19, 1.09	0.40	0.15, 1.08
Th2 AD (19)	8	0.75	0.28, 2.02	0.76	0.28, 2.04
Stage					

In-situ and local					
No AD (1575)	121	1.0 (referent)		1.0 (referent)	
Th1 AD (82)	5	0.49	0.12, 2.00	0.50	0.12, 2.04
Th2 AD (39)	5	0.51	0.07, 3.69	0.48	0.07, 3.46
Regional and distant					
No AD (1048)	368	1.0 (referent)		1.0 (referent)	
Th1 AD (53)	10	0.46	**0.23, 0.92**	0.44	**0.21, 0.93**
Th2 AD (14)	6	1.09	0.45, 2.63	1.07	0.44, 2.60
Hormone medication					
Yes					
No AD (1608)	220	1.0 (referent)		1.0 (referent)	
Th1 AD (84)	6	0.33	0.11, 1.03	0.33	0.11, 1.03
Th2 AD (29)	4	0.61	0.15, 2.46	0.55	0.14, 2.21
No					
No AD (1049)	283	1.0 (referent)		1.0 (referent)	
Th1 AD (52)	9	0.57	0.27, 1.20	0.61	0.27, 1.38
Th2 AD (24)	7	0.69	0.26, 1.84	0.90	0.34, 2.43

[1]Adjusted for chemotherapy and radiation therapy

Abbreviations used: AD (autoimmune disease), Th1 (T-helper 1), Th2 (T-helper 2), HR (hazard ratio), CI (confidence interval)

Chapter 5
Discussion

Our study found that there was a significant difference in breast cancer-specific survival among those with a Th1 dominant AD versus those without an AD diagnosis. This research suggests that the Th1 immune response that is associated with the Th1 dominant ADs may play a protective role for breast cancer mortality. This study was the first of its kind to analyze the association between breast cancer survival and the hypothesized Th1 and Th2 dominant ADs.

An autoimmune disease occurs when B cells develop antibodies to the body's organs and/or tissues, resulting in an attack on the body's otherwise healthy organs and tissues[10]. The T helper cells, Th1 and Th2, coordinate and direct the B cells. The Th1 cytokines enhance the antitumor immune response through the secretion of IFN-γ, causing the anti-tumor directed B cell factors and the CD8+ T cells to all work together to "favor tumor rejection"[4]. In contrast, the Th2 cytokines secrete pro-growth factors which ultimately decrease the CD8+ T lymphocytes, resulting in tumor promotion[4]. This biological plausibility aligns with the results of this study, showing that the Th1 dominant ADs, Crohn's disease, Hashimoto's thyroiditis, Multiple Sclerosis, Psoriasis, Sjögren's syndrome, Rheumatoid arthritis, Type I diabetes mellitus, and Uveitis, collectively play a protective role in reducing breast cancer mortality. The conclusions

of this study are consistent with that of other studies. A study conducted by Campbell and colleagues analyzed the peripheral blood lymphocytes of 84 breast cancer patients and 26 healthy controls, and found that Th1 cytokines were significantly lower in breast cancer patients prior to treatment compared to the healthy controls[21]. An additional study conducted on over 12,000 breast cancer patients in the United Kingdom and Canada found that among the women with estrogen receptor negative tumors, the presence of CD8+ T cells within the tumor, a response that is linked with an increase in Th1 cytokines, was significantly associated with a 28% reduction in breast cancer mortality[20].

While there have been no studies to date looking at the association between the Th1 dominant ADs and cancer mortality, there have been a few studies that have analyzed the association that exists individually for the Th1 ADs that have been identified in this study. A cohort study conducted in Ontario, Canada identified 178,186 women with breast cancer and found that those with Hashimoto's thyroiditis had a significantly lower risk of dying compared to those that did not have an AD (HR: 0.87, 95% CI: 0.77 to 0.98)[1]. Hemminki and colleagues conducted a study in Sweden, analyzing the risk and survival of female cancers for individuals ADs, finding a significant reduction in breast cancer mortality among psoriasis patients (HR: 0.68, 95% CI: 0.50 to 0.94)[25].

Strengths of this study include the comprehensive records of each patient that encompassed the medical claims information from the Best Chance Network and the

vital status information of each individual from the SCCCR, which updates its' database using the National Death Index and the South Carolina Vital Registry. In addition, the use of both the South Carolina Employee State Health Plan and the South Carolina Medicaid Program provided a cohort of women that are racially, geographically, and socioeconomically diverse, providing strong external validity for this study. A weakness of this present study was the unavailability of data for age at menarche and menopause, oral contraception, and hormone replacement therapy, all factors that have been associated with both breast cancer and AD. Many studies have attributed a reduced risk of cancer seen among individual ADs to immunosuppressive therapy and anti-inflammatory drug therapies that are often used among AD patients[25]. Studies have suggested a link between these therapies and an earlier age at menopause, thus reducing the risk of developing breast cancer[25]. Future studies are needed to look at the potential implications that this may have on breast cancer survival.

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