Prevention of Trastuzumab and Anthracycline-Induced Cardiotoxicity Using Angiotensin-Converting Enzyme Inhibitors or Beta-Blockers in Breast Cancer Patients

by

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Abstract

Objectives: The purpose of this study was aimed to1) examine treatment patterns of anti-neoplastic agents prescribed to breast cancer patients, 2) estimate the incidence of and identify factors associated with adjuvant chemotherapy-induced cardiotoxicity and all-cause mortality among breast cancer patients, and 3) compare the effect of angiotensin-converting enzyme inhibitors and/or β blockers (ACEIs/BBs) in prevention of trastuzumab- and anthracycline-induced cardiotoxicity and all-cause mortality.

Methods: A retrospective cross-sectional analysis using the 2006-2010 National Ambulatory Medical Care Survey (NAMCS) data was conducted for aim 1. Breast cancer treatments were categorized. A visit-level descriptive analysis estimated national prescribing trends and multiple logistic regression analyses identified factors associated with anti-neoplastic agent used. Two population-based cohort studies of women newly diagnosed with breast cancer were conducted for aim 2 and 3, using the 2000-2010 Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database. Adjuvant chemotherapy was classified and ACEIs/BBs exposure group was defined as a filled prescription before/after the initiation of trastuzumab/anthracyclines. Cumulative rates of cardiotoxicity and all-cause mortality were estimated and Cox models and/or marginal structural models were used to determine factors associated with cardiotoxicity

and all-cause mortality adjusting for baseline covariates and time-dependent variable, respectively.

Results: The proportion of visits in which anti-neoplastic agents were documented remained stable over time. Factors including patient socio-demographics, types of insurance, and cancer stage were associated with types of breast cancer treatment. Next, compared with hormones, risk of cardiotoxicity was higher in patients treated with adjuvant anthracycline and trastuzumab-based, trastuzumab-based, and anthracycline-based regimens, respectively. Risk of all-cause mortality was higher in patients treated with taxane-based regimens compared with hormones. Further, the ACEIs/BBs exposure group had lower risk of cardiotoxicity and all-cause mortality compared to the non-exposed group. Baseline characteristics, including socio-demographics, tumor characteristics, comorbidity, and concomitant treatment were associated with an elevated risk of all-cause mortality and/or cardiotoxicity (all $P<0.05$)

Conclusions: Anti-neoplastic treatment patterns differ among breast cancer patients treated in ambulatory settings. Among breast cancer patients undergoing adjuvant chemotherapy, those treated with trastuzumab-based/anthracycline-based regimens had increased cardiotoxicity risk compared with hormones. An initiation of ACEIs/BBs in those received adjuvant trastuzumab/anthracyclines may prevent cardiotoxicity and improve survival.

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ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin-receptor blockers
β-blockers	Beta-blockers
CCBs	Calcium channel blockers
CI	Confidence interval
CM	Cardiomyopathy
ER	Estrogen receptor
HER2 receptor	Human epidermal growth factor type 2 receptor
HF	Heart failure
HR	Hazard ratio
NAMCS/NHAMCS	the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS)
OR	Odds ratio
RR	Relative risk
SEER-Medicare	the Surveillance, Epidemiology, and End Results (SEER) Medicare data
USCS	the United States Cancer Statistics

Chapter 1

Introduction

Overview

According to the American Cancer Society, breast cancer is the most common cancer among women in the United States and remains the second leading cause of cancer death among women regardless of race and ethnicity.[1,2] The United States Cancer Statistics (USCS) reported that the incidence of female breast cancer was 123.1 per 100,000 women, accounting for 205,974 female breast cancers in 2009. In 2015, the incidence is expected to be higher than 2009. To be specific, an estimate of 231,840 women with new diagnoses is expected to occur, accounting for 28.61% of all new cancer cases among women.[1] Generally, the 5-year relative survival rate of women with breast cancer has improved over the last 30 years. Specifically, recent statistics from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics have reported that the overall 5-year relative survival rate was 75.2 % in 1975, compared with 90.5 % in 2005.[1,2]

Improvements in breast cancer survival and declines in breast cancer mortality have also come with substantial cost. In fact, national cancer care expenditures were highest for female breast cancer, accounting for $16.50 billion in 2010.[3] Further, in 2020 total expenditures for breast cancer care are projected to reach approximately $20.50 billion.[3] On an individual level, the estimates of lifetime per-patient costs of breast cancer ranged from $US20,000 to $US100,000.[4] Further, indirect costs, including losses in time and

productivity also contribute to the economic burden of breast cancer. In 2010, indirect costs of breast cancer ranked among the top three most expensive cancers and were estimated to be $10.9 billion, accounting for approximately 9% of the total present value of lifetime earning lost.[5]

Generally, breast cancer therapy may be 1) local (i.e., surgery or radiation therapy) and/or 2) systemic (i.e., chemotherapy). Treatment selection and prognosis are influenced by certain predictive factors, for instance, stage of disease, presence of human epidermal growth factor type 2 receptor (HER2/neu) overexpression, and patient characteristics. [1,6,7] The use of systemic therapy is recommended for breast cancer patients if the adverse effects of systemic therapy are outweighed by the benefits of treatment for breast cancer. That is, reducing the risk of recurrence and increasing survival. In general, systemic therapy for breast cancer, including chemotherapy, hormone, and targeted therapy, may be administered orally or intravenously before or after local therapy. As of more recent years, breast cancer patients treated with systemic therapy do not have to be admitted to the hospital because certain treatments may be administered in physician's offices or outpatient hospital settings.

Substantial evidence supports the benefits of breast cancer treatment, but there is some concern regarding treatment disparities which might affect long-term outcomes and eventually patient survival.[8,9] In response to this concern, there were some population-based studies examining breast cancer treatment patterns. However, recently most of the studies were based on cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) Medicare databases which focused on breast cancer patients who are older than 65 years of age and have Medicare insurance.[9,10] Consequently, there is a

current knowledge gap in evaluating treatment patterns and factors associated with treatment using data which are representative across different population groups. Additionally, despite the shift in chemotherapy administration from hospital settings to ambulatory settings, little is known about patterns of and factors-related to breast cancer treatment in ambulatory settings. This information may help improve access to care as well as the quality of care for the U.S. populations.

Although evidence indicates improvements in outcomes of breast cancer treatment over the last two decades, this favorable effect of anti-neoplastic agents was also associated with adverse effects or toxicities, particularly, uncommon but serious chemotherapy-induced cardiotoxicity. Chemotherapy-induced cardiotoxicity, especially with anthracyclines and trastuzumab, has become increasingly recognized since a report of doxorubicin-induced heart failure in 1967.[11,12] Multiple studies have suggested that anthracyclines are a class of conventional chemotherapy agents most likely to be associated with cardiotoxicity.[12,13] The incidence of anthracycline-induced cardiotoxicity (e.g., symptomatic congestive heart failure) ranges between 0.9%-48%.[12] Likewise, trastuzumab, a novel agent, has been reported to be associated with an incidence of cardiac dysfunction between 0.5-34%.[14-16]

Cardiotoxicity such as heart failure in cancer patients may cause serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis.[17] This cardiac adverse event may compromise the clinical effectiveness of chemotherapy and eventually lead to premature death.[17-19] Although cardiac function may be recovered after withholding chemotherapy, it is important to note that patients with a history of chemotherapy-induced cardiotoxicity are more likely

to develop further decline in cardiac function when being exposed to more cycles of chemotherapy.[20,21] Consequently, prevention of chemotherapy-induced cardiotoxicity may be beneficial for cancer patients.

To date, there is no specific guideline to manage cancer therapy-related cardiotoxicity. Nevertheless, a number of clinical practice guidelines, meta-analyses, and systematic reviews have supported the benefit of angiotensin-converting enzyme inhibitors (ACEIs) or β-blockers (BBs) in patients with chemotherapy-induced cardiotoxicity.[12,16,22-30] Indeed, ACEIs and BBs appear to be associated with long-term improvement in left ventricular systolic function by reducing ventricular remodeling.[26-28,31-33] This may eventually delay or slow clinical progression to heart failure in patients undergoing chemotherapy.[26,28,33] Therefore, using ACEIs and/or BBs as a prophylactic or concurrent regimen in breast cancer patients treated with trastuzumab and/or anthracycline therapy may be beneficial in the prevention of cardiotoxicity. However, available evidence to support the potential benefits of using ACEIs and/or BBs in prevention of cardiotoxicity is currently insufficient, particularly using real world data. Consequently, research investigating the effect of ACEIs and/or BBs in prevention of trastuzumab- and/or anthracycline- induced cardiotoxicity is needed and should provide essential information in this high-risk breast cancer population.

Overall Objective

This study examined treatment patterns of anti-neoplastic agents prescribed to breast cancer patients, estimated the incidence of and identify factors associated with trastuzumab and/or anthracycline-induced cardiotoxicity and all-cause mortality among breast cancer patients, and compared the effect of ACEIs and/or BBs in prevention of

trastuzumab and anthracycline-induced cardiotoxicity and all-cause mortality. The underlying hypothesis of the proposed study was that breast cancer patients who were exposed to ACEIs and/or BBs (i.e., ACEI/BB users) during or before trastuzumab and/or anthracycline therapy have a lower incidence of cardiotoxicity compared with breast cancer patients who were unexposed to ACEIs and/or BBs (i.e., ACEI/BB nonusers).

Specific Aims

1. **To examine treatment patterns of anti-neoplastic agents prescribed to nationally representative breast cancer patients and identify factors associated with the anti-neoplastic agents prescribed in ambulatory care settings.**

This aim examined treatment patterns of use of anti-neoplastic agents for patients with breast cancer using the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), nationally representative surveys designed to provide information about the provision and use of medical care services in ambulatory settings. Treatment patterns for anti-neoplastic agents among breast cancer patients were examined across patient demographic characteristics, health insurance, and care setting, with the goal of understanding treatment trends and identifying possible disparities.

2. **To estimate the incidence of and identify factors associated with cardiotoxicity and all-cause mortality in breast cancer patients.**

We defined trastuzumab- and/or anthracycline- induced cardiotoxicity based on the definition given by the Cardiac Review and Evaluation Committee (CRCE), including cardiomyopathy (CM), symptoms of heart failure (HF), and associated signs of HF.[31,34] We examined the overall incidence of trastuzumab- and/or anthracycline-induced

cardiotoxicity and all-cause mortality by quantifying the incidence of cardiotoxicity, defined as heart failure (HF) and cardiomyopathy (CM), and all-cause mortality among patients undergoing trastuzumab and/or anthracyclines, taxane-based, and other adjuvant chemotherapy and those with other treatments (defined as those who were prescribed hormonal therapy). Then we identified factors associated with cardiotoxicity or all-cause mortality, which included 1) factors related to chemotherapeutic therapies, such as concomitant chemotherapy and radiation; and 2) factors related to patients, such as age, race/ethnicity, socioeconomic status, presence of comorbidity (e.g., cardiovascular risk factors and cardiovascular disease), and surgery.

3. **To compare the effect of ACEIs and/or BBs in prevention of trastuzumab- and anthracycline-induced cardiotoxicity in breast cancer patients.**

For breast cancer patients treated with trastuzumab and/or anthracyclines therapy, we compared the incidence of cardiotoxicity and all-cause mortality between ACEI/BB users (defined as patients who were prescribed ACEIs and/or BBs before/after the initiation of trastuzumab and/or anthracyclines therapy) and ACEI/BB nonusers (defined as patients who were never prescribed ACEIs/BBs). We treated ACEI/BB as a primary predictor of interest and also examined baseline covariates, including demographics, tumor characteristic, socioeconomics, breast cancer treatment (e.g., concomitant chemotherapy, radiation, surgery), presence of comorbidity (e.g., cardiovascular risk factors and cardiovascular disease), ACEIs/BBs treatment dosage and duration, and other antihypertensive medications, to identify the relationship between these factors with development of cardiotoxicity and all-cause mortality in breast cancer patients. Additionally, we also adjusted for a time-dependent confounder which is use of

trastuzumab and/or anthracycline to produce unbiased estimates of the treatment effect of ACEIs/BBs on prevention of cardiotoxicity. This is because use of trastuzumab and/or anthracyclines may simultaneously influence cardiotoxicity events and current ACEIs/BBs treatment. In turn, they can also be influenced by past ACEIs/BBs treatment history.

Importance of Proposed Research Plan

Although there were some population-based studies examining breast cancer treatment patterns, there is a current knowledge gap in evaluating treatment patterns and factors associated with treatment using data which are representative across different population groups, characteristic of health care settings or geographical location. Additionally, despite the shift in chemotherapy administration from hospital settings to ambulatory settings, little is known about patterns of and factors-related to breast cancer treatment in ambulatory settings.

Further, despite the fact that evidence supports the role of ACEIs and BBs in preservation of cardiac function in chemotherapy-induced cardiotoxicity, few studies have examined the benefits of ACEIs and/or BBs as a prophylactic agent in breast cancer patients who undergo chemotherapy. Also, while the existing studies focused on clinical settings or standardized conditions, none of them were conducted using real-world population-based data. Additionally, due to the inherent nature of clinical trials, limited sample sizes may make it difficult to generalize to real-world setting. For example, those patients at greater risk of some clinical conditions (e.g., inadequate creatinine clearance) are less likely to be treated.

Consequently, research using real world data to investigate breast cancer treatment patterns based on characteristic of the health system and the effect of ACEIs and/or BBs in prevention of trastuzumab- and anthracycline- induced cardiotoxicity is needed and may help improve access to care, the quality of care for U.S. populations as well as provide additional information in this high-risk breast cancer population.

We performed analyses of encounter-based survey and population-based data which reflect the real-world data. The information gained from real world data may provide a more reliable estimate of breast cancer treatment pattern in the U.S. as well as the risk associated with chemotherapy-induced cardiotoxicity and the effect of ACEIs/BBs therapy in preventing cardiotoxicity in breast cancer patients receiving chemotherapy. Also, it covers a large population over a period of time which may generalize to the U.S population. First, we used national survey data (the NAMCS and NHAMCS) to examine treatment patterns of anti-neoplastic agents prescribed to breast cancer patients. Then we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare data to estimate incidence of and identify factors associated with cardiotoxicity and all-cause mortality among breast cancer patients who underwent chemotherapy. Finally, we used the SEER-Medicare data to compare the effect of ACEIs and/or BBs in prevention of trastuzumab- and anthracycline-induced cardiotoxicity and all-cause mortality.

The findings obtained through this study may make a valuable contribution to clinical practice, public health, and care of cancer patients. First, findings fill the knowledge gap for research on breast cancer treatment access and disparities among a nationally representative sample. Our results also estimated incidence of and identify factors associated with cardiotoxicity and all-cause mortality, which may help

oncologists target patients at high-risk for these adverse outcomes. Additionally, our findings also yield information for clinical practice on the effectiveness of ACEIs and BBs in preventing chemotherapy-induced cardiotoxicity. As a result, oncologists may have sufficient evidence about appropriate disease management in order to maximize the benefit of chemotherapy with the total dose that can safely be administered as well as minimize this cardiovascular adverse effect. With regards to public health, results gained from this study could improve prevention of cardiotoxicity and help reduce burden of cancer and heart disease, which are the two most common leading causes of death among female Americans. In fact, the evidence shows that the probability of mortality from cardiovascular disease, particularly heart disease, was significantly higher than that for breast cancer itself.[35] In terms of cancer patients, preventing chemotherapy-therapy induced cardiotoxicity would allow more breast cancer patients to successfully complete their chemotherapy cycles while decreasing delays, dose reductions, or discontinuation of the ongoing therapy. Completion of chemotherapy cycles with adequate dose may improve breast cancer treatment outcomes.[18,19]

Chapter 2

Background and Rationale

Breast Cancer: Burden and Trends in the United States

According to the American Cancer Society, breast cancer is the most common cancer among women in the United States.[1] An estimated one in eight women born today will be diagnosed with breast cancer during their lifetime, based on data from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics.[2] In 2006-2010, the median age at diagnosis and at death for breast cancer was 61 and 68 years of age, respectively.[2] The incidence rate decreased by 7% between 2002 and 2003 due to decline in hormone therapy utilization.[36,37] Nevertheless, recent evidence shows that overall breast cancer incidence rates did not change over the time period of 2005-2009.[1] The United States Cancer Statistics (USCS) reported that the incidence of female breast cancer was 123.1 per 100,000 women, accounting for 205,974 female breast cancers in 2009. Particularly, the incidence of late-stage (e.g., regional or distant cancer stage) breast cancer was greatest among African-American women.[38] In 2014, an estimate of 232,670 women are expected to have new diagnoses, accounting for 29% of all new cancer cases among women.[1]

Although breast cancer mortality rates have decreased over the last 20 years, it remains the second leading cause of cancer death among women (after lung cancer)

regardless of races and ethnicities.[1,39] The decline in mortality rate of women with breast cancer is attributable to improvement in earlier detection and treatment.[1] Further, data from the National Vital Statistics System (NVSS) show that the age-adjusted mortality rate of women with breast cancer in 2009 was 22.2 deaths per 100,000. Among women of all races, African-American women had the highest mortality rate (30.5 death per 100,000).[40] Approximately 39,620 breast cancer deaths are expected to occur among women in 2013, accounting for 14% of death for all cancer sites among women.[1]

Breast cancer risk factors include female gender, older age, family history of breast cancer at young age, early menarche, late menopause, older age at first live childbirth, high-dose radiation, recent use of oral contraceptives, prolonged hormone replacement therapy, benign breast cancer, and increased mammographic breast density.[1,41] Modifiable risk factors include being overweight or obese, physical inactivity, and alcohol consumption.[1] In addition to family history, inherited genetic mutations are responsible for approximately 5-10% and 4-40% of all female and male breast cancer.[1] These include mutations mostly in breast cancer susceptibility gene (BRCA)1 and BRCA2 genes.[1]

Generally, the 5-year relative survival rate of women with breast cancer has improved over time, from 75.2 % in 1975 to 90.5 % in 2005.[1,2] Recent statistics from 18 SEER graphic areas have reported that the overall 5-year relative survival for 2003-2009 was 89.2%, with 90.4% in Caucasian American women and 78.7% in African American women.[2] Survival rates also vary among stages. For instance, the 5-year relative survival for female breast cancer patients diagnosed with localized stage (i.e., confined to primary

site) is 98.6%, compared with only a 24.3% 5-year relative survival for those diagnosed with distant stage (i.e., metastasis).[1,2]

Improvements in breast cancer survival and declines in breast cancer mortality have also come with substantial cost. In fact, national cancer care expenditures have been is constantly increasing in the US. In 2010, national direct expenditures of all cancer sites were $124.57 billion US. Specifically, costs were highest for female breast cancer, accounting for $16.50 billion.[3] Further, in 2020 total expenditures of care for all cancer sites are projected to reach approximately $173 billion for all cancer sites and $20.50 billion for breast cancer, assuming a 2 percent annual increase in medical costs in the initial (i.e., the period after diagnosis) and final phases (i.e., the last year of life) of care. The largest proportion of increases in expenditures are expected for female breast cancer and prostate cancer in the continuing phase (i.e., the period between the initial phase and last year of life phase), accounting for 32% and 42% respectively.[3] When looking at individual patient spending, the estimates of lifetime per-patient costs of breast cancer ranged from $US20,000 to $US100,000.[4] Indirect costs such as losses in time and productivity associated with cancer mortality are also another component of the economic burden of breast cancer. In 2010, indirect costs of breast cancer ranked among the top three most expensive cancers and were estimated to be $10.9 billion, accounting for approximately 9% of the total present value of lifetime earning lost.[5]

Overview of Breast Cancer Treatment Strategies

Typically, breast cancer treatments are 1) local (i.e., surgery, radiation therapy, or both) and/or 2) systemic (i.e., chemotherapy, hormone therapy, biologic therapy, targeted therapy, or combination of these). Treatment selection and prognosis are influenced by

certain predictive factors, including the following: clinical and histopathological features of the primary tumor, stage of disease, estrogen and progesterone receptor status, presence of human epidermal growth factor type 2 receptor (HER2/neu) overexpression, and patient characteristics (i.e., comorbidity, age, and menopausal status).[1,6,7] In general, breast cancer can be classified into: 1) non-invasive (stage 0) and 2) invasive breast cancers. Invasive breast cancer can also be further categorized into an early stage or cancer that has not spread to the skin, chest wall, or distant organ (stages I and II) and later stage or advanced stage (stages III and IV). Anticancer drugs can target either non-invasive or invasive breast cancer.

For non-invasive breast cancer (i.e., ductal carcinoma in situ (DCIS)) that is estrogen receptor (ER) positive, hormone therapy such as tamoxifen for 5 years may be recommended for women after breast surgery and radiation therapy. Similarly, hormone therapy is also an option for invasive ER positive breast cancer. Treatment will vary by menopause status: 1) premenopausal women with ductal carcinoma in situ (DCIS) may be given hormonal therapy (e.g., tamoxifen) after breast surgery and radiation, and 2) postmenopausal women with DCIS may benefit from treatment with an aromatase inhibitor (e.g., letrozole, anastrozole, or exemestane) upfront or sequentially after tamoxifen. Generally, the overall duration of optimal adjuvant treatment is 5 and 10 years.[42] The benefits of hormone therapy have been reported in meta-analyses conducted by the Early Breast Cancer Trialists's Collaborative Group (EBCTCG).[43,44] That is, women with ER-positive receptors who are treated with tamoxifen for 5 years have demonstrated a 31% and 39% reduction in annual mortality rate and recurrence rate of invasive breast cancer, respectively.[43,44]

Further, anti-neoplastic agents for invasive breast cancer can be classified into 1) neoadjuvant therapy (any regimen given preoperatively) and 2) adjuvant (any regimen given postoperatively). Neoadjuvant therapy is indicated for reducing large operable tumor size whereas adjuvant therapy is suggested for increasing the chance of long-term survival.[42] Evidence shows that the same regimens recommended for neoadjuvant therapy are seemingly equivalent to the same regimens for adjuvant therapy in terms of survival and overall disease progression.[45] For instance, a study from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 has demonstrated that use of neoadjuvant doxorubicin and cyclophosphamide is as effective as the use of adjuvant doxorubicin and cyclophosphamide in women with operable breast cancer. Specifically, preoperative doxorubicin and cyclophosphamide was not significantly different from postoperative doxorubicin and cyclophosphamide in terms of disease-free survival (DFS), distant disease-free survival (DDFS), or survival.[46]

Adjuvant chemotherapy is recommended for patients with uncertain or absent tumors. At present, choices of treatment modality require stage and molecular features including ER and HER2 status besides considering between risks and benefits of reducing disease recurrence.[42] There is no gold standard regarding optimal duration of adjuvant therapy. Duration of each regimen and line of therapy (e.g., second- or third-line chemotherapy) should be individualized to each patient.[47] Usually, at least four cycles of chemotherapy (or approximately 12-16 weeks) is recommended and a total duration of 18-24 weeks is preferred for patients with higher risk of recurrence.[42] For trastuzumab adjuvant, an optimum duration of 1 year is recommended.[42,47]

Typically, anthracyclines (e.g., doxorubicin, epirubicin, idarubicin, and daunorubicin) are largely used for treatment of adults and children with many solid and hematologic malignancies such as breast cancer, sarcoma, gynecological cancer, lymphoma, and leukemia. Particularly, anthracyclines are among the most effective antineoplastic agents and appear to be a key component of many regimens in combination with other drugs (i.e., anthracycline-based regimens) for the treatment of breast cancer.[48-50] Examples of anthracycline containing regimens in breast cancer are cyclophosphamide (AC), cyclophosphamide and 5-fluorouracil (CAF), cyclophosphamide, 5-fluorouracil, and epirubicin (FEC), or dose-dense AC followed by sequential paclitaxel (AC-T). In women with metastatic breast cancer, anthracycline-based regimen show statistically significant advantage for overall responses (OR, 1.40; 95% CI 1.26 to 1.56) and time to progression (HR, 0.76; 95% CI 0.69 to 0.83).[49] Consistent results were seen in a meta-analysis that reported that 6 months of anthracycline-containing therapy contributed to a 38% and 20% reduction in the annual breast cancer death rate for women younger than 50 years of age and for those of age 50-69 years when diagnosed, respectively.[44] This translated into an absolute survival benefit of 3% at 5 years and 4% at 10 years.[44]

Further, taxanes, as many other chemotherapeutic agents, have been used in the treatment of metastatic cancer both in adjuvant and neoadjuvant regimens. A number of studies have supported the benefit of adding a taxane (paclitaxel, or docetaxel) to anthracycline containing regimens (e.g., docetaxel plus doxorubicin and cyclophosphamide (TAC)) or using it as anthracycline-free regimens (e.g., docetaxel plus cyclophosphamide (TC)) with similar or superior efficacy.[44,51,52] Evidence supports the

use of taxane-containing therapies in women with operable early breast cancer, with improved overall survival (HR, 0.81; 95% CI 0.75 to 0.88) and disease-free survival (HR, 0.81; 95% CI 0.77 to 0.86).[52] The results were consistent with metastatic breast cancer in terms of improving overall survival (HR, 0.90; 95% CI 0.84 to 0.97), time to progression (HR, 0.87; 95%CI 0.81 to 0.93), and overall response (OR, 1.29; 95%CI 1.13 to 1.47).[51]

In addition to hormone therapy and classical chemotherapy, there has been an increase in the use of novel therapies with specific cellular targets for breast cancer. Approximately 20-25% of women with early and invasive breast cancer had an amplification of the *HER2* gene and overexpression of the gene product.[53] The over-expressed HER-2 receptor is associated with a poor prognosis, including increased tumor growth rates, high risk of relapse after initial treatment, decreased rates of disease-free and overall survival, and death from metastatic disease.[16,53,54] The FDA approved HER2-targeted therapies include trastuzumab and lapatinib. Recently, adjuvant treatment for HER2-positive breast cancer is focused on use of trastuzumab, a humanized monoclonal antibody. Trastuzumab is widely recommended for women who over-express HER2 both in early and metastatic breast cancer. Previous studies have demonstrated that trastuzumab improves survival by 20% in metastatic HER-2 positive breast cancer as well as reduces risk of mortality by 50% in early HER-2 positive breast cancer.[54,55] Evidence has demonstrated benefits of trastuzumab when used as a single agent and also significant improvements in both disease-free survival (DSF) and overall survival (OS) when used in combination, including with anthracyclines-based or taxane-based regimens.[56-58] Specifically, data from a Cochrane review have shown that women with HER-2 positive early and locally advanced breast cancer treated with trastuzumab-

containing regimens had significant OS (HR, 0.66; 95% CI 0.57 to 0.77) and DFS (HR, 0.60; 95% CI 0.50 to 0.71) benefits.[59] Further, the addition of trastuzumab to either anthracycline- or taxane-based regimen was superior to the same regimen without trastuzumab in terms of significant improvement in overall response (50% vs 32%) and OS (25 vs. 20 months).[57]

A small molecule tyrosine kinase inhibitor, lapatinib, is approved for those postmenopausal women with ER-and HER2-postive metastatic breast cancer who had disease progression on prior therapy including anthracyclines, taxanes, and trastuzumab.[60-62] Previous studies have supported that a combination of 1) lapatinib with capecitabine or 2) lapatinib with trastuzumab significantly improved median time to progression and progression free survival (PFS).[56,61,62] For example, Blackwell and colleagues found that lapatinib in combination with trastuzumab significantly improved PFS (HR, 0.73; 95% CI 0.57 to 0.93) in women with HER2-positive and trastuzumab-refractory metastatic breast cancer as compared to lapatinib alone.[62]

Breast Cancer Treatment Patterns in the U.S.

Although evidence largely supports the benefits of cancer treatment, there has been a question of whether the benefit of cancer treatment that has been shown to be effective in clinical studies is equally accessible and available to all patients in the U.S.[9] This issue raises a concern regarding cancer treatment disparities among cancer patients in the U.S., including timeliness of diagnosis, receipt of treatment, and health outcomes.[9,63,64] Cancer health disparities, as defined by the National Cancer Institute (NCI), are adverse differences in cancer incidence, cancer prevalence, cancer death, cancer survivorship, and burden of cancer or related health conditions that exist among

specific population groups in the U.S. In an effort to address this concern, recently there were some population-based studies examining breast cancer treatment patterns in order to provide better information on the patterns of treatment across different segments of the U.S. population. Understanding trends in breast cancer treatment among populations, which could be classified by demographic (e.g., age, sex, ethnicity/race), socioeconomic status (e.g., income, education level), geographical location, access to effective health care, or insurance coverage, may help oncologists, researchers, and policy makers to identify appropriate strategies in order to eliminate disparities and improve long-term health outcomes.

Evidence from the Surveillance, Epidemiology, and End Results (SEER) Medicare database examining treatment of early-stage breast cancer (i.e., stage I and II) shows that the proportion of breast cancer patients who underwent breast-conserving surgery followed by radiation therapy increased during the past 20 years.[9] Nevertheless, treatment disparity exists by age groups. Particularly, younger patients (age <65 years) were more likely to receive both surgery and radiation therapy compared with patients 65 years or older.[9] Besides patient age, treatment patterns also differ among pre-existing conditions. For instance, a study conducted by Ballard-Barbash and colleagues indicates that age and comorbid conditions at diagnosis were factors associated with the receipt of radiation therapy.[65] That is, patients with pre-existing conditions were less likely to receive radiation therapy than those with no comorbid conditions (OR=0.33; 95% CI: 0.24-0.46). Also, patients aged 80 years or more were less likely to receive radiation therapy than those younger patients defined by age 65-69 (OR =0.12; 95% CI: 0.10-0.14).[65]

In addition to age and pre-existing conditions, disparities exist among race/ethnicities, particularly in incidence, survival rates, and treatment patterns among African Americans and Caucasian Americans.[66] Baquet and colleagues report that the incidence of invasive breast cancer in African American women was higher than those for Caucasian American women aged 40 and younger (incidence rate ratio (IRR)=1.16; 95% CI:1.10–1.23).[66] African American women also had a lower five-year survival rate than Caucasian American women (77.1% vs. 89.7%, P<0.0001). Further, African American women with invasive breast cancer were less likely to undergo surgery than Caucasian American women (88.8% vs. 94.0%, P<0.0001). With regards to surgery recommended for their invasive breast cancer and radiation therapy, African American women were more likely to not have surgery recommended (5.4% vs. 2.5%, P<0.0001) nor receive radiation therapy (60.8% vs.54.3%, P<0.0001) compared with Caucasian American women.[66]

Further, a recent study conducted by Silber and colleagues, using the SEER-Medicare database, has found differences in breast cancer survival between African American and Caucasian American women associated with patient baseline characteristics and treatment.[67] Specifically, treatment differences are that African Americans had a lower proportion of treatment received, including surgery, radiation therapy, and chemotherapy (87.4%vs 91.8%; P < .001); had longer time from diagnosis to treatment (29.2 vs 22.8 days; P < .001); and had a higher proportion undergoing breast-conserving surgery without other treatments (8.2%vs 7.3%; P = 0.04) compared with Caucasian Americans. Of those African Americans who received treatment, the

proportion of anthracyclines and taxanes prescribed was lower than Caucasian American patients (3.7%vs 5.0%; P < .001).

Data also show that differences in breast cancer treatment and survival may be attributable to socioeconomic status among women in the U.S.[68] For example, Bradley and colleagues have reported that breast cancer patients with higher poverty levels (i.e., ≥13%) were less likely than those patients with lower poverty levels (i.e., <5%) to receive breast-conserving surgery (adjusted OR = 0.68; 95% CI= 0.56-0.82) and subsequent radiation therapy (adjusted OR= 0.78; 95% CI = 0.60 to 1.00).[68] In addition, women with breast cancer with Medicaid insurance, which reflected low socioeconomic status, were associated with receiving inadequate treatment and poor survival. Specifically, those who were enrolled in Medicaid (i.e., the Medicaid fee-for-service plan) were more likely to be diagnosed with late-stage disease (OR=1.93; 95% CI=1.50-2.49) and were less likely to receive radiation therapy following breast-conserving surgery (OR=0.37; 95%CI=0.24-0.57) than women who were not enrolled in Medicaid.[68] Likewise, the type of insurance coverage is another factor associated with receipt of treatment. For example, a study conducted by Riley and colleagues indicates that on average, early-stage breast cancer patients enrolled in health maintenance organizations (HMOs) were more likely to receive breast-conserving surgery followed by radiation therapy than those who were enrolled in fee-for-service (FFS) (HMO, 69.0%; FFS, 63.7%; difference, 5.3%; 95% CI: 2.9%-7.7%).[69]

A number of studies have investigated demographic, socioeconomic status, and accessibility to care variation-related factors associated with breast cancer treatment. However, most of the studies were based on cancer registry data from the SEER-

Medicare database which focused on breast cancer patients who are older than 65 years of age and have Medicare insurance.[9,10,66-69] Although there are emerging studies using information obtained from breast cancer population-based state registries, there is concern over whether diversity of the population in a certain state can be generalized to represent American women. [70,71] Ultimately, relatively few studies have examined breast cancer treatment patterns based on characteristic of the health system. For instance, little research has been published on whether factors such as facility (e.g., outpatient, ambulatory settings), type of insurance, or geographical location of the settings are attributable to treatment patterns. Therefore, there is a gap in understanding of breast cancer treatment patterns and factors associated with treatment using population-based data which are representative across different population groups. Evaluating treatment patterns is essential to better understanding of trends in breast cancer treatment. This evidence may help health care professionals and policy makers effectively identify certain groups that have issues of accessibility or disparity and eventually improve equal access to care as well as high quality of care in all areas and populations of the United States.

Adverse Effects in Cancer Therapy: Cardiotoxicity

The improvement in outcomes of cancer patients, including survival rate, has largely increased over the last two decades. Unfortunately, this favorable effect of anti-neoplastic agents was also associated with adverse effects or toxicities. Adverse effects can occur and may vary depending on certain drugs and dosages used in each regimen. Generally, the most common adverse effects (e.g., nausea, vomiting, mucositis, and alopecia) appear to be spontaneously reversible or short-term toxicity. On the other hand,

less common but serious toxicities, particularly chemotherapy-induced cardiotoxicity, became increasingly recognized since a report of doxorubicin-induced heart failure in 1967.[11,12] Chemotherapy-induced cardiotoxicity in cancer patients may cause serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis.[17] This cardiac adverse event may eventually cause severe morbidity and lead to premature death.[17]

Until recently, there is no clear and specific definition of chemotherapy-induced cardiotoxicity. The National Cancer Institute has defined cardiotoxicity in a general term as 'toxicity that affects the heart'. Detailed information is available at www.cancer.gov/dictionary/. Another definition, which is more associated with chemotherapy-related cardiotoxicity, has been defined by the Cardiac Review and Evaluation Committee (CRCE) as one or more of the following: 1) cardiomyopathy in terms of decrease in cardiac left ventricular ejection fraction (LVEF), either global or more severe in the septum; 2) symptoms of heart failure (HF); 3) associated signs of HF (e.g., S3 gallop, tachycardia, or both); and 4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of HF, or a decline in LVEF of at least 10% to less than 55% without accompanying signs or symptoms.[31]

Overview of Cardiotoxicity in Cancer Therapy

There has been growing attention to cardiovascular disease in cancer patients because it was reported to be one of most frequent health problems affecting cancer survivors.[72] In fact, it is well recognized that both cancer and cardiovascular disease have common risk factors, including age and obesity.[31] Hence, there is a possibility that a cancer patient may have burden of cardiovascular comorbidity, particularly in an aging

population.[31,73] Indeed, cardiovascular disease, such as heart failure may lead to substantial negative impact on cancer patients. The evidence shows that the mortality rate from cardiovascular disease is greater than that from cancer itself. For instance, a study using SEER data investigating breast cancer specific and non-breast cancer-related mortality indicated that probability of mortality from cardiovascular disease, particularly heart disease, was significantly higher than that for breast cancer itself.[35]

Cancer treatment has increasingly involved complex combinations of primary treatment (i.e., radiation therapy or surgery) and chemotherapeutic agents. The likelihood and severity of cardiotoxicity during chemotherapy depends on various factors, including not only the chemotherapeutic agent itself. This is because each agent may have adverse cardiac effects and this effect can be potentiated when it is administered under certain circumstances.[26] Generally, these factors can be categorized as 1) factors related to chemotherapeutic therapies, including the drug class, dose administered during each cycle, cumulative dose, schedule and route of administration, regimen, concomitant chemotherapy or radiation therapy; and 2) factors related to patients, including age, presence of comorbidity (e.g., cardiovascular risk factors, cardiovascular disease) and prior mediastinal radiation therapy.[74] Consequently, there is wide variation in the incidence of chemotherapy-induced cardiotoxicity, with a report as high as 48% incidence of heart failure from doxorubicin at cumulative dose of 700 mg/m^2 [32,75] and as low as an incidence of heart failure of 0.5% from imatinib.[12] Generally, there is evidence of cardiotoxicity in patients undergoing anthracyclines and other chemotherapy, including trastuzumab, high dose cyclophosphamide, taxanes, antibiotics (i.e., mitomycin-c), and 5-fluorouracil.[30]

Additionally, cardiotoxicity such as heart failure in cancer patients may cause serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis.[17] This cardiac adverse event may compromise the clinical effectiveness of chemotherapy and eventually lead to premature death.[17-19] Although cardiac function may be recovered after withholding chemotherapy, it is important to note that patients with a history of chemotherapy-induced cardiotoxicity are more likely to develop further decline in cardiac function when being exposed to more cycles of chemotherapy.[20,21]

Cardiotoxicity of antineoplastic agents, clinical features, and incidences, are fully listed in **Appendix A. Table A1.** In brief, ***anthracyclines*** have been recognized as the drug class most likely to be associated with cardiotoxicity. Further details of anthracyclines will be elaborated on in the following sections. ***Alkylating agents*** are another well-known class of chemotherapeutic agents used in solid tumors as well as hematologic malignancies and they may induce cardiotoxicity including heart failure, myocarditis, and pericarditis. For example, cyclophosphamide-induced acute cardiotoxicity has been reported in 7-28% of patients. The incidence appears to be associated with high dose, particularly when administered in high-dose conditioning regimens for bone marrow transplantation (e.g., doses of 120-170 mg/kg over 1 to 7 days).[76] Also, heart failure is possible in patients older than 50 who underwent cyclophosphamide combined with or sequentially used with anthracycline containing regimens.[12,26,76] Fortunately, it is well tolerated and unlikely to be associated with cardiotoxicity at lower dose.[26] Further, ***platinum agents*** such as cisplatin have been associated with an 8.5% incidence of thromboembolism, in addition to potential

nephrotoxicity.[12] Specific cardiotoxicity is rarely reported[74]; however, Meinardi and colleagues suggested that cisplatin can be associated with late cardiovascular complications, including arterial hypertension, myocardial ischemia and infarction as long as 10 to 20 years after the remission of metastatic testicular cancer.[77] Also, ***taxanes*** have demonstrated adverse cardiac effects, mainly reversible ventricular arrhythmias and bradycardia. The incidence of bradycardia with paclitaxel ranges from 0.1 to 31%.[78] Taxanes have been reported to cause heart failure, ischemia, and myocardial infarction; however, these events mostly occurred in patients with underlying cardiac disease or when taxanes were used in combination with doxorubicin.[74,76]

Likewise, the incidence of cardiotoxicity with ***antimetabolites*** such as use of fluorouracil (5-FU) in the treatment of many solid tumors varies from 1.1%-4.5%, depending on underlying coronary artery disease.[26] The most commonly reported cardiotoxic effect is ischemic syndrome, which ranges from angina-like chest pain to acute MI or sudden death.[26] In most cases, the ischemia is reversible after termination of the 5-FU and/or administration of anti-ischemia therapy (e.g., nitrates or calcium channel blockers).[26,76] High-doses of ***biologic response modifiers*** such as interleukin-2 or interferon-α are associated with cardiotoxicity, including arterial hypotension, arrhythmias, cardiomyopathy and vascular thrombosis. Adverse cardiac effects mainly have involved arrhythmias, with incidence of 6-20%; this cardiomyopathy appears to be reversible.[78] ***Hormonal agents***, including tamoxifen, are another class of therapies with an incidence of thromboembolic events.[31] Tamoxifen is associated with an increased risk of deep vein thrombosis (1.34 events per 1000 women), pulmonary embolism (0.69

events per 1000 women), and stroke (1.45 events per 1000 women), primarily in women aged 50 years or older.[79]

Further, ***targeted therapies***, including monoclonal antibodies (mAbs), tyrosine kinase inhibitors, and proteasome inhibitors, histone deacetylase inhibitors (HIDAC), and mammalian target of rapamycin (mTOR) inhibitors, also have demonstrated cardiotoxicity. Generally, adverse events with these novel intravenous therapies are infusion-related reactions such as hypotension. Nevertheless, some targeted therapies may alter signaling pathways involved in cardiomyocyte physiology and may lead to adverse cardiac effects.[17] The most common cardiac toxicities are arterial hypertension, fluid retention, thromboembolism, and pericardial effusion. Still, other cardiac toxicities such as prolonged QT interval associated with arrhythmias and left ventricular dysfunction that could lead to a heart failure have been frequently reported with some agents.[17] The severity of targeted therapy associated cardiotoxicity can range from mild with no long-term toxicity as observed with rituximab (arrhythmias and angina <1%) to severe, including left ventricular dysfunction and heart failure, as documented with trastuzumab. Further detail regarding trastuzumab will be explained in the following sections.

Furthermore, ***miscellaneous agents*** such as all-trans retinoic acid and arsenic trioxide have reported incidence of fluid retention (i.e., pleural or pericardial effusion) in 26% of cases and QT prolongation in more than 50% of cases, respectively.[26,78] Lastly, ***radiation therapy*** can cause cardiac structure damage (i.e., pericardium, myocardium, valves, coronary arteries, and peripheral vessels), generally due to the progression of coronary atherosclerosis.[78] Cardiotoxicity from radiation therapy can be acute, as

observed after a single dose of anthracycline-based therapy, or it can take 10 years to develop late cardiac injury. For instance, a nationwide study of 90,000 Swedish women with breast cancer reported a mortality ratio of 1.13 (95% confidence interval (CI): 1.03 to 1.25) for ischemic heart disease 10 years after radiotherapy.[80] Fortunately, techniques for radiation therapy have been developed to reduce the radiation dose (e.g., reducing dose or choosing different radiation energy) in the last three decades. Currently, these techniques appear to reduce the incidence of cardiotoxicity in patients treated with radiation therapy.[78]

The following paragraphs discuss anthracycline-induced cardiotoxicity and trastuzumab-induced cardiotoxicity, respectively.

Anthracycline-Induced Cardiotoxicity

A meta-analysis of the risk of cardiotoxicity in patients with solid and hematologic malignancies who were treated with anthracyclines agents was conducted by Smith and colleagues.[13] The analysis included 55 published randomized controlled trials in which the majority of the population had advanced breast cancer. The results show that, compared with non-anthracycline regimens, the risk of anthracycline-induced cardiotoxicity was 5.43 fold higher (Odd ratio (OR), 5.43; 95% CI: 2.34 to 12.62), and subclinical cardiotoxicity (defined as abnormal systolic function or an increased afterload measured by echocardiography)[81] was 6.25 fold higher (OR, 6.25; 95% CI: 2.58 to 15.13).[13] In general, one of the potential risk factors in the development of cardiotoxicity is total cumulative dose of anthracycline agents. For instance, the incidence of anthracycline-induced heart failure in patients treated with doxorubicin was 3-5% with a 400 mg/m2 cumulative dose and was 18-48% with a 700 mg/m2 cumulative dose.[12]

The incidence of cardiotoxicity can be categorized into 1) *early onset anthracycline-induced cardiotoxicity* defined as incidence of cardiotoxicity such as left ventricular dysfunction during therapy or less than one year of therapy and 2) *late onset anthracycline-induced cardiotoxicity* defined as incidence of cardiotoxicity as left ventricular dysfunction presenting at least a year after the completion of therapy. On average, early-onset chronic cardiotoxicity occurs in 1.6%-2.1% of patients treated with anthracyclines with highest incidence at about 3 months after treatment. Additionally, 1.6%-5% of patients developed late-onset chronic cardiotoxicity at least one year after completion of therapy.[12] However, the late onset cardiotoxicity could be as high as 38.4% as reported by a study using the Surveillance, Epidemiology and End Results (SEER) database. This study demonstrated a 38.4% incidence of heart failure in women at 10 years after completion of anthracycline-based therapy.[13,48]

Anthracycline-induced cardiotoxicity can be described as **Type I cardiotoxicity** which is caused by cardiomyocyte death either through necrosis or apoptosis. The injury from Type I chemotherapy cardiotoxicity is irreversible and the occurrence is dose- and schedule-dependent. The cardiotoxicity is related to the cumulative dose > 500 mg/m^2. Generally, the mechanism of cardiotoxicity is related to free-radical formation and the mitochondrial apoptosis pathway caused by the effect of anthracycline-induced DNA damage in cancer cells.[50,82] Additionally, other potential factors of anthracycline-induced cardiotoxicity are: route of administration, female sex, pre-existing cardiovascular disease, diabetes, age (younger and older age), mediastinal radiation therapy, and concomitant chemotherapy, including cyclophosphamide (high-dose), etoposide, melphalan, paclitaxel, mitoxantrone, and trastuzumab.[13] For example, Pinder and

colleagues found hypertension is a risk factor for the development of heart failure in patients undergoing anthracycline-based regimens (hazard ratio (HR): 1.45; 95% CI, 1.39 to 1.52).[48] Likewise, anthracyclines in combination with trastuzumab has resulted in high incidence of cardiotoxicity, compared with non-trastuzumab therapy (27% vs 8%).[34] In breast cancer, data from clinical trials reported that the incidence of heart failure and/or cardiomyopathy increased by 2% with anthracyclines alone and 4% if followed by trastuzumab.[83]

Trastuzumab-Induced Cardiotoxicity

The emerging trend of novel therapies with specific cellular targets has been introduced to medical practice over the last decade and demonstrates favorable benefits for cancer treatment. Targeted therapies, including tyrosine kinase receptor inhibitors (TKs), play an important role. Tyrosine kinase is involved in cancer initiation and progression via molecular pathways that regulate cell growth, differentiation, metabolism, migration and apoptosis. Recent evidence indicates that the inhibition of TKs has improved cancer treatment, including breast cancer, by improving time-to-progression (TTP) and survival as well as reducing cancer recurrence and mortality rate.

Therapies that selectively inhibit TK receptors can be categorized into two classes: 1) mAbs targeting the TK receptor and 2) small molecules or tyrosine kinase inhibitors (TKIs), targeting both receptor and nonreceptor tyrosine kinases. For example, trastuzumab (Herceptin) is a mAb that binds to the ErbB2 receptor of tyrosine kinase. Some other mAbs do not bind to the tyrosine kinase receptors themselves but they bind to the growth factor ligands that activate the receptors. For instance, bevacizumab (Avastin) targets vascular endothelial growth factor A (VEGF-A) leading to the inhibition of the

tyrosine kinases. **Since breast cancer was the cancer of interest of the proposed study, we focused on trastuzumab because it is used to treat breast cancer.**

Trastuzumab (Herceptin®; F.Hoffmann-La Roche Ltd., Basel, Switzerland) is a humanized monoclonal antibody targeting the HER-2/ ErbB-2 family of receptor tyrosine kinase and is used in the treatment of early and metastatic breast cancer. Despite promising benefits, adverse effects have been reported with targeted therapies in several studies, including cardiotoxicity or vascular conditions (e.g., arterial hypertension, arrhythmias, heart failure, or left ventricular ejection fraction (LVEF) reduction or heart failure).[59,83-86] Generally, the incidence of cardiac dysfunction was 0.5-34% of patients in the clinical trials of trastuzumab.[14-16,87] Likewise, the Cochrane Database of Systematic Reviews recently reported that women with early breast cancer treated with trastuzumab containing regimens (e.g., docetaxel plus trastuzumab) had significantly increased risk of congestive heart failure (relative risk (RR) 5.11; 95% CI 3.00 to 8.72) and left ventricular ejection fraction decline (RR 1.83; 95% CI 1.36 to 2.47).[59] In addition to early breast cancer, trastuzumab also significantly increased risk of congestive heart failure in metastatic disease (RR 4.75; 95% CI 1.93 to 11.71).[88]

The mechanism of trastuzumab-induced cardiotoxicity is not yet completely understood yet. Trastuzumab-related cardiotoxicity, unlike anthracyclines, can be categorized as **Type II injury**. This cardiotoxicity is less predictable because it is not dose-related.[85] Also, it is often reversible after withholding or withdrawing the therapy because it does not cause damage to the myocardium nor cell death.[16,85,86,89] The potential mechanism of toxic effect is more likely due to the inhibition of the HER-2/ErbB-2 receptor expressed on cardiomyocytes. Both HER-2/ErbB2 signaling and its ligand

neuregulin-1 demonstrated a protective effect on cardiac function. As a result, the disruption of the ErbB2-Neurgulin 1 (NRG1) signaling cascade may interfere with the normal growth and repair of cardiomyocytes.[12,31,84-86]

Additionally, higher incidence of cardiotoxicity was also found with a history of heart disease and previous treatment with anthracyclines.[13,53,88] This is consistent with the results from a meta-analysis conducted by Chen and colleague.[88] The findings have demonstrated that breast cancer patients treated with trastuzumab and anthracycline-based chemotherapy had significantly increased risk of heart failure (RR, 4.27; 95% CI 2.75 to 6.61), as compared to patients who received non-anthracycline chemotherapy.[88] The reason is because interruption of the signaling pathway inducted by targeted therapies may result in cardiotoxicity due to impaired myocyte and endothelial cells.[85] Risk factors may also include age over 60 years, prior or concomitant treatment with anthracyclines plus cyclophosphamide (27% of patients developed cardiac dysfunction),[34] paclitaxel (13% of patients developed cardiac dysfunction),[34] fluorouracil, certain comorbidities (e.g., uncontrolled arterial hypertension arrhythmias), and higher BMI.[34,88,90,91]

The Role of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and β-Blockers (BBs) in Preventing Cardiotoxicity

Cardiotoxicity remains a major issue for women with breast cancer undergoing chemotherapy, particularly with anthracyclines and trastuzumab.[30] This adverse cardiac event, especially left ventricular dysfunction, could eventually lead to cardiomyopathy and heart failure.[30] Evidence has suggested that chemotherapy-induced cardiotoxicity appears to be responsive to dose reduction, withholding, or termination. Nevertheless, the

limitation of total dose that can safely be administered raises a concern of unfavorable consequences, considering that it may compromise the drug's efficacy and negatively affect patient outcomes.[18,19] An alternative approach is to identify patients at high risk to reduce the morbidity and mortality from cardiotoxicity. However, no standard guidelines addressing this have been developed. Also, current screening methods to detect and measure adverse cardiac events by surveillance of left ventricular dysfunction (e.g., transthoracic electrocardiogram (ECHO) and Eco-Doppler) may be limited by variability and insensitivity of available imaging modalities; hence, the methods might underestimate left ventricular volume.[33] Ultimately, increasing evidence has demonstrated that chemotherapy-induced left ventricular dysfunction seems to be asymptomatic and the development of heart failure may occur several years after completing chemotherapy regimens.[18] Therefore, the possibility of identifying an early marker with sufficient predictive power to detect late cardiac dysfunction is still challenging.[30,31]

Another promising strategy is a protective chemoprevention approach in order to reduce cardiotoxicity from chemotherapeutic agents without losing their anticancer activity.[31] There is evidence that asymptomatic and symptomatic left ventricular dysfunction may be managed with pharmacotherapy including angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers (BBs). Specifically, the role of ACEIs and BBs in treatment and prevention of cardiovascular disease, including left ventricular dysfunction and heart failure, has been widely supported by a number of clinical practice guidelines, meta-analyses, and systematic reviews.[12,16,22-30] According to the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA)

Guideline for the Management of Heart Failure, the initiation of ACEIs for patients with stage A, B, and C heart failure and other cardiovascular risk factors is recommended in order to prevent symptomatic heart failure and reduce mortality.[30] Similarly, addition of BBs to patients with stage B and C heart failure is also recommended by the 2013 ACCF/AHA guideline to reduce mortality.[30] Indeed, both ACEIs and BBs have been recommended for patients with a reduced ejection fraction to prevent symptomatic heart failure, even if they do not have a history of myocardial infarction.[30]

To date, there is no specific guideline for cancer therapy-related cardiotoxicity in terms of risk assessment or management. However, an increasing amount of literature has supported the benefit of both ACEIs and BBs in patients with chemotherapy-induced cardiotoxicity. Indeed, ACEIs and BBs appear to be associated with long-term improvement in left ventricular systolic function by reducing ventricular remodeling.[26-28,30-33] This may eventually lead to delay and slow clinical progression to heart failure in patients undergoing chemotherapy.[26,28,33] For example, a systematic review and meta-analysis conducted by Kalam and colleagues has elucidated the significant role of ACEIs and BBs as a cardioprotective treatment for reducing chemotherapy-induced cardiotoxicity. This study indicated a significantly lower risk of adverse cardiac events, including reduction in ejection fraction and/or the development of heart failure, in patients who received ACEIs (RR, 0.11; 95% CI 0.04 to 0.29) and BBs (RR, 0.31; 95% CI 0.16 to 0.63) as compared to those who did not (i.e. the control arm).[27]

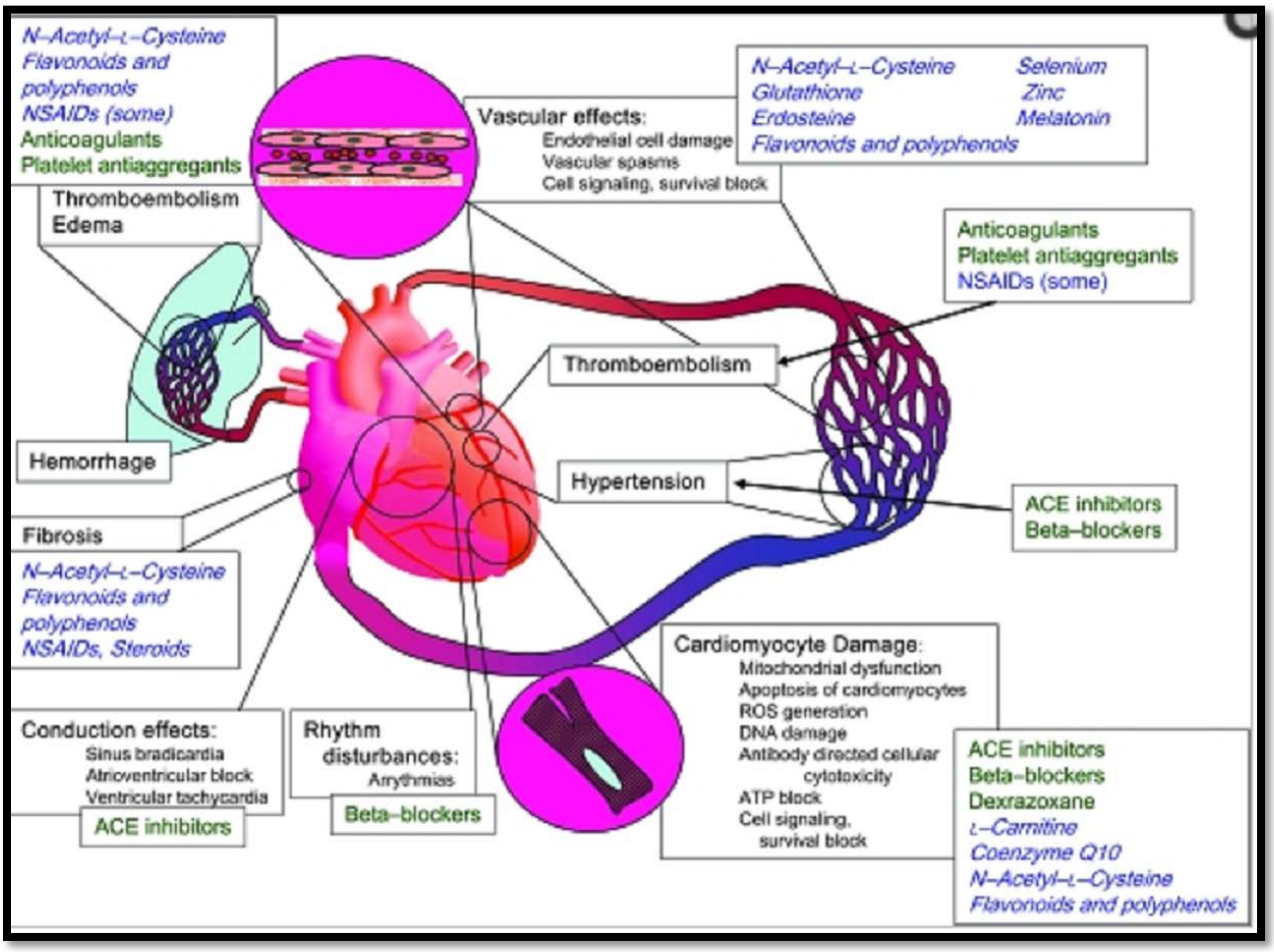
Similarly, a prospective, randomized clinical study conducted by Cardinale and colleagues demonstrated the efficacy of early treatment with ACEIs in preventing the development of high-dose chemotherapy induced-cardiotoxicity (e.g., anthracyclines,

alkylating agents, and platinum-based).[16] They found a significant reduction in left ventricular ejection fraction and an increase in end-diastolic and end-systolic volumes in patients with high-dose chemotherapy who were not treated with enalapril compared with those who were treated with enalapril. Further, the incidence of cardiotoxicity (e.g., death and heart failure) was significantly higher in the enalapril nonusers than in the enalapril users (43% versus 0%; P<0.001).[92] **(see Appendix B. Table B1 for relevant studies)**

Likewise, evidence for BBs suggests preservation of left ventricular function and diastolic function in chemotherapy-induced cardiotoxicity, and also neuroprotective and vasculoprotective properties.[93,94] For example, a study conducted by Kalay and colleagues indicated protective effects of carvedilol for systolic and diastolic left ventricular dysfunction in patients with anthracycline-induced cardiomyopathy.[94] Also, there is evidence regarding the role of ACEIs and BBs as a combination therapy for preventing left ventricular systolic dysfunction[95].[20,33] The preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies (OVERCOME) randomized controlled trial evaluated the efficacy of ACEIs and BBs in patients undergoning chemotherapy. The results suggested that compared to nonusers, the enalapril and carvedilol users had a lower incidence of the event of death or heart failure (6.7% vs. 22%, p=0.036), and of death, heart failure or a final LVEF<45% (6.7% vs. 24.4%, p=0.02). [20]

To maximize the benefits of chemotherapy with the total dose that can safely be administered as well as minimize this cardiovascular adverse effect, it is essential to maintain or support the cardiovascular system. Since ACEIs and BBs have been proven

in prevention and treatment of heart failure in various conditions, they may have the same efficacy in preventing trastuzumab- and anthracyclines- induced cardiotoxicity as well[30] (Figure 1).



ROS= reactive oxygen species. The original work of this figure belongs to the review article conducted by Albini and colleagues.[31]

Figure 1. Example of major mechanisms causing cardiotoxicity of chemotherapy (black text) and clinically used therapeutic agents (green text)

Therefore, using ACEIs and/or BBs as a prophylactic or concurrent regimen in breast cancer patients treated with trastuzumab and/or anthracycline therapy may be beneficial in the prevention of cardiotoxicity. Preventing chemotherapy-therapy induced cardiotoxicity would allow more breast cancer patients to successfully complete their

chemotherapy cycles while decreasing delays, dose reductions, or discontinuation of the ongoing therapy.

Although these questions are ideally answered by randomized controlled trials (RCTs), such trials are very expensive and are often not viable for relatively rare events with long follow-up such as cardiotoxicity with chemotherapy as compared to research using real world data. In addition, RCTs may have some limitations, including generalizability. For instance, a previous randomized controlled trial study conducted by Cardinale and colleagues investigated the role of ACEIs in the prevention of cardiotoxicity in patients with high-dose chemotherapy, but there are some potential concerns due to restrictive inclusion and exclusion criteria. More specifically, the study excluded older patients (i.e., age≥65 years), patients with certain comorbidities (i.e., uncontrolled hypertension, abnormal renal or hepatic function), and the study sample was not representative of diverse races/ethnicities and patients of varying socioeconomic status. This may lead to generalizability issue; hence, patients in the study may not be representative of the population nor reflect patients in routine practice. Further, the study primarily focused on high-dose chemotherapy-induced cardiotoxicity and disregarded other chemotherapies, including trastuzumab; nevertheless, there is growing evidence regarding trastuzumab-induced cardiotoxicity in breast cancer patients.

Hence, there is a need for studies that apply to diverse populations in heterogeneous health care settings. Indeed, a population-based observational study which combines data from a cancer registry and claims data may provide insights into the evidence of trastuzumab- and anthracycline-induced cardiotoxicity and benefits of

ACEIs/BBs treatment of breast cancer patients underrepresented in randomized-controlled trials (RCTs) and may supplement the information provided by RCTs.

However, available evidence, particularly using real world data to support the potential benefits of using ACEIs and/or BBs in prevention of cardiotoxicity is currently insufficient. Therefore, research investigating the effect of ACEIs and/or BBs in prevention of trastuzumab and anthracycline induced cardiotoxicity is needed and may help improve the quality of care for the U.S. populations as well as provide additional information in this high-risk breast cancer population.

Chapter 3

Methods

Description of the Study

This retrospective study examined treatment patterns of anti-neoplastic agents prescribed to nationally representative breast cancer patients and identified factors associated with the anti-neoplastic agents prescribed in ambulatory care settings (aim 1), estimated the incidence of and identified factors associated with cardiotoxicity and all-cause mortality in breast cancer patients (aim 2), and compared the effect of ACEIs and/or BBs in prevention of trastuzumab- and anthracycline-induced cardiotoxicity in breast cancer patients (aim 3). Data were obtained from cross-sectional visit-level data from nationally representative surveys in ambulatory settings (aim 1) and cohorts of population-based cancer registries with claims information, including pharmacy claims (aims 2 and 3). The target population was breast cancer patients. The following sections describe the research questions and hypotheses, study designs, sources of data, target patient selection, inclusion and exclusion criteria**,** and statistical methods.

Research Questions and Hypotheses by Aim

Research questions and hypotheses for Aim 1:

<u>Part 1 (descriptive part):</u>

What were patterns of anti-neoplastic agents prescribed to nationally representative breast

cancer patients in ambulatory settings?

Part 2 (analytical part):

What was the likelihood of receiving prescribed anti-neoplastic agents for breast cancer patients in ambulatory setting, controlling for demographic (age, sex, race/ethnicity), cancer stage, comorbidities, type of insurance coverage, geographical location, and type of setting (office-based and hospital-based setting?

H_0: *None of the predictors affected the likelihood that breast cancer patients receive anti-neoplastic agents.*

H_A: *At least one predictor affected the likelihood that breast cancer patients receive anti-neoplastic agents*

Research questions and hypotheses for Aim 2:

Part 1 (descriptive part):

What were incidences of cardiotoxicity or all-cause mortality in breast cancer patients?

Part 2 (analytical part):

What was the estimated risk of having cardiotoxicity or all-cause mortality in patients with breast cancer treated with trastuzumab and/or anthracyclines, taxane-based, and other adjuvant chemotherapy compared with those treated with hormone therapy controlling for patient characteristic, tumor characteristic, socioeconomic status, chemotherapy, radiation, surgery, and comorbidities?

H_0: *Adjuvant chemotherapy did not affect the relative risk that breast cancer patients have cardiotoxicity or all-cause mortality, controlling for baseline covariates at a given time*

H_A: *Adjuvant chemotherapy affected the relative risk that breast cancer patients have cardiotoxicity or all-cause mortality, controlling for baseline covariates at a given time*

Research questions and hypotheses for Aim 3:

What was the estimated hazard ratios associated with treatment effect of ACEIs/BBs usage on cardiotoxicity or all-cause mortality in patients with breast cancer treated with trastuzumab and/or anthracyclines therapy compared with those who were not exposed to ACEIs/BBs at a given time in months, controlling for baseline covariates and time-dependent confounders?

H_0: *ACEIs/BBs treatment did not affect the relative risk that breast cancer patients treated with trastuzumab/anthracycline have cardiotoxicity or all-cause mortality at a given time, controlling for baseline covariates and time-dependent variables*

H_A: *ACEI/BB treatment affected the relative risk that breast cancer patients treated with trastuzumab/anthracycline have cardiotoxicity or all-cause mortality at a given time, controlling for baseline covariates and time-dependent variables*

Study designs

This study consisted of a cross-sectional study and cohort study designs. First, a cross-sectional, retrospective study of trends in breast cancer treatment was used to answer research question 1. Specifically, descriptive analyses were conducted to estimate the patterns of anti-neoplastic agents prescribed to breast cancer patients in ambulatory settings and multivariable logistic regression was used identified factors associated with receipt of breast cancer treatment. Next, retrospective cohort study designs were used to answer research questions 2 and 3. To be specific, descriptive analyses examining the incidence of adjuvant chemotherapy and hormone-induced cardiotoxicity or all-cause

mortality were performed to answer part 1 of research question 2. Next, Cox proportional hazard ratios examining likelihood of adjuvant chemotherapy and hormone-induced cardiotoxicity or all-cause mortality episodes compared with those treated with hormone therapy were used to answer part 2 of research question 2. Further, marginal structural Cox proportional hazards models examining risks of trastuzumab- and/or anthracyclines-induced cardiotoxicity or all-cause mortality episodes with concurrent use of ACEIs/BBs compared with those who were not exposed to ACEIs/BBs answered part 2 of research question 3.

Data Source by aims

Aim 1

For aim 1, we used records-based or encounter level data of two national surveys from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) between 2006 and 2010. According to the National Health Statistics Report, ambulatory medical care, including physician office- and hospital-based settings, is a primary method of providing health care services in the U.S.[96] The NAMCS and the NHAMCS are national, annual probability sample surveys supplying information about care in ambulatory settings. The NAMCS and NHAMCS use a complex, stratified, multistage, probability sampling design and were conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention since 1973 and 1992, respectively. Specifically, the NAMCS is a national survey designed to provide information regarding provision and use of ambulatory medical care services based on a national sample of visits to non-federal employed office-based physicians who are primarily engaged in direct patient care. Similarly, the NHAMCS is

designed to collect data on the utilization and provision of ambulatory care services based on a national sample of visits to the emergency departments and outpatient departments of noninstitutional general and short-stay hospitals (<30 days).

Data were recorded by the physician or office staff on an encounter form provided for that purpose. Data were obtained on patients' symptoms, physicians' diagnoses, and medications ordered or provided. Demographic characteristics of patients and services provided (e.g., information on diagnostic procedures, patient management, and planned future treatment) as well as expected sources of payment, causes of injury (emergency department and ambulatory surgery center only), and certain characteristics of the facility (e.g., geographic region) were also reported.

For each visit, the NAMCS and NHAMCS record up to three diagnoses (i.e., primary diagnosis and two other diagnoses) based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) and up to three reasons for visits which are based on the patient's complaints or symptoms. The surveys also collected up to eight medications that the patient was prescribed or provided at the visit. Detailed information on NAMCS and NHAMCS, including the survey design and survey operation manuals, is published and available at http://www.cdc.gov/nchs/ahcd/about_ahcd.htm.

Aims 2 and 3

For aim 2 and 3, we used the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer claims data from the Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database from 2000-2010. The SEER-Medicare database is a joint effort between the

National Cancer Institute (NCI), SEER, and the Centers for Medicare and Medicaid Services (CMS). The SEER program is a population-based cancer registry which collects clinical data (e.g., cancer site, stage, grade, comorbidities), demographic, and cause of death information for persons with cancer. The Medicare program provides claims data which cover health care services from the time of a person's Medicare eligibility (age 65 and older) until death, including hospital and hospice bills (i.e., Part A), and physician, outpatient, and home health bills (i.e., Part B). The linkage of persons in the SEER data to their Medicare claims is performed by NCI and CMS.

The SEER-Medicare database provides 19 tumor sites and can be used for a variety of health services research studies such as cancer screening, treatment, outcomes, patterns of care, and expenditures. The SEER-Medicare database is a unique data resource that makes it possible to conduct longitudinal research as well as derive incidence- and prevalence-based estimates of cancer-related outcomes by site and stage of disease, by treatment approach, and for age and gender strata for individuals older than 65 years and those who received Social Security Disability Insurance (SSDI) and became eligible for Medicare. Detailed information on The SEER-Medicare database is published and available at http://appliedresearch.cancer.gov/seermedicare/

Patient Selection, Variables, and Measures by aims

Aim 1

Study population.

Since the NAMCS and NHAMCS provide visit-level data, the study population was defined as visits to primary care providers/practice staffs in ambulatory settings (both

office-based and hospital settings). Specifically, a visit in which breast cancer diagnosis was documented in the Patient Record form was our population of interest.

Inclusion criteria.

To be eligible for the study each visit was required to meet the following criteria:

1. A visit was documented in the NAMCS or NHAMCS during 2006-2010;
2. A patient visit must be officially diagnosed with breast cancer. This information is obtained from physician diagnoses in the Patient Record form, using International Classification of Diseases, Ninth Revision (ICD-9) codes. Specifically, 3 digits of ICD-9 codes for breast cancer (174-175) must be documented during at least one encounter. Diagnosis of breast cancer was ascertained through the NAMCS and NHAMCS in item 5 (physician's diagnosis) of the Patient record form (i.e.,[DIAG]).

Exclusion criteria.

A visit was not documented in the NAMCS or NHAMCS during 2006-2010.

Measures.

Aim 1 sought to estimate the patterns of anti-neoplastic agents prescribed to nationally representative breast cancer patients in ambulatory settings and identify factors associated with the anti-neoplastic agents prescribed. The information was retrieved from two data sources (NAMCS and NHAMCS) which were earlier described in source of data.

Receipt of anti-neoplastic agent

Our main outcome, receipt of anti-neoplastic agent, was defined as a visit in which anti-neoplastic agent(s) was/were prescribed. Receipt of medication was ascertained through the NAMCS and NHAMCS in item 10 of the Patient record form

asking “Were medications ordered/provided?” Use of anti-neoplastic agent was defined by a generic drug code (DRUGID1-DRUGID8) recorded in at least one of the following breast cancer treatments: alkylating agents, antibiotics, antimetabolites, hormones, mitotic inhibitors, tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF/VEGFR) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, and human epidermal growth factor receptor2 (HER2) inhibitors as coded and classified by the Lexicon Plus® in Multum Lexicon Database. For additional information on the Multum Lexicon Drug Database, please refer to the following Web site: http://www.multum.com/Lexicon.htm. Further, medication class was grouped as novel, classical, and hormone agents, respectively. (See table 3.1)

Predictors and covariates

Potential predictors for receipt of breast treatment included demographics (age, sex, and race), cancer staging, comorbid conditions, total chronic diseases, source of payment, geographic location, and ambulatory setting (office- and hospital-based) available in the NAMCS and NHAMCS survey. Age was categorized into four categories as ≤ 44, 45-64, 65-74, and 75 and above. Sex (male and female) and race (white, African American, Hispanic, and others) were categorized based on data in the Patient Record form. Other races include Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and multiple races. Cancer staging was ascertained as a code recorded in item 5B of the Patient Record form. A cancer staging system was applied using the scheme as summarized by the Surveillance, Epidemiology and End Results (SEER) as in-situ, localized, regional, distant, and unknown. Comorbid condition by visit, including cerebrovascular disease, congestive heart failure, chronic obstructive

pulmonary disease (COPD), depression, diabetes, hyperlipidemia, hypertension, ischemic heart disease, obesity, and osteoporosis was ascertained as a positive response to NAMCS and NHAMCS questions asking “regardless of the diagnose written in (item) 5A, does the patient now have: [disease]?”. Total chronic disease was grouped into four categories as 1-3, 4-6, >6 and unknown.

Table 3.1 Summary of outcome variables, measures, and statistical methods for aim 1

Aim1	Outcome variables	Measures	Statistical methods
		Part 1	
	Binary variables: Receipt of anti-neoplastic agent for breast cancer by treatment category: Novel agents (1 vs 0) Classical agents (1 vs 0) Hormones (1 vs 0)	Number of positive response (i.e, 1) to breast cancer treatment category: Novel agents [a] Classical agents [b] Hormones [c]	Descriptive analyses examining proportion of visit in which anti-neoplastic agent was prescribed by treatment category, using the complex multistage design of visit sampling weights
	Binary variables: Receipt of anti-neoplastic agent for breast cancer by drug class: Alkylating agents (1 vs 0) Antibiotics (1 vs 0) Antimetabolites (1 vs 0) Hormones (1 vs 0) Mitotic inhibitors (1 vs 0) TKIs (1 vs 0) VEGF/VEGFR inhibitors (1 vs 0) EGFR inhibitors (1 vs 0) HER2 inhibitors (1 vs 0)	Number of positive response (i.e., 1) to drug class for breast cancer: Alkylating agents Antibiotics Antimetabolites Hormones Mitotic inhibitors TKIs VEGF/VEGFR inhibitors EGFR inhibitors HER2 inhibitors	Descriptive analyses examining proportion of visit in which anti-neoplastic agent was prescribed by drug class, using the complex multistage design of visit sampling weights

	Binary variable: Receipt of *any* anti-neoplastic agent for breast cancer (1 vs 0)	Number of positive response (i.e., 1) to *any* anti-neoplastic agents for breast cancer, including Alkylating agents Antibiotics Antimetabolites Hormones Mitotic inhibitors TKIs VEGF/VEGFR inhibitors EGFR inhibitors HER2 inhibitors	Descriptive analysis examining proportion of visit in which any anti-neoplastic agent was prescribed, using the complex multistage design of visit sampling weights
Part 2			
	Binary variables: Receipt of anti-neoplastic agent for breast cancer by treatment category: Novel agents (1 vs 0) Classical agents (1 vs 0) Hormones (1 vs 0)	Number of positive response (i.e, 1) to breast cancer treatment category: Novel agents [a] Classical agents [b] Hormones [c]	Multivariable logistic regression analyses examining likelihood of visit in which anti-neoplastic agent was prescribed by treatment category, controlling for demographic, cancer stage, comorbidities, total chronic disease, type of insurance coverage, geographical location, and ambulatory care setting
	Binary variable: Receipt of any anti-neoplastic agent for breast cancer (1 vs 0)	Number of positive response (i.e., 1) to *any* anti-neoplastic agents for breast cancer, including Alkylating agents Antibiotics Antimetabolites Hormones Mitotic inhibitors TKIs VEGF/VEGFR inhibitors	Multivariable logistic regression analysis examining likelihood of visit in which anti-neoplastic agent was prescribed by drug class, controlling for demographic, cancer stage, comorbidities, total chronic disease, type of insurance coverage, geographical location, and ambulatory care setting

		EGFR inhibitors HER2 inhibitors	

[a] Novel agents include epothilones (a new class of mitotic inhibitors), tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF/VEGFR) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, and human epidermal growth factor receptor2 (HER2) inhibitors

[b] Classical agents include Alkylating agents, antibiotics, antimetabolites, and mitotic inhibitors

[c] Hormones include selective estrogen receptor modulators and aromatase inhibitors

Aims 2 and 3

Study population.

Patients were included into the analysis if they were female who were ≥66 years of age at first diagnosis of breast cancer. **(Figure2).** This information was obtained from Medicare inpatient, outpatient and physician claims data, using the first 3 digits of the ICD-9 and current procedural terminology (CPT) codes **(Appendix C, table C1, C4, C5, and C6).**

Inclusion criteria.

To be eligible for the study, patients were required to meet these following criteria:

1. Patients who were enrolled in Medicare and were 66 years old or older at first diagnosis. We included only patients who were at least 66 years old or older at the time of their breast cancer diagnosis to ensure adequate period of Medicare claims for defining comorbidities;
2. Their month of diagnosis and cancer stage must not be missing in SEER;
3. They must be officially diagnosed with breast cancer (ICD-9: 174-175) and had already started reporting to SEER at time of diagnosis;
4. The pre-index eligibility: they were required to be continuously enrolled in the Medicare fee-for-service Part A or Part B coverage
    a. Aim2: for at least 12 months before time of diagnosis to ensure adequate period of Medicare claims for defining comorbidities. We selected this period based on previous studies[67,83,88],
    b. Aim3: for at least 6 months before time of diagnosis. We selected this period due to a potential small sample size in aim 3.

5. The post-index eligibility: if patients were alive during the entire study period (2000-2009):
    a. They must be continuously enrolled in the Medicare fee-for-service Part A or Part B for 12 months after the index date, for a total of at least 24 months of continuous enrollment (12+12) for aim 2 and for a total of at least 18 months of continuous enrollment (6+12) for aim 3. We selected 12 months after the index date to follow-up each patient based on recent data that anthracyclines and/or trastuzumab induced cardiotoxicity may have late-onset cardiotoxicity at least 1 year after completion of therapy.[12]

    If patients died after diagnosis:

    b. They must be continuously enrolled in Medicare fee-for-service Part A or Part B for at least 1 month after the index date, for a total of at least 13 months of continuous enrollment (12+1).
6. They must have at least one pharmacy claim for chemotherapy after breast cancer diagnosis within 12 months after time of breast cancer diagnosis. In addition, '*the index date'* was the first initiation date of chemotherapy
    a. Anthracyclines-based and/or trastuzumab-based, taxane-based, and other adjuvant chemotherapy (exposure) or;
    b. Hormone therapy (control)
7. Patients were included in the analyses for aim 2 if
    a. they met inclusion criteria 1 to 6.a and 6.b and
    b. information of relevant covariates were available from SEER or Medicare for the study period;

8. Patients were included in the analyses for aim 3 if
    a. they met inclusion criteria 1 to 6.a and
    b. information of relevant covariates were available from SEER, Medicare, and Part D (prescription plan) for study period and
    c. they were prescribed anthracyclines and/or trastuzumab during the study period
    d. for the exposure group: they had a least one pharmacy claims during the study period that reflected use of antihypertensive medications (i.e., use of ACEIs and/or BBs).

Exclusion criteria.

1. Patients who were qualified for Social Security Disability Insurance and had Medicare (SSDI/Medicare). Specifically, this group of patients required 24 months after first receiving cash benefits from SSDI before being eligible for Medicare which may generate ascertainment bias. Therefore, we excluded those with SSD/Medicare because we needed to ensure a minimum of 6 months of Medicare claims from which to ascertain comorbidities, particularly previous history of heart failure (HF) or cardiomyopathy (CM)
2. Patient who were qualified for dual-eligible beneficiaries of Medicare and Medicaid because the SEER Medicare data do not capture healthcare services paid by Medicaid for the dual enrollees;
3. Patients who were previously diagnosed with HF and CM within the preceding 6 months of breast cancer diagnosis and/or before trastuzumab or anthracyclines containing regimen initiation were excluded from the study. The reason was

because these diagnoses may confound the outcome of interest, which was to identify incidence of cardiotoxicity events that were potentially attributable to anthracyclines or trastuzumab. Additionally, this 6-month-wash-out period ensured that our study population includes most of patients with a first cardiotoxicity event (i.e., heart failure or cardiomyopathy) instead of a mixture of patients with a different number of cardiotoxicity events. This approach also has been used in previous studies.[83,97]

4. Breast cancer was not the initial primary tumor diagnosis reported to SEER-Medicare data.
5. Patients with breast cancer who were not continuously enrolled in Medicare data (refer to inclusion criteria 4 and 5).

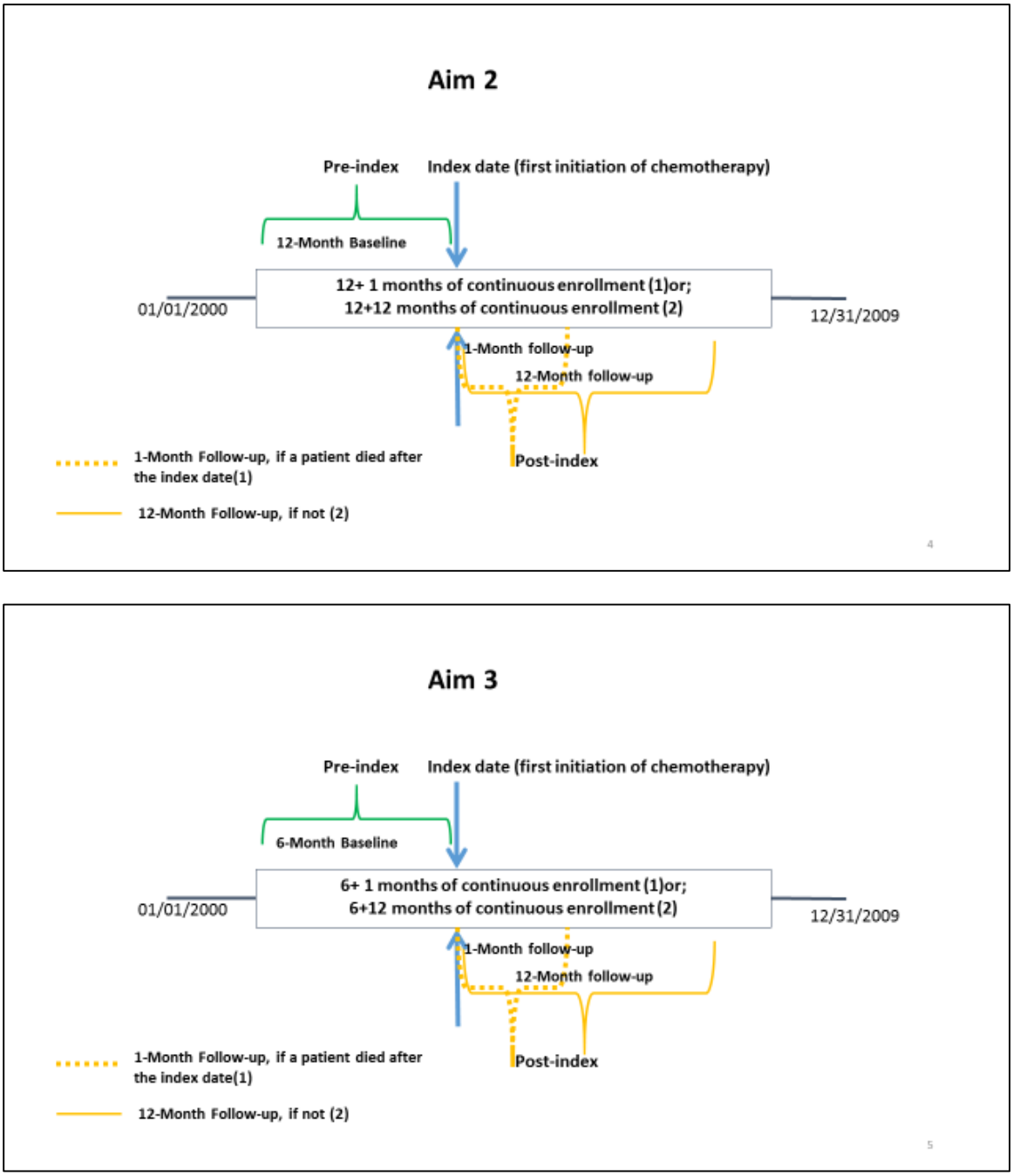


Figure 3.1. Study timeline for aims 2 and 3

Measure.

Aim 2 sought to examine the incidence rate of and identify factors associated with adjuvant chemotherapy induced cardiotoxicity compared with those treated with hormone therapy. Aim 3 sought to examine effects of using ACEIS and/or BBs in prevention of

trastuzumab- and anthracycline-induced cardiotoxicity in breast cancer patients compared with those who had never been prescribed ACEIs/BBs while adjusting for use of chemotherapy as a time-dependent confounder. The information was retrieved from the SEER-Medicare-linked database which was earlier described in the sources of data section.

Cardiotoxicity and all-cause mortality outcomes

Cardiotoxicity, defined as HF or CM, and all-cause mortality were the outcomes of interest. We used HF or CM diagnoses according to the following ICD-9-CM codes: HF(402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, 428.x) or CM (425.x). These codes have been used in previous studies.[48,97] Data were retrieved from Medicare inpatient, outpatient, and physician claims data. Patients with ICD-9-CM diagnosis codes that appeared in at least 1 inpatient claim or 2 outpatient or physician claims during 12 months after the initiation of chemotherapy were assigned as having chemotherapy-induced cardiotoxicity. For physician and outpatient claims, cardiotoxicity diagnoses must appear on at least two different claims that are more than 30 days apart.[98] Additionally, patients who died at least 1 month after the initiation of chemotherapy were assigned as having all-cause mortality. We identified all-cause mortality using date of death which was available in both SEER and Medicare files.

Predictors and covariates

Aim 2

1. Baseline characteristics and comorbidies.

For each patient, we assessed breast cancer characteristics as follows:

1.1 patient characteristics and geographical area, including age in years at breast cancer diagnosis, ethnicity/race, and region (state level)

1.1.1 socioeconomic status

Since patient-level data were not available in SEER, we used median household income, education level, poverty level from the census tract variables to represent socioeconomic status.[88,99,100]

1.2 patient tumor characteristics, including stage, grade, tumor size, estrogen receptor status, and number of positive lymph nodes were obtained from the SEER database

1.3 comorbidities were calculated from the macros for calculation of comorbidity weight provided by the National Cancer Institute (NCI).[98] We used modified Charlson comorbidity index by Klabunde[101] as suggested by the NCI.[98] The reason is because it included the diagnoses from the physician claims. Since more patients visit a physician at a physician's office than are hospitalized, incorporating physician claims into the analysis may increase the possibility of identifying more comorbid conditions.[98,101] Comorbidities were extracted from inpatient, outpatient, and physician Medicare claims for specific ICD-9-CM codes at any time during 1 year before the breast cancer diagnosis. For physician and outpatient claims, a patient's diagnoses must appear on at least two different claims that are more than 30 days apart.[98] Additionally, other potential cardiovascular risk factors, including: coronary artery disease, ischemic heart disease, stroke, hypertension, diabetes mellitus, renal failure,

arrhythmias, and hyperlipidemia, as ascertained by ICD-9-CM codes were included in the analyses **(Appendix C: Table C1)**;

2. Breast cancer treatment variables, including surgery, radiation, and chemotherapy were defined by billing codes in the Medicare claims and/or the SEER database.

2.1 Chemotherapy exposure

We assigned each patient to the exposed and the unexposed groups using propensity scoring technique. First, we categorized adjuvant chemotherapy into five mutually exclusive treatment categories: 1) trastuzumab-based (with or without non-anthracycline chemotherapy); 2) anthracyclines-based (with or without non-trastuzumab chemotherapy); 3) anthracyclines plus trastuzumab; 4) taxane-based chemotherapy, 5) other chemotherapy (e.g., alkylating agents, anti-metabolites) and 6) hormone therapy. Those patients who met treatment categories 1-5 were assigned to the exposed group; whereas those treated with hormone therapy were assigned to the control group (i.e., the unexposed group). We selected hormone therapy as a control group based on a relatively low incidence report of cardiotoxicity compared to other drug classes.[30,31,76] We collected data on chemotherapy administration using breast cancer chemotherapy codes from a previous study.[67] Data were retrieved from CPT billing codes during 12 months of time after the breast cancer diagnosis. **(Appendix C. Table C4)**

2.2 Surgery

We collected data on surgery, including conserving and non-conserving surgery during 12 months after time of breast cancer diagnosis using ICD-9

and CPT procedure cods from a previous study.[67] Data were retrieved from Medicare inpatient claims, outpatient claims, and Part B bills. **(Appendix C. Table C5)**

2.3 Radiation

We collected data on radiation during 12 months after time of breast cancer diagnosis using ICD-9, CPT, revenue center codes, and SEER variables (radiation delivery) from previous study.[67] Data were retrieved from Medicare inpatient claims, outpatient claims, Part B bills, and SEER (radiation delivery variables and codes). **(Appendix C. Table C6)**

Aim 3

In addition to aim 2, we included ACEI/BB exposure in the analysis.

ACEI/BB exposure (ACEI/ BB users).

ACEI/BB exposure, as referred to ACEI/BB users, was defined as a filled prescription as either 1) at least one prescription of ACEIs/BBs anytime before the initiation of anthracyclines or trastuzumab therapy (i.e., the index date), in other words, at least one prescription of ACEIs/BBs anytime during the pre-index period or 2) at least one prescription of ACEIs/BBs during 12 months following initiation of anthracyclines or trastuzumab therapy, in other words, at least one prescription of ACEIs/BBs during the 12 month-post index period. Also, exposed participants who started ACEIs/BBs during the pre-index period were required to have at least one prescription of ACEIs/BBs during12 month-post index period (i.e., after the initiation of anthracyclines or trastuzumab therapy). The reason that we extended use of ACEIs/BBs until the initiation of anthracyclines or trastuzumab therapy is because if we only included breast cancer

patients taking ACEIs/BBs before the initiation of anthracyclines or trastuzumab therapy, this may affect our ACEIs/BBs cohort, as physicians may start ACEIs/BBs simultaneously during cycles of chemotherapy.

The time that an exposed breast cancer patient filled her ACEIs/BBs prescription before the initiation of trastuzumab and/or anthracycline was considered as time zero, before the index date history. Similarly, the time that an exposed breast cancer patient filled her ACEIs/BBs prescription after the initiation of trastuzumab was considered as time zero after the index date. Such duration was assessed and classified in the following categories: ≤ 6 months, 6-12 months, or ≥12 months. Use of ACEIs and/or BBs was categorized based on duration of exposure to the medication.

In addition, the duration from time zero (i.e., the time that the first ACEIs/BBs prescription was filled) to the end of study or to the first cardiotoxicity event or all-cause mortality, whichever came first, was assigned as duration of exposed treatment and classified in the following categories: ≤ 6 months, 6-12 months, or ≥12 months. We categorized time of ACEIs/BBs exposure based on previous randomized controlled trial studies. Specifically, the previous studies included patients who were received ACEIs or BBs anytime before the initiation of trastuzumab and/or anthracycline chemotherapy but no later than the first cycle of chemotherapy and ACEI/BB treatment was required to continue for 6-12 months after the first cycle of chemotherapy.[33,92,94]

Since a number of studies indicated that a class effect may result in different efficacy or effectiveness, we used dose comparison across drugs within each drug class (ACEIs and BBs) for a sensitivity analysis. Since equivalent dose guidelines for ACEIs or BBs are not available, we used an approach of comparative dose classification system

previously used by Gartlehner and colleagues.[102] To be specific, we used dosage range (mg/day) of ACEIs **(refer to Appendix C. Table C2)** and BBs **(refer to Appendix C. Table C3)** as suggested by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guideline.[103] Then we divided each usual range by the upper (Q3) and lower quartile (Q1) to create three levels, including low (Q1), medium (Q2), and high (Q3). This three-level dose classification approach helped standardize daily doses of other agents in the same drug class based on quartile. For example, if a patient was prescribed daily dose of enalapril 5 mg, this dose was converted to a low level dose classification (<13.75 mg/day). Therefore, this patient was given a dosing category of low. Similarly, if a patient was prescribed daily dose of lisinopril 10 mg, this dose was converted to a low level dose classification (<17.5 mg/day). Consequently, this patient was be given the same category as the previous patient with enalapril.

ACEI/BB nonexposure or ACEI/BB nonuser:

Patients with breast cancer were assigned to this group if they had never been prescribed any ACEIs or BBs before and after the initiation of anthracyclines or trastuzumab therapy. Artificial time zero was randomly assigned and matched to the non-exposed group based on overall distribution of time zero of the exposed group as mentioned earlier.[104-106]

Both the ACEI/BB user and nonuser groups were followed to cardiotoxicity event, death, or the end of the study follow-up, whichever came first.

Time-dependent confounder:

The candidate time-dependent confounder in this study was use of chemotherapy. Use of chemotherapy behaved as a potential risk factor of cardiotoxicity. At the same time, it may be both a predictor of subsequent antihypertensive treatment and a predictor of antihypertensive treatment history.

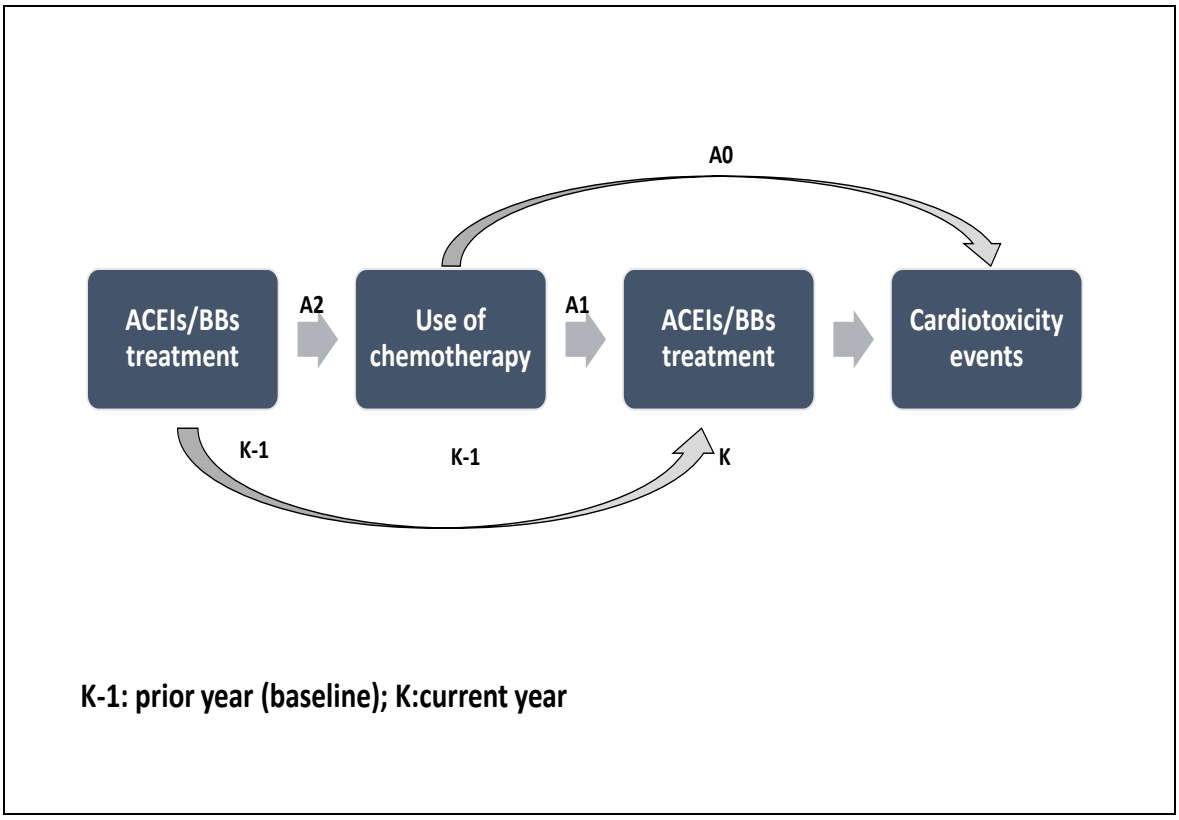


Figure 3.2. Directed acyclic graph of the hypothetical relation between variables

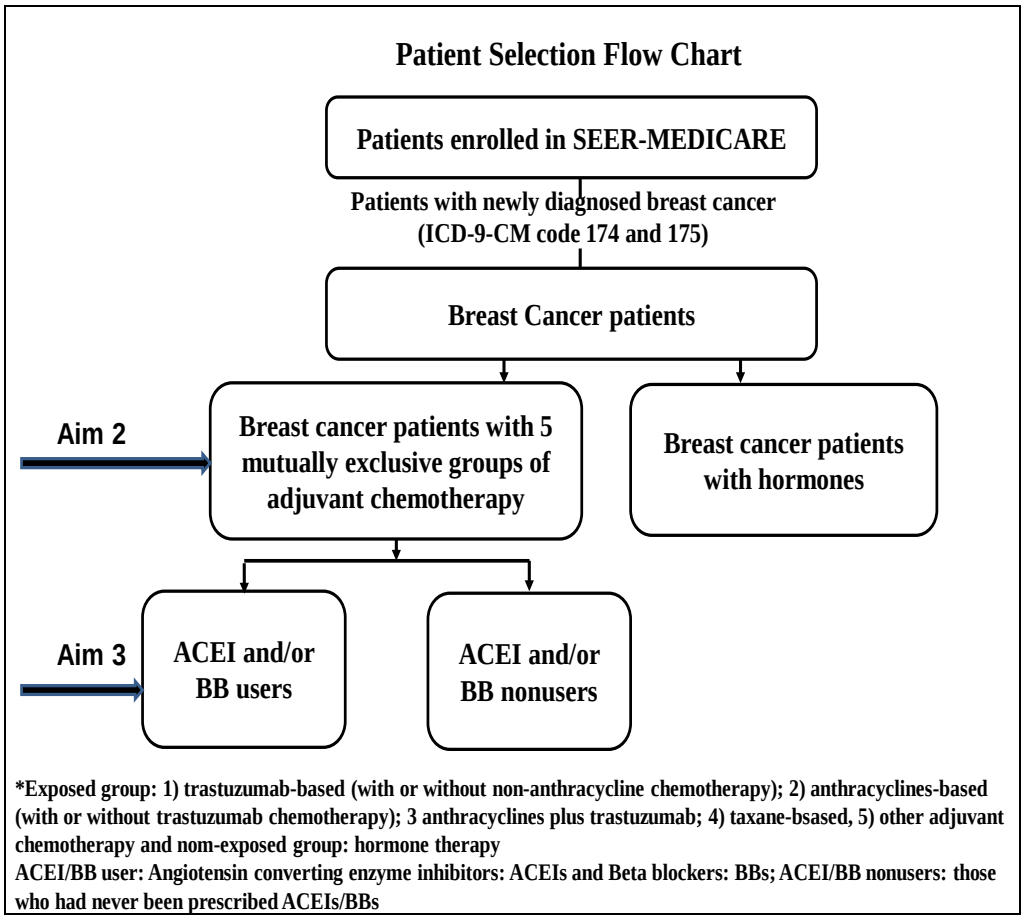
Figure 3.1 represents plausible causal relationships between variables in the study using a directed acyclic graph (DAG). Use of chemotherapy (e.g., anthracyclines or trastuzumab) was the time-dependent confounder because it was a risk factor of cardiotoxicity (A0). Additionally, it may both predict subsequent ACEIs/BB exposure (A1) and be predicted by past ACEIs/BBs exposure (A2). If use of chemotherapy was not controlled for in the analysis, then use of chemotherapy confounded the association of ACEIs/BBs treatment at time 1 with the outcomes (cardiotoxicity), because it

simultaneously affected both ACEIs/BBs treatment at time 1 and the risk for cardiotoxicity events.

Matching

A propensity scoring technique was used to reduce a potential selection bias that affected both the treatment and the outcome of interest. Specifically, the approach used to estimate the probability (or propensity) that an individual patient received a particular treatment (i.e., trastuzumab/anthracycline-based, taxane-based, and other adjuvant chemotherapy for research question 2 and ACEIs/BBs for research question 3). Matching variables for the propensity score were a patient's baseline covariates: patient characteristics, including age (in years at breast cancer diagnosis), gender, race/ethnicity; socioeconomic status; tumor characteristics, including stage, grade, estrogen receptor (ER) status; diagnosis year; modified Charlson comorbidity index; chemotherapeutic drug class (e.g., taxane-based); SEER region; surgery; and radiotherapy.

Next, we assigned a propensity score to each breast cancer patient regarding the probability of receiving chemotherapy (research question 2) and the probability of receiving ACEIs/BBs treatment (research question 3) using logistic regression models. The age of each patient was based on the difference in time between the index date and the date of birth.



Exposed group: 1) trastuzumab-based (with or without non-anthracycline chemotherapy); 2) anthracyclines-based (with or without trastuzumab chemotherapy); 3 anthracyclines plus trastuzumab; 4) taxane-bsased, 5) other adjuvant chemotherapy and **Non-exposed group:** hormone therapy
ACEI/BB user: Angiotensin converting enzyme inhibitors: ACEIs and Beta blockers: BBs; **ACEI/BB nonusers:** those who had never been prescribed ACEIs/BBs

Figure 3.3. Patient selection flow chart for aim 2 and 3

Table 3.2 Summary of outcome variables, measures, and statistical methods for aim 2

Aim2	Outcome variables	Measures	Statistical methods
		Part 1	
	Binary variable: Cardiotoxicity episode (HF and CF) or all-cause mortality (1 vs 0)	The incidence of cardiotoxicity or all-cause mortality (1 vs 0) after post-index period among patients with breast cancer who received: Exposed group: (1) trastuzumab-based (with or without non-anthracycline); 2) anthracyclines-based (with or without trastuzumab); 3 anthracyclines plus trastuzumab 4) taxane-based, 5) other adjuvant chemotherapy vs. non-exposed group: hormone therapy	Descriptive analyses examining proportion of patients with breast cancer who had cardiotoxicity events or die after received adjuvant chemotherapy
		Part 2	
	Binary variable: Cardiotoxicity episode (HF and CF) or all-cause mortality (1 vs 0) at a given time period t	Cardiotoxicity or all-cause mortality episode (1 vs 0) after post-index period among: patients with breast cancer who received trastuzumab-based and/or anthracycline based-, taxane-based, other adjuvant chemotherapy (exposed group) vs. those treated with hormone therapy (non-exposed group)	A Cox proportional hazard model estimating the risks of cardiotoxicity or all-cause mortality episode in patients with breast cancer treated with: trastuzumab and/or anthracyclines-based, taxane-based, other adjuvant chemotherapy vs. those treated with hormone therapy, controlling for patient characteristic, tumor characteristic, socioeconomic status, chemotherapy, radiation, surgery, pre-existing cardiovascular conditions, and comorbidities

Table 3.3 Summary of outcomes variables, measures, and statistical methods for aim 3

Aim3	Outcomes variables	Measures	Statistical methods
	Binary variable: Cardiotoxicity episode (HF and CF) or all-cause mortality (1 vs 0) at a given time in months	Cardiotoxicity or all-cause mortality episode (1 vs 0) during post-index period among breast cancer patients who received: Exposed group: ACEIs/BBs (ACEI/BB user) vs. nonexposed group: those who had never been prescribed ACEIs/BBs before or after the initiation of trastuzumab and/or anthracyclines	A Marginal structural Cox proportional hazard model with time-dependent inverse probability weights estimating the risks of cardiotoxicity or all-cause mortality episode in patients with breast cancer treated with trastuzumab and/or anthracyclines therapy with concurrent ACEIs/BB usage vs. nonexposed group, controlling for baseline covariates, covariates (i.e., duration of exposure, concurrent use of other antihypertensive medications)

Statistical Analysis by aim

Aim 1

A visit-level descriptive analysis using visit sampling weights for estimated national prescribing trends was described demographically. Weighted chi-square tests were used to compare differences in treatment pattern across patient demographic, health insurance, and setting. Also, proportions of receipt of treatment by drug class (alkylating agents, antibiotics, antimetabolites, hormones, mitotic inhibitors, TKIs, VEGF/VEGFR inhibitors, EGFR inhibitors, HER2 inhibitors) and drug category (classic, novel, hormone agents) across predictors were examined. Multivariable logistic regression identified factors associated with anti-neoplastic agent, controlling for demographic, cancer stage, comorbidities, type of insurance coverage, geographical location, and ambulatory care setting.

Dichotomous response variable (Y): receipt of anti-neoplastic agents in breast cancer patients (y=yes/no)

Predictors: demographic (age, sex, race/ethnicity), cancer stage, comorbidities, type of insurance coverage, geographical location, and type of setting

Logit (E(Yi))=natural log (odds)=$\beta 0+\beta 1X$demographic+ $\beta 2X$cancer stage+ $\beta 3X$comorbidities+ $\beta 4X$total chronic diseases + $\beta 5X$type of insurance+ $\beta 6X$geographical location+ $\beta 7X$setting

Aim 2

Baseline patient characteristics were compared across chemotherapy categories using the chi-squared test. Hazard Ratios (HRs) and 95% CIs of HF or CM episodes or all-cause mortality at a given time were compared across chemotherapy categories

therapy groups using Cox proportional hazards model, with hormone therapy as the reference group. The model adjusted for covariates, including patient characteristic, tumor characteristic, socioeconomic status, chemotherapy, radiation, surgery, comorbidities, and pre-existing cardiovascular conditions. Cox's proportional hazards model has been selected to examine the effect of exposure to adjuvant chemotherapy (i.e., trastuzumab, anthracyclines, taxane, and others) on time until cardiotoxicity episode or all-cause mortality. This is because its applicability to provide unbiased estimates of the likelihood of cardiotoxicity episode or all-cause mortality developing in the exposed group compared to the control group by adjusting for confounding factors at baseline. The hazard ratio provides the relative risk of cardiotoxicity based on comparison of event rates. Additionally, the Cox model is capable of handling right censoring under an assumption of a constant hazard function over time. [107]

Dichotomous outcome of interest variable (Y): the hazards function of cardiotoxicity and all-cause mortality in breast cancer patients at a given time (Y=0,1)

Exposure: adjuvant chemotherapy (i.e.,trastuzumab and/or anthracyclines, taxane-based, and other adjuvant chemotherapy (non-exposure: hormone therapy)

Covariates: patient demographic, tumor characteristic, socioeconomic status, radiation, surgery, pre-existing cardiovascular conditions, and comorbidities

The Cox proportional hazards model:

$h(t|X)= h_0(t)\exp(\beta 1 X\text{demographic}+ \beta 2 X\text{tumor characteristic}+ \beta 3 X\text{socioeconomic status}+ \beta 4 X\text{type of chemotherapy}+ \beta 5 X\text{radiation}+ \beta 6 X\text{surgery}+ \beta 7 X\text{pre-existing cardiovascular conditions}+\beta 8 X\text{comorbidities})$

Where h(t|x)= a conditional hazards of cardiotoxicity episode or mortality (0,1) given other covariates, $h_0(t)$= an unspecified baseline hazards, and t=a patient's time of cardiotoxicity episode or mortality with time measured in months

Aim 3

Baseline patient characteristics were compared across ACEI/BB user and ACEI/BB nonuser groups using the chi-squared test. Hazard Ratios (HRs) and 95% CIs of HF or CM episodes or all-cause mortality were compared across ACEI/BB users and ACEI/BB nonusers, using marginal structural Cox proportional hazards model. Marginal structural Cox proportional hazard model estimated the effect of ACEIs/BBs on the hazard of cardiotoxicity episode while addressing the effect of time-varying confounders that can influence treatment (i.e., ACEIs/BBs) over time. A time-dependent covariate/confounder 1) behaves as a risk factor for the outcome of interest and a predictor of subsequent exposure and 2) is affected by previous exposure/treatment. In our study, the time-dependent covariate was use of chemotherapy. For instance, patients undergoing chemotherapy whose cardiovascular conditions worsen may increase use of ACEIs/BBs in order to treat symptoms. On the contrary, those with an improvement of cardiovascular conditions may decrease use of ACEIs/BBs. However, use of chemotherapy itself may influence outcomes of cardiotoxicity episode.

Addressing the issue of time-varying confounding is important in observational studies because the effect of treatment (i.e., ACEIs/BBs) may be confounded by risk factors for cardiotoxicity, resulting in change in treatment over time (e.g., switching and stopping therapy). Although standard statistical approaches adjust for covariates by including them in the regression model as regressors, these approaches may not allow

proper adjustment for time-dependent covariates. The reason is because standard modeling approaches adjust for confounding factors at baseline and provide unbiased estimates of the effect of the early treatment exposure. However, they do not address concerns regarding loss to follow-up (i.e., right-censoring) and therapy change over time due to the time-varying confounder. In other words, Cox regression alone may provide biased estimated of the treatment effect of ACEIs/BBs in prevention of cardiotoxicity because of the time-varying confounder of chemotherapy use. Hence, we used Robins' marginal structural models (MSMs)[108] which are casual models based on inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs) to adjust for time-dependent confounders and informative loss to follow-up. The MSM approach has been used in previous studies, including HIV, arthritis, cancer, cardiovascular disease, and diabetes.[108-114]

Dichotomous outcome of interest variable (Y): the hazards function of cardiotoxicity or all-cause mortality in breast cancer patients treated with trastuzumab and/or anthracyclines at a given time in months (Y=0,1)

Exposure: ACEIs/BBs treatment (non-exposure: those who were never exposed to ACEIs/BBs)

Covariates: patient characteristic, tumor characteristic, socioeconomic status, comorbidities, time since exposure to ACEIs and/or BBs, treatment (i.e., radiation, surgery, chemotherapy), time since expose to antihypertensive treatment (duration), the initiation of antihypertensive treatment (before/after chemotherapy), other concurrent use of antihypertensive medications

Time-dependent confounder: use of trastuzumab and/or anthracycline chemotherapy

Marginal structural Cox proportional hazards model:

$\lambda_T(t|\bar{A}(t)V) = \lambda_0(t)\exp(\beta 1 A(t) + \beta 2 V)$

Where $\lambda_T(t|\bar{A}(t)V)$= a conditional hazard of cardiotoxicity or all-cause mortality of time t, as a function of ACEIs/BBs usage among breast cancer patients with baseline covariates V, $\lambda_0(t)$=an unspecified baseline hazards, A(t)=current ACEIs/BBs treatment

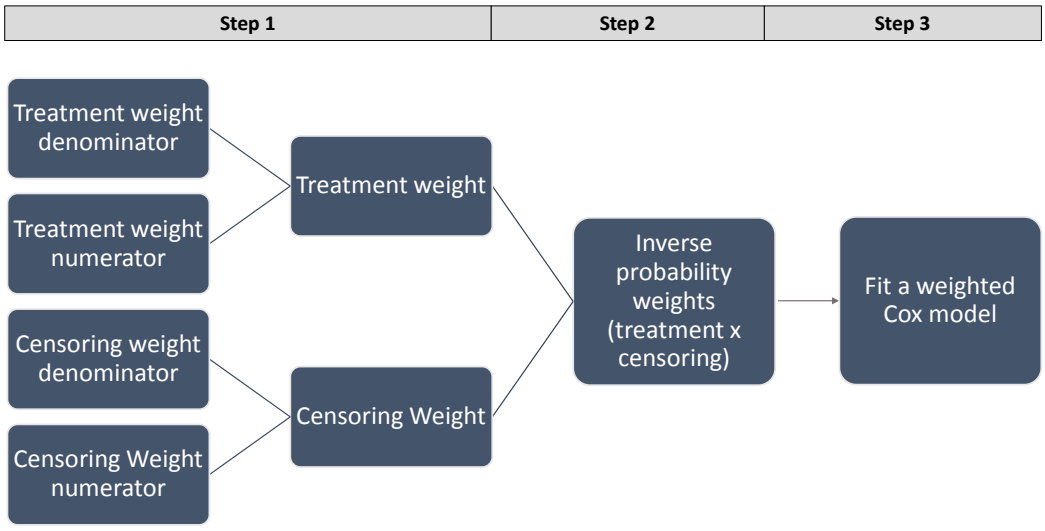


Figure 3.4. Marginal structural model process

Step 1. Estimate two weights (i.e., treatment and censoring weights) for each observation using logistic regression

Step 1.1 adjusting for treatment selection

To adjust for treatment selection, we calculated a stabilized weight of a patient's probability of having ACEIs/BBs treatment at each time point given the patient's covariates (baseline covariates and time-dependent covariates) as follows:

Numerator: Propensity scoring (i.e., the probability of receiving treatment using only baseline covariates)

Denominator: The overall probability of having treatment using baseline covariates and time-dependent covariate (i.e., use of trastuzumab/anthracycline chemotherapy)

Outcomes: Treatment (ACEI/BB user and ACEI/BB nonuser)

Step 1.2 adjusting for treatment discontinuation/right censoring

Similarly, to adjust for censoring by discontinuation of ACEIs/BBs treatment, we used the same procedure in step 1.1 to calculate stabilized weights based on each patient's probability at each time point to be censored given the patients' covariates (baseline covariates and time-dependent covariates) as follows:

Numerator: The probability of censoring using only baseline covariates

Denominator: The overall probability of censoring using baseline covariates and the time-dependent covariate (i.e., use of trastuzumab/anthracycline chemotherapy)

Outcomes: Treatment censoring (Yes/No)

Step 2: Conduct inverse probability weights of treatment selection and right censoring using results from step 1

Step 3: conduct a weighted repeated measures model analysis using generalized estimating equations (GEE)

We assessed model adequacy in order to evaluate how well the fitted statistical models surface describes the cloud of the data. This procedure assureed the robustness of the findings. For example, we performed scatterplots over time of the log-hazard function. In addition, sensitivity analyses were performed to examine the robustness of our findings across 1) ACEIs and BBs dose (low, average, and high) and 2) combination ACEIs and

BBs therapy on the risk of cardiotoxicity and all-cause mortality **(refer to Appendix C. Table C2 and C3).** All analyses were performed by SAS statistical software (version 9.3; SAS Institute, Inc., Cary, NC, USA) and the significance level was set at 0.05.

Chapter 4

Results

Aim 1

Abstract

Background: Despite the availability of previous studies, little research has examined how types of anti-neoplastic agents prescribed differ among various populations and health care characteristics in ambulatory settings, which is a primary method of providing care in the U.S. Understanding treatment patterns can help identify possible disparities and guide practice or policy change.

Objectives: To characterize patterns of anti-neoplastic agents prescribed to breast cancer patients in ambulatory settings and identify factors associated with receipt of treatment.

Methods: A cross-sectional analysis using the National Ambulatory Medical Care Survey data in 2006-2010 was conducted. Breast cancer treatments were categorized by class and further grouped as chemotherapy, hormone, and targeted therapy. A visit-level descriptive analysis using visit sampling weights estimated national prescribing trends (n=2,746 breast cancer visits, weighted n= 28,920,657). Multiple logistic regression analyses identified factors associated with anti-neoplastic agent used.

Results: The proportion of visits in which anti-neoplastic agent(s) was/were documented remained stable from 2006 to 2010 (20.47% vs 24.56%; $P>0.05$). Hormones were commonly prescribed (29.69%) followed by mitotic inhibitors (9.86%) and human epidermal growth factor receptor2 inhibitors (5.34%). Patients with distant stage were

more likely than patients with in situ stage to receive treatment (Adjusted Odds Ratio [OR]=2.79; 95% CI 1.04-7.77), particularly chemotherapy and targeted therapy. Patients with older age, being minorities, co-morbid depression, and having Medicaid insurance were less likely to receive targeted therapy (P<0.05). Patients with older age, having co-morbid obesity and osteoporosis were less likely to receive chemotherapy, while patients seen in hospital-based settings and settings located in metropolitan areas were more likely to receive chemotherapy (P<0.05).

Conclusions: Anti-neoplastic treatment patterns differ among breast cancer patients treated in ambulatory settings. Factors predicting treatment include certain *socio-demographics*, cancer stages, comorbidities, metropolitan areas, and setting.

Keywords: breast cancer; prescribing pattern; ambulatory care; disparities; chemotherapy

Introduction

Despite the availability of previous studies on breast cancer treatment patterns,[2,9,10,64,67-69,115-117] little research has focused on ambulatory medical care which is, according to the National Health Statistics Report, a primary method of providing health care services in the U.S.[96] Therefore, estimating trends in breast cancer treatment in ambulatory settings may help fill a gap in understanding breast cancer treatment patterns and factors associated with treatment or treatment disparities in various populations.

Although evidence largely supports the benefits of cancer treatment,[1] there has been concern regarding treatment disparities among cancer patients in the U.S.[63,64] Previous research has reported variations in breast cancer treatment among patients with different socioeconomic status and races,[10,67-69,115] particularly disparities in receipt of treatment, health outcomes, and survival.[2,9,68,115-117] However, existing evidence has come from hospital- or population-based registries and is limited to some geographic areas, types of insurance, settings, or locations of practice.[9,10,67-69,118,119] For example, studies using hospital-based registries might be more likely to capture certain types of treatment such as intravenous chemotherapy while less likely to represent hormones or oral chemotherapy regimens which are usually administered in ambulatory settings.[120] In addition, using some population-based registries may limit generalizability. For instance, studies using Surveillance, Epidemiology, and End Results (SEER) or SEER-Medicare data are usually limit to elderly Medicare patients.[10,64,67,119,121] Hence, younger populations or those with other types of insurance, including Medicaid or private insurance, may not be well represented.

Additionally, studies examining how types of anti-neoplastic agents prescribed differ among various populations are limited. Specifically, little research has addressed whether factors such as setting where care was provided, type of insurance, or location of practice, are related to treatment patterns. These factors can be categorized as structural barriers that have potential impact on the receipt of cancer treatment.[118] Since treatment of breast cancer has been reported to decrease the mortality rate from breast cancer,[122] examining whether or not breast cancer treatments are used with similar frequency across population subgroups receiving ambulatory health care is important because it may help identify treatment disparities among diverse, geographically representative populations.

In order to fill these existing knowledge gaps, the objective of this study was to characterize the patterns of anti-neoplastic agents prescribed to nationally representative breast cancer patients across time in ambulatory settings. This study also examined factors associated with the anti-neoplastic agents prescribed. These findings can help understand breast cancer treatment patterns and possible treatment disparities.

Methods

Study design and data source

This is a cross-sectional, retrospective study using the 2006-2010 records-based or encounter level data of two national surveys – the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (NAMCS/NHAMCS) conducted by the National Center for Health Statistics (NCHS). The NAMCS/NHAMCS are national, annual probability sample surveys supplying information about provision and use of ambulatory medical care services. The NAMCS/NHAMCS use a complex, stratified, multistage, probability design involving a

national sample of patient visits to non-federal physician offices and to non-institutional short-stay hospitals, including emergency departments (EDs) and outpatient departments (OPDs), respectively.

Data from the sampled visits are recorded by the physician or staff on an encounter form during a certain period that is randomly assigned for each practice. Data are obtained on physicians' diagnoses (using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)) and medications ordered. Demographic characteristics, services provided, sources of payment, and characteristics of the facility (e.g., location) are also reported. The therapeutic classification of drugs is based on the Multum Lexicon's therapeutic categories.[123] Detailed information on NAMCS/NHAMCS is published and available online.[124]

Study population

The NAMCS/NHAMCS provide patient visit-level data; therefore, the study sample was defined as visits to physicians/practice staffs in ambulatory settings (hospital- and office-based) during 2006-2010 (n=501,527 visits, representing 6,022,378,314 visits (i.e., weighted n) after applying sample weights provided by NAMCS/NHAMCS). Then this study was limited to visits in which a breast cancer diagnosis was documented using at least one ICD-9-CM diagnosis code for breast cancer (174-175) during the encounter (i.e., breast cancer visits). The final sample size included a total of 2,746 breast cancer visits (weighted n= 28,920,657).

Study variables

Receipt of anti-neoplastic agent

The main outcome, receipt of anti-neoplastic agent, was defined as a visit in which anti-neoplastic agent(s) was/were prescribed. Use of anti-neoplastic agent included at least one of the following medication classes: alkylating agents, antibiotics, antimetabolites, hormones, mitotic inhibitors, vascular endothelial growth factor (VEGF/VEGFR) inhibitors, and human epidermal growth factor receptor2 (HER2) inhibitors. Classes were provided by NAMCS/NHAMCS and classified by the Lexicon Plus®. These medication classes were further grouped in to three groups in a manner consistent with the National Comprehensive Cancer Network (NCCN) guidelines,[41] including targeted therapy, chemotherapy, and hormones. Specifically, targeted therapy was defined as use of VEGF/VEGFR inhibitors (e.g., bevacizumab) and HER2 inhibitors (e.g., trastuzumab and lapatinib). Chemotherapy was defined as use of adjuvant/neoadjuvant chemotherapy, including alkylating agents (e.g, cyclophosphamide), antibiotics (e.g., doxorubicin), antimetabolites (e.g., fluorouracil), and mitotic inhibitors (e.g., paclitaxel). Hormones included selective estrogen receptor modulators and aromatase inhibitors (e.g, tamoxifen).

Covariates

Covariates included patient characteristics, setting of visit characteristics, and source of payment. Specifically, patient characteristics included sociodemographic variables (including age, sex, race/ethnicity, insurance, residence in poverty area -- using ≥20% poverty in patient's zip code as a measure of high poverty level),[125] cancer stage, comorbid conditions, and total chronic diseases recorded during each visit. The setting of

visit characteristics included geographic location of practice (Northeast, Midwest, South, and West), metropolitan statistical area, and type of setting (hospital- and office-based). Groups of variables were combined if they had less than 30 un-weighted cases in each cell, as recommended by the NCHS.[126] Cancer stage was defined as current staging during a patient visit. The staging system was applied using the Surveillance, Epidemiology, and End Results (SEER) Summary Stage, as in-situ, localized, regional, distant, and unknown.[127]

Statistical analysis

The unit of analysis was the visit-level. Descriptive and multiple logistic regression analyses using the complex multistage design with visit sampling weights provided by the NCHS were conducted to estimate national prescribing trends for breast cancer patients visiting ambulatory care settings between 2006-2010. Weighted chi-square tests were used to compare differences in treatment class and category by setting of visit and time. Multiple logistic regression identified factors associated with use of any anti-neoplastic agent, controlling for patient age category, race/ethnicity, cancer stage, comorbidity, source of payment, region, poverty level, metropolitan status, and setting. Male patient visits were excluded from logistic analyses due to the number of unweighted cases < 30. The final sample size after excluding male patient visits was 2,721; weighted n= 28,770,446 visits. All statistical analyses were conducted using SAS (version 9.2; SAS Institute, Cary, NC) and the two-sided significance was defined as $P<0.05$.

Results

Patient and setting characteristics

Table 1 presents overall characteristics of visits to hospital-and office-based settings for breast cancer patients. Of the 2,746 breast cancer visits between 2006 and 2010 (representing 28,920,657 visits), approximately 14.40(±2.39)% were hospital-(representing 4,166,051 visits) and 85.59(±2.39)% were office-based settings (representing 24,754,606 visits). Among the visits to hospital- and office-based settings, receipt of anti-neoplastic agents was identified in 48.83(±5.68)% and 43.07(±2.97)% of the visits, respectively. Generally, the results show some variations between office- and hospital-based settings in terms of the distribution of types of anti-neoplastic agents. Particularly, a higher proportion of patients received alkylating agents and antibiotics in hospital-based settings as compared to office-based settings ($P<0.05$), while receipt of other agents in hospital-based were similar to office-based settings. Receipt of hormones was documented among almost one-third of breast cancer visits in both hospital-based and office-based settings. In terms of patient's characteristics, a higher proportion of those with older age (≥65), being White, and having more chronic diseases were found in visits to office-based settings. Contrastingly, a greater proportion of patients with Medicaid insurance were seen in hospital-based settings (all $P<0.05$). There was no difference between hospital-or office based-settings in terms of cancer stage, residence in poverty areas, location in metropolitan areas, and region of practice.

Table 2 summarizes descriptive characteristics of patients with breast cancer by anti-neoplastic drug category. In general, the results show some variations in the distribution of receipt of treatment among patient and health care characteristics and this

is consistent across drug category (i.e., chemotherapy, hormone, and targeted therapy). For instance, patients who were younger than 65 years old, White, had invasive cancer, and had fewer chronic diseases more commonly received treatment of any type. Likewise, each drug category was predominantly prescribed during visits at ambulatory settings located in metropolitan areas. Contrastingly, the proportion of patients receiving treatment during visits, regardless of drug category, was low for patients with Medicaid or other insurances (e.g., self-pay) and residence in high poverty areas.

Trends of anti-neoplastic agents among breast cancer visits by year

Figure 1 describes trends for visits across receipt of chemotherapy, hormone, and targeted therapy in 2006-2010. Overall, no statistically significant differences were found in receipt of anti-neoplastic agents over time, with 20.47% receiving treatment in 2006 and 24.56% receiving treatment in 2010 ($P>0.05$ for test of trend regarding receipt of any anti-neoplastic agents). For all ambulatory settings combined (hospital-and office-based), the weighted number of visits with receipt of anti-neoplastic agent was approximately 2.6 million in 2006, increasing to 3.1 million in 2010. Likewise, receipt of chemotherapy, hormone, and targeted therapy during visits were stable across year from 2006-2010.

Patterns of anti-neoplastic agents among breast cancer visits by cancer stage

Figure 2 illustrates the distribution of anti-neoplastic agents documented during visits across cancer stage. Overall, a smaller proportion of visits received any treatment in carcinoma in-situ (non-invasive), compared to invasive stages. Anti-neoplastic agents were prescribed in more than 90% of visits among patients with distant stage breast cancer. In terms of individual anti-neoplastic agents across cancer stage, hormonal therapy accounted for the highest proportion of anti-neoplastic treatment during visits,

regardless of cancer stage (ranging from 26.05-37.84%). The other common agents were mitotic inhibitors and HER-2 inhibitors which were widely prescribed, ranging from non-invasive to invasive breast cancer. However, the use of certain anti-neoplastic agents such as antimetabolites, mitotic inhibitors, and VEGF/VEGFR inhibitors was higher in advanced breast cancer. Specifically, the highest proportion of receipt of antimetabolites or mitotic inhibitors was seen in patients with distant stage as compared to other stages ($P<0.05$)

Factors associated with receipt of anti-neoplastic agents

Table 3 includes the results of four multiple logistic regression models examining factors associated with receipt of anti-neoplastic agents, overall and by drug category (i.e., chemotherapy, hormone, and targeted therapy). In terms of cancer stage during a visit, patients with distant stage cancer were more likely than patients with in situ stage to receive any anti-neoplastic agents (Adjusted Odds Ratio [OR]=2.79; 95% CI, 1.04-7.77). Similarly, those with distant stage cancer were more likely to receive chemotherapy (OR=6.79; 95% CI, 2.44-18.88) and targeted therapy (OR=7.12; 95% CI, 2.03-14.97). In addition to distant stage, those with regional stage were also more likely to receive chemotherapy (OR=3.63; 95% CI, 1.15-12.56). Regarding sociodemographics, patients ≥65 years old (vs. 45-64 years old) were less likely to receive either chemotherapy or targeted therapy. Additionally, patients being a racial/ethnic minority (e.g., Asian or American Indian) and having Medicaid insurance (vs. Medicare) were less likely to receive targeted therapy. Likewise, patients with co-morbid osteoporosis and obesity were less likely to receive chemotherapy, while those with co-morbid depression were less likely to receive targeted therapy (all $P<0.05$). Regarding setting characteristics,

patients seen in hospital-based settings were more likely to receive chemotherapy as compared to those seen in office-based settings (OR=2.06; 95% CI, 1.07-4.23). In addition, ambulatory settings located in metropolitan areas were associated with receipt of chemotherapy (OR=1.66; 95% CI, 1.02-2.80).

Discussion

This is the first study to provide nationally representative estimates of breast cancer treatment patterns and receipt of treatment by different types of anti-neoplastic agents in ambulatory medical care. This study also identified patterns of treatment across cancer stage, as well as several factors associated with receipt of specific types of anti-neoplastic treatments including patient sociodemographic factors, comorbidities, and certain characteristics of the treatment setting (e.g., metropolitan areas and type of settings).

The results demonstrate that among ambulatory medical settings, office-based settings appear to be a common location for treatment of breast cancer patients compared to hospital-based settings, and this is consistent with a previous study using NAMCS/NHAMCS.[8] In terms of breast cancer treatment, findings indicate that proportions of patients who received any anti-neoplastic agents during visits are similar across years and settings. Specifically, results of this study indicate that hormonal therapy is the most common anti-neoplastic treatment prescribed during visits in ambulatory settings regardless of cancer stage and health care setting. This may be explained by the evidence that hormone therapy is recommended for breast cancer in patients with estrogen receptor (ER) positive tumors, both in early and advanced breast cancer.[41,42,47]

Regarding patterns of treatment across cancer stage, patients in ambulatory settings appear to receive breast cancer treatment that is broadly consistent with guidelines. That is, the proportion of receipt of any treatment was lower among patients with carcinoma in-situ and substantially higher among patients with advanced stage cancer. One obvious explanation to support this assumption is that cancer guidelines for advanced breast cancer recommend use of hormones, chemotherapy, and targeted therapy, either as single agents or combination regimens.[41,47] Likewise, a relatively lower proportion of treatment of carcinoma in-situ might be explained by the fact that chemotherapy and targeted therapy are not recommended by treatment guidelines except for cases where patients are ER-positive or HER-2 positive.[41,42]

Similar rates of receipt of any anti-neoplastic agents were observed across subgroups defined by sociodemographic characteristics such as age group, race/ethnicity, and type of insurance. However, when narrowing down to drug category, findings in this study demonstrated that older patients were less likely to receive chemotherapy and targeted therapy compared to younger patients (age $\leq$ 65). Findings in this study are similar to a previous population-based study using SEER-Medicare data in that receipt of chemotherapy decreased significantly with age group, particularly in those age 75 years and older.[10] In addition, minority women with breast cancer were less likely to receive targeted therapy during visits, which is consistent with a previous study conducted by Bickell and colleagues which demonstrated a racial disparity in receipt of anti-neoplastic agents.[128] Likewise, this study emphasizes findings from a previous study that found a significant association between insurance coverage and the selection of breast cancer chemotherapy regimens.[115,125] Specifically, the odds of receipt of targeted therapy were

significantly lower among women with Medicaid as compared to those with Medicare. Similarly, the results from this study are consistent with a previous study using SEER data in terms of differences across metropolitan statistical areas.[121]

Cancer stage is another significant factor associated with an increased likelihood of receiving anti-neoplastic agents. Specifically, cancer with distant locations is associated with the likelihood of receiving any anti-neoplastic agents, and also receipt of chemotherapy and targeted therapy. Similarly, Griggs and colleagues reported that breast cancer patients with higher stage or higher tumor grade were more likely to receive chemotherapy.[129] Importantly, findings reported in this study also demonstrate that patients appear to receive treatment concordant with standard guidelines.[41,47] For instance, the NCCN guidelines recommend systemic therapy as a primary approach for patients with recurrent or metastatic breast cancer.[41] Particularly, a variety of chemotherapy regimens are recommended for this population regardless of ER status (positive/negative), while combination chemotherapy with targeted therapy such as trastuzumab is recommended for HER2-positive patients. In addition, findings in this study indicated that patients with certain comorbidities, including depression, osteoporosis, and obesity were less likely to receive certain types of treatment. This study yields consistent results with a previous study that demonstrated that women diagnosed with depression were significantly less likely to receive breast cancer treatment compared with those without depression (59.7% vs 62.2%).[130] Further, findings in this study suggest that obese breast cancer patients were less likely to receive chemotherapy. It is noteworthy that the results in this study may be indicative of recent evidence from the

American Society of Clinical Oncology that approximately 40% of obese cancer patients received inadequate doses of chemotherapy.[131]

Findings in this study have a number of clinical and public health implications. First, findings based on encounter level data may help to understand practice variation and the effectiveness of practice guideline dissemination. A better understanding of geographic variability in practice may heighten awareness of the importance of linking clinical research to routine practice, which can result in better treatment outcomes in breast cancer patients. Second, although this study suggested that patients were likely to receive guideline-concordant treatment during ambulatory visits, it also underscores that treatment disparities exist among the ambulatory U.S. breast cancer population, specifically in terms of race/ethnicity, age, type of insurance, and metropolitan areas. Hence, the findings may provide evidence to policy makers in order help achieve the American Cancer Society (ACS) 2015 challenge goals for eliminating cancer disparities across diverse cancer populations in the U.S. For instance, policy makers may use information regarding disproportionate distribution in breast cancer treatment by health insurance to improve equal access to care. Also, policy makers may pay attention to office-based settings when modifying policies relevant to breast cancer care, since the majority of patients with breast cancer visited this setting. Third, factors associated with receipt of treatment should be considered when assessing breast cancer patients in ambulatory settings in order to help identify potentially undertreated patients. In addition, this study calls attention to future research to examine treatment patterns among breast cancer patients with comorbid depression and obesity because evidence suggests that treatment of these conditions in cancer patients are often inadequate.[131,132] Overall,

treatment rates and the types of treatment patterns were expected to be relatively consistent across population subgroups. However, given the variation in the clinical practice patterns relative to newer more expensive drugs, this is likely evidence of treatment differences related to physician preference, patients' ability to pay, or severity of breast cancer among settings. Further research is needed to investigate these treatment differences.

Several limitations and strengths in this study should be noted. First, NAMCS/NHAMCS data are cross-sectional, visit-based surveys so the study can only provide estimated associations instead of causality. Further, without patient-level identifiers, the results in this study can not reflect patient-level data nor account for multiple visits by the same patient. Despite the limitations of encounter-based data, strengths of this current study included its large complex survey design providing nationally representative estimates of breast cancer treatment patterns, with generalizable estimates by age and racial/ethnic groups in the U.S. Also, this study is not subject to recall bias because relevant information from the medical record was collected by physicians/staff, rather than from patients. The small sample size for some anti-neoplastic agents is a limitation. However, this issue has been addressed by pooling multiple years, combining settings (hospital- and office-based settings), and grouping variables (chemotherapy, hormone, targeted therapy) to improve the reliability of estimates in this study.[133] Further, certain factors that may have an impact on receipt of treatment were not available in the data, such as physicians/patients decision-making regarding treatment modality, prognostic indicators, or patient factors (e.g., transportation).[41,42,47,134] Furthermore, patterns of breast cancer treatment are limited to ambulatory settings and

may not be generalized to other settings such as long-term stay hospital settings. Finally, clinical information such as biological characteristics or genetic biomarkers of the tumor (e.g., hormone receptor status or HER2 status) in NAMCS/NHAMCS is limited, preventing possible inferences about the appropriateness of treatment.[134] Consequently, this study did not intend to imply whether receipt of anti-neoplastic agent(s), or receipt of a specific agent, was/were appropriate or not.

Conclusions

The proportion of breast cancer patients receiving ambulatory treatment remains stable across time. Factors predicting type of treatment include sociodemographic characteristics such as age, race/ethnicity, type of insurance, cancer stage, and certain comorbidities, as well as ambulatory care characteristics, including setting and metropolitan areas. These findings provide opportunities for research on treatment access and health disparities in order to improve quality of care in breast cancer patients.

Table 1: Characteristics of visits to hospital-based clinics and office-based physicians of breast cancer patients

Characteristics	Visits to hospital-based clinics(1,637)[a]		Visit to office-based physicians(1,184)[b]	
	Un-weighted	Weighted distribution[c]	Un-weighted	Weighted distribution[c]
	Number of visits	%(SE)	Number of visits	%(SE)
Anti-neoplastic agents				
No	842	51.17(5.68)	649	56.93(2.97)
Yes	720	48.83(5.68)	535	43.07(2.97)
Chemotherapy	300	19.14(4.54)	168	12.04(2.26)
Hormone	393	29.52(3.00)	350	29.72(2.35)
Targeted therapy	129	7.10(1.36)	74	5.82(1.11)
Drug class				
Alkylating agents[d]	102	8.39(2.24)	37	2.74(0.83)
Antibiotics[d]	80	5.88(1.70)	26	1.38(0.41)
Antimetabolites	65	3.99(1.22)	36	2.79(0.80)
Hormone	393	29.52(3.00)	350	29.72(2.35)
Mitotic inhibitors	188	12.67(2.52)	118	9.07(1.98)
VEGF/VEGFR inhibitors	27	1.13(0.52)	11	0.60(0.21)
HER2 inhibitors	110	6.08(1.39)	63	5.22(1.10)
Age[d]				
≤44	215	14.46(2.08)	121	9.77(1.36)
45-64	838	56.65(2.65)	561	47.56(2.72)
65-74	293	15.94(1.34)	289	23.39(2.47)
>75	216	12.96(1.93)	213	19.29(2.13)
Sex				
Female	1546	98.93(0.56)	1175	99.57(0.19)
Male	16	1.07(0.56)	9	0.43(0.19)
Race/Ethnicity[d]				
White	1143	68.41(5.52)	954	77.84(2.04)
African-American	265	20.18(5.41)	110	11.40(2.02)
Hispanic	89	7.79(2.03)	85	8.65(1.58)
Others[e]	65	3.62(1.21)	35	2.11(0.56)
Cancer stage[f]				
In situ	102	6.12(1.89)	88	6.84(1.59)
Localized	320	18.66(2.25)	275	22.41(3.03)
Regional	211	10.67(3.24)	178	12.64(1.71)
Distant	165	6.77(1.39)	106	6.33(1.16)

Table 1. (continued)

Unknown	764	57.79(4.62)	537	51.78(4.23)
Total chronic diseases[d]				
1	854	58.83(3.58)	623	48.84(2.33)
2	354	20.67(2.23)	260	21.79(1.90)
3	212	13.60(1.84)	164	17.53(1.82)
>3	142	6.90(2.17)	137	11.85(1.95)
Source of payment[d]				
Medicare	465	26.61(1.85)	445	36.46(2.69)
Private insurance	714	46.40(4.69)	578	50.53(2.72)
Medicaid	200	16.22(3.07)	79	5.99(1.05)
Other[g]	183	10.77(2.46)	82	7.02(1.38)
Poverty level[h]				
Low	1282	72.94(5.30)	983	83.79(2.69)
High	280	27.06(5.30)	201	16.21(2.69)
Metropolitan status				
MSA	1340	88.32(8.25)	1077	89.31(5.15)
Non-MSA	222	11.68(8.25)	107	10.69(5.15)
Region of practice				
Northeast	537	25.02(7.98)	248	16.19(2.69)
Midwest	222	15.32(4.21)	306	25.98(4.78)
South	632	50.13(9.25)	331	39.06(5.90)
West	171	9.53(2.99)	299	18.78(4.45)

Abbreviations: VEGF/VEGFR inhibitors, vascular endothelial growth factor receptor inhibitors; HER2 inhibitors, human epidermal growth factor receptor2 inhibitors; SE, standard error of percent; MSA, Metropolitan Statistical Area.

[a] Represents 4,166,051 hospital-based and visits.

[b] Represents 24,754,606 office-based visits.

[c] Percentages were calculated using weighted national survey estimates.

[d] $P<0.05$.

[e] Other races include Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, multiple races.

[f] Cancer stage was defined as current staging during a visit.

[g] Other includes self-pay, other source of payment, worker's compensation, charity, unknown, and no charge.

[h] High poverty level was defined as at ≥20% of poverty in patient's zip code.

Table 2: Characteristics of visits by breast cancer patients on anti-neoplastic by drug category

Characteristics	Chemotherapy[a]	Hormone[b]	Targeted therapy[c]
	Weighted distribution[d] %(SE)	Weighted distribution[d] %(SE)	Weighted distribution[d] %(SE)
Age			
≤44	15.43(3.47)	7.98(1.53)	10.26(2.96)
45-64	49.92(5.04)	51.17(4.17)	69.80(6.81)
65-74	15.17(2.56)	25.91(3.79)	12.54(3.85)
>75	19.49(3.87)	14.93(2.75)	7.40(3.97)
Sex			
Female	99.41(0.42)	99.44(0.20)	99.34(0.67)
Male	0.59(0.42)	0.56(0.20)	0.66(0.64)
Race/Ethnicity			
White	80.60(4.02)	76.04(3.42)	74.60(6.25)
African-American	8.34(2.50)	13.22(3.54)	18.67(6.13)
Hispanic	7.65(1.34)	8.56(1.49)	2.09(1.32)
Others[e]	3.40(1.82)	2.18(0.65)	4.64(3.60)
Cancer stage[f]			
In situ	4.89(1.75)	5.99(1.95)	4.10(2.06)
Localized	16.41(4.05)	27.87(5.00)	24.25(11.59)
Regional	22.38(5.24)	13.58(3.07)	14.24(4.93)
Distant	16.93(4.00)	6.38(1.65)	16.59(3.68)
Unknown	39.39(6.08)	46.18(6.25)	40.82(8.98)
Total chronic diseases			
1	66.59(4.64)	49.08(4.92)	60.57(8.00)
2	13.44(2.59)	19.85(2.77)	9.46(2.28)
3	11.12(2.28)	19.83(3.33)	18.08(4.17)
>3	8.85(3.50)	11.24(2.67)	11.89(6.17)
Source of payment			
Medicare	33.90(3.71)	33.22(3.84)	24.62(8.07)
Private insurance	52.71(3.19)	50.81(3.97)	67.53(8.33)
Medicaid	9.20(2.69)	7.92(1.30)	1.05(0.38)
Other[g]	4.74(1.22)	8.05(2.00)	6.80(3.81)
Poverty level[h]			
Low	85.81(3.69)	82.41(3.30)	81.27(7.64)
High	14.19(3.69)	17.59(3.30)	18.73(7.64)
Metropolitan status			
MSA	92.79(4.18)	88.43(5.65)	87.98(7.72)
Non-MSA	7.20(4.18)	11.57(5.65)	12.02(7.72)

Table 2. (continued)

Region of practice			
Northeast	17.19(4.13)	17.41(3.10)	21.21(5.26)
Midwest	23.19(5.85)	24.96(5.01)	23.84(4.55)
South	34.05(6.96)	42.10(6.41)	36.85(9.12)
West	25.57(12.20)	18.23(5.76)	18.10(5.74)

Abbreviations: SE, standard error of percent; MSA, Metropolitan Statistical Area.
[a] Chemotherapy included alkylating agents, antibiotics, antimetabolites, and mitotic inhibitors, n=468, representing 3,777,371visits.
[b] n=743, representing 8,587,453visits.
[c] Targeted therapy included vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitors and human epidermal growth factor receptor(HER)2 inhibitors, n=203, representing 1,736,807 visits.
[d] Percentages were calculated using weighted national survey estimates.
[e] Other races include Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, multiple races.
[f] Cancer stage was defined as current staging during a visit.
[g] Other includes self-pay, other source of payment, worker's compensation, charity, unknown, and no charge.
[h] High poverty level was defined as at ≥20% of poverty in patient's zip code.

Table 3: Logistic regressions of cancer treatment among patients who visited hospital-based clinics and office-based clinics (n=2,721 visits; weighted n= 28,770,446visits)

Characteristic	Receipt of treatment			
	Any anti-neoplastic agents[a]	Chemotherapy[a]	Hormone[a]	Targeted therapy[a]
	OR(95% CI)[b]	OR(95% CI)[b]	OR(95% CI)[b]	OR(95% CI)[b]
Age				
45-64	REF	REF	REF	REF
≤44	0.71(0.44-1.14)	1.31(0.65-2.61)	0.69(0.41-1.18)	0.63(0.27-1.48)
65-74	0.85(0.52-1.38)	0.48(0.30-0.75)[d]	1.15(0.68-1.93)	0.25(0.11-0.56)[d]
≥75	0.65(0.38-1.12)	0.86(0.41-1.78)	0.75(0.43-1.32)	0.17(0.05-0.53)[d]
Race/Ethnicity				
White	REF	REF	REF	REF
African-American	0.83(0.49-1.41)	0.45(0.20-1.02)	0.97(0.58-1.64)	1.20(0.57-2.54)
Hispanic	0.63(0.35-1.12)	0.85(0.26-2.75)	0.96(0.53-1.76)	0.33(0.08-1.30)
Others[c]	0.96(0.35-2.65)	0.94(0.20-4.41)	0.79(0.35-1.80)	0.34(0.10-0.96)[d]
Cancer stage[e]				
In situ	REF	REF	REF	REF
Localized	1.83(0.90-3.74)	1.37(0.35-5.34)	1.55(0.69-3.46)	2.31(0.58-9.23)
Regional	1.74(0.80-3.79)	3.63(1.15-12.56)[d]	1.22(0.56-2.63)	2.05(0.62-6.82)
Distant	2.79(1.04-7.77)[d]	6.79(2.44-18.88)[d]	1.11(0.41-2.98)	7.12(2.03-14.97)[d]
Unknown	0.94(0.47-1.86)	1.21(0.44-3.33)	0.90(0.43-1.88)	1.50(0.44-5.06)
Comorbidity				
Cerebrovascular disease	0.51(0.15-1.75)	0.17(0.02-1.68)	0.78(0.22-2.74)	0.59(0.09-3.94)
Heart failure	0.73(0.24-2.23)	1.36(0.17-10.91)	0.64(0.18-2.24)	2.27(0.31-16.34)
COPD	2.52(0.53-11.91)	0.73(0.21-2.58)	3.09(0.65-14.74)	2.68(0.96-7.52)

Table 3. (continued)

Depression	0.64(0.34-1.19)	0.66(0.27-1.64)	0.81(0.41-1.58)	0.11(0.05-0.41)[d]
Diabetes	0.93(0.50-1.74)	1.05(0.40-2.77)	1.16(0.64-2.09)	0.48(0.12-1.97)
Hyperlipidemia	0.97(0.58-1.63)	1.36(0.63-2.95)	1.05(0.62-1.76)	1.38(0.38-5.05)
Hypertension	1.19(0.81-1.76)	0.76(0.47-1.25)	1.26(0.83-1.90)	1.94(1.04-3.61)[d]
Ischemic heart disease	0.61(0.21-1.78)	0.49(0.06-4.07)	0.92(0.34-2.49)	0.19(0.02-1.54)
Obesity	0.69(0.26-1.82)	0.34(0.14-0.84)[d]	0.71(0.28-1.82)	0.87(0.20-3.81)
Osteoporosis	1.21(0.62-2.38)	0.25(0.10-0.61)[d]	1.81(0.92-3.54)	0.49(0.13-1.84)
Source of payment				
Medicare	REF	REF	REF	REF
Private insurance	1.01(0.62-1.64)	0.72(0.49-1.05)	1.14(0.71-1.84)	0.88(0.34-2.29)
Medicaid	1.21(0.65-2.26)	1.03(0.41-2.54)	1.27(0.70-2.33)	0.12(0.04-0.33)[d]
Other[f]	1.09(0.55-2.14)	0.44(0.19-1.06)	1.29(0.63-2.64)	0.57(0.11-2.86)
Poverty level[g]				
Low	REF	REF	REF	REF
High	0.98(0.65-1.48)	0.84(0.51-1.40)	0.92(0.56-1.50)	1.47(0.55-3.93)
Metropolitan status				
Non-MSA	REF	REF	REF	REF
MSA	1.07(0.74-1.55)	1.66(1.02-2.80)[d]	0.99(0.63-1.53)	1.10(0.46-2.63)
Region of practice				
Northeast	REF	REF	REF	REF
Midwest	1.06(0.65-1.72)	1.04(0.66-1.64)	1.30(0.74-2.29)	0.59(0.25-1.42)
South	1.17(0.78-1.75)	0.92(0.54-1.56)	1.37(0.85-2.23)	0.60(0.28-1.30)
West	1.30(0.51-3.31)	1.56(0.52-4.65)	1.39(0.77-2.52)	0.70(0.29-1.67)
Setting				
Office-based	REF	REF	REF	REF

Hospital-based	1.28(0.76-2.15)	2.06(1.07-4.23)[d]	1.02(0.69-1.51)	1.23(0.66-2.30)

Abbreviations: COPD, chronic obstructive pulmonary disease; REF, reference; OR, odds ratio; CI, confidence interval; MSA, Metropolitan Statistical Area.

[a] Received any anti-neoplastic agents n=1,242, representing 12.62 million visits; chemotherapy included alkylating agents, antibiotics, antimetabolites, and mitotic inhibitors n=463 representing 3.76 million visits; received hormone n=735, representing 8.54 million visits; targeted therapy included vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitors and human epidermal growth factor receptor(HER)2 inhibitors n= 201, representing 1.73 million visits.

[b] Adjusted Odds Ratio controlling for patient age category, patient race/ethnicity, cancer stage, comorbidity, source of payment, region, poverty level, metropolitan status, and setting.

[c] Other races includes Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, multiple races.

[d] $P<0.05$.

[e] Cancer stage was defined as current staging during a visit.

[f] Other includes self-pay, other source of payment, worker's compensation, charity, unknown, and no charge.

[g] High poverty level was defined as at ≥20% of poverty in patient's zip code.

Figure 1. Number of visits in which chemotherapy, hormone, targeted therapy was documented, by year

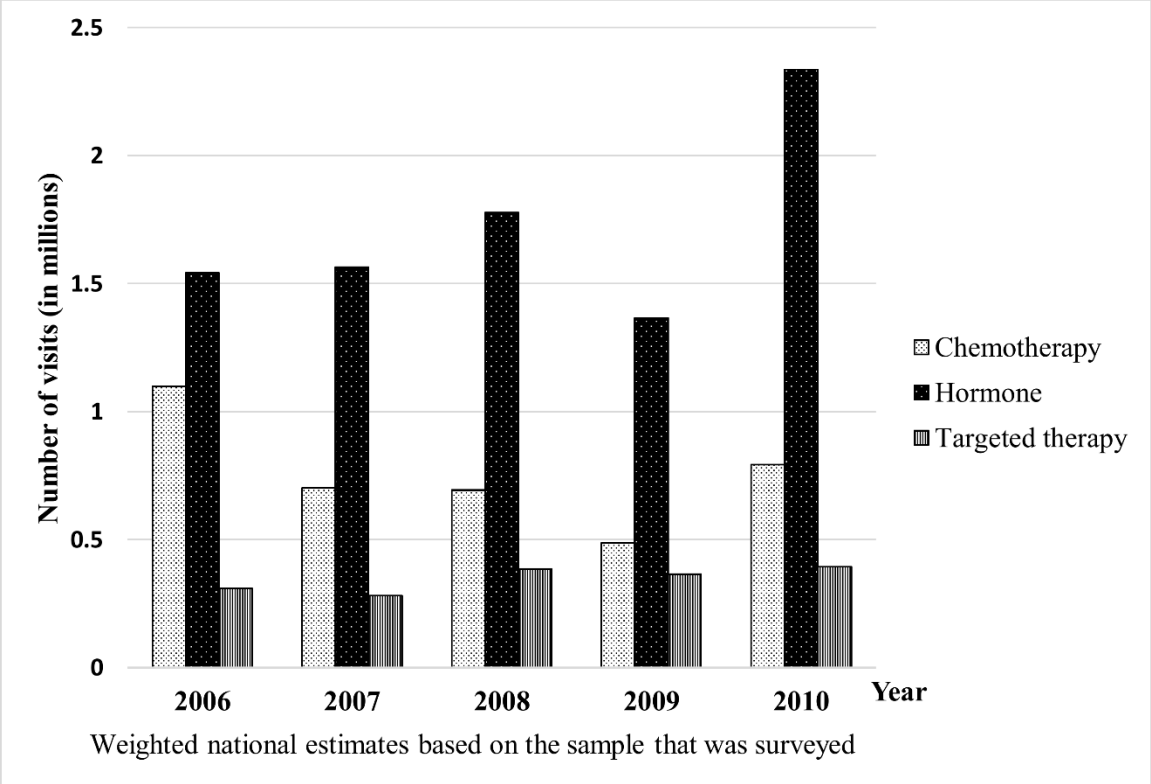
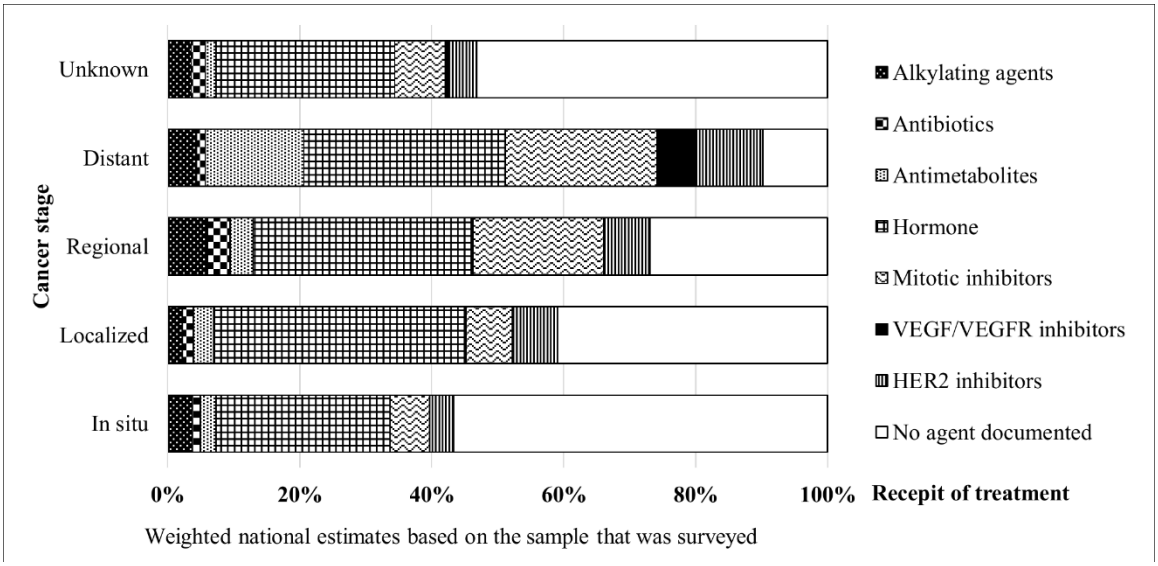


Figure 2. Proportion of visits in which anti-neoplastic agent was documented, by cancer stage[a]



Abbreviations: VEGF/VEGFR inhibitors, vascular endothelial growth factor receptor inhibitors; HER2 inhibitors, human epidermal growth factor receptor2 inhibitors.

[a] Cancer stage was defined as current staging during a visit.

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Aim 2

Abstract

Objectives: The purpose of this study was to estimate incidence of and identify factors associated with all-cause mortality and cardiotoxicity, defined as heart failure and/or cardiomyopathy, in breast cancer patients receiving chemotherapy or hormones.

Methods: A retrospective, population-based cohort study of 138,320 women (≥66 years of age) newly diagnosed with breast cancer from 2001-2009 was conducted using the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database. Chemotherapy was classified as mutually exclusive groups: trastuzumab-based, anthracycline-based, anthracycline and trastuzumab-based, taxane-based, and other chemotherapy. Propensity score matching adjusted for differences in patient characteristics across treatments. The final sample included a total of 12,168 women. Cumulative rates of cardiotoxicity and all-cause mortality were calculated and multivariable Cox proportional models estimated hazard ratios (HRs) of cardiotoxicity and all-cause mortality adjusting for sociodemographics, cancer characteristics, comorbidities, surgery and radiation, region, and year at diagnosis.

Results: Compared with hormones, risk of cardiotoxicity was higher in patients treated with anthracycline and trastuzumab-based (adjusted HR=2.02; 95% confidence intervals [CI]=1.62-2.51), trastuzumab-based (HR=1.45; 95%CI=1.24-1.69), and anthracycline-based (HR=1.28; 95%CI=1.14-1.44) regimens compared to patients treated with hormones, respectively. Certain baseline characteristics were significant predictors of cardiotoxicity, including demographics (older age (vs. ≤70), non-hispanic black), cancer characteristics (advanced stage), cardiovascular or renal failure comorbid, year at diagnosis, and West region. Additionally, risk of all-cause mortality was higher in

patients treated with taxane-based (HR=1.49; 95%CI=1.38-1.62) regimens compared to hormones. Baseline characteristics including sociodemographics, cancer characteristics, cardiovascular or renal failure comorbidity, year at diagnosis, and South region were significant predictors of all-cause mortality (all $P<0.05$).

Conclusions: Women with breast cancer treated with trastuzumab-based and/or anthracycline-based regimens had increased cardiotoxicity risk compared with hormones, while those treated with taxane-based regimens had higher rates of all-cause mortality. Types of chemotherapy are associated with increased risk of cardiotoxicity and all-cause mortality. Practitioners should further evaluate type of treatment and patient characteristics for risk mitigation strategies.

Introduction

Despite the benefits of anti-neoplastic agents for decreasing mortality from breast cancer, these favorable effects are also associated with adverse effects, particularly cardiotoxicity. Anti-neoplastic agents, including conventional chemotherapy (i.e., anthracyclines) and targeted therapy (i.e. trastuzumab), have become increasingly recognized to cause cardiotoxicity, including heart failure (HF) and cardiomyopathy (CM).[12,13,59,97,135] For example, a study using the Surveillance, Epidemiology and End Results (SEER) database demonstrated a 38.4% incidence of heart failure in women at 10 years after completion of anthracycline-based therapy.[13,48] Likewise, the incidence of cardiac dysfunction was 0.5-34% of patients in the clinical trials of trastuzumab.[14-16] In terms of combination regimens, anthracyclines in combination with or followed by trastuzumab resulted in high incidence of cardiotoxicity, compared with non-trastuzumab therapy.[34,83] Chemotherapy-induced cardiotoxicity may cause serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis.[17] This cardiac adverse event may compromise the clinical effectiveness of chemotherapy and eventually lead to premature death.[17-19]

Current data regarding the risk of cardiotoxicity in chemotherapy, particularly with trastuzumab, outside of clinical trials are limited. Although previous clinical studies examined chemotherapy-induced cardiotoxicity in chemotherapy, there are some possible concerns, particularly generalization to the real-world practice or heterogeneous populations. Recent observational studies reported increased risk of cardiotoxicity among trastuzumab and/or anthracycline therapy in breast cancer; nevertheless, limited data are available on potential factors, including socioeconomics, geographical location, or

comorbid conditions that might have an impact on long-term incidence and risk of cardiotoxicity.[48,83,97]

To date, there is no specific guideline to manage chemotherapy-related cardiotoxicity among cancer patients in general. Therefore, understanding potential factors associated with increased risk of chemotherapy-induced cardiotoxicity may be beneficial for cancer patients to undergo chemotherapy while minimizing cardiac events. Consequently, our study builds on previous work by including longer follow-up, more data, and addressing potential factors related to cardiotoxicity risk, including socioeconomics, comorbidity, pre-existing cardiovascular disease, and receipt of other non-anthracycline treatments (e.g., taxane-based and hormone). We also examined risk of all-cause mortality. In this study we estimated the incidence of factors associated with chemotherapy-induced cardiotoxicity and all-cause mortality in breast cancer patients using large population-based data sources.

Patients and Methods

Data Source and Study Population

We used the linkage of two large population-based sources of data that provide detailed information about cancer cases, linked with Medicare claims data. These data, known as the Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database were accessed from 2000-2010. The SEER program is a population-based cancer registry which collects clinical data (e.g., cancer site, stage, grade, comorbidities), demographics, and cause of death. The Medicare program provides claims data which cover health care services from the time of a person's Medicare eligibility (individuals aged 65 and older and those who received Social Security Disability Insurance (SSDI))

until death. The claims data include hospital, physician/supplier, outpatient, and home health claims. Detailed information on The SEER-Medicare database is published and available at http://appliedresearch.cancer.gov/seermedicare/.

Females who were continuously enrolled in the Medicare fee-for-service Part A or Part B during 12 months before diagnosis of breast cancer (i.e., the index date) and ≥66 years of age at first diagnosis from 2001 to 2009 were included. Age 66, as opposed to age 65 when beneficiaries are initially eligible for Medicare, was used to ensure an adequate period of Medicare claims for defining comorbidities. Patients were excluded if: 1) not continuously enrolled in the SEER-Medicare data 12 months after the index date or 1 month after the index date if patients died after diagnosis; 2) qualified for SSDI or had dual-eligible Medicare and Medicaid; 3) previously diagnosed with HF and CM within the preceding 6 months of breast cancer diagnosis and/or before trastuzumab- or anthracycline-based regimen initiation[83,97]; 4) breast cancer was diagnosed at autopsy or not the initial primary tumor diagnosis; or 5) missing or unknown cancer stage (Please refer to Figure 1, CONSORT Diagram).

Chemotherapy exposure

Each patient was assigned to the exposed and the unexposed groups using a propensity scoring technique. Receipt of chemotherapy from Medicare claims 12 months after breast cancer diagnosis was identified through the Healthcare Common Procedure Coding System codes and the Common Procedural Terminology J codes[67,97,136](Appendix) and categorized into five mutually exclusive treatment groups: 1) trastuzumab-based (with or without non-anthracycline chemotherapy); 2) trastuzumab and anthracycline-based; 3) anthracyclines-based (with or without non-trastuzumab

chemotherapy); 4) taxane-based; 5) other chemotherapy (e.g., alkylating agents, anti-metabolites); and 6) hormone therapy. Those patients who met treatment categories 1-5 were assigned to the exposed group; whereas those treated with hormone therapy were assigned to the control group (i.e., the unexposed group). We selected hormone therapy as a control group based on a relatively low reported incidence of cardiotoxicity compared to other drug classes.[30,31,76] Data on chemotherapy administration were defined using breast cancer chemotherapy codes from a previous study.[67]

Cardiotoxicity and all-cause mortality outcomes

Cardiotoxicity, defined as HF or CM, were identified using to the following ICD-9-CM codes: HF (402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, 428.x) or CM (425.x).[48,97] Data were retrieved from Medicare inpatient, outpatient, physician, home health agencies, and hospice file Medicare claims data. Patients with ICD-9-CM diagnosis codes that appeared in at least 1 inpatient claim or 2 outpatient or physician claims after the initiation of chemotherapy or hormone were assigned as having chemotherapy-induced cardiotoxicity. For physician and outpatient claims, cardiotoxicity diagnoses must appear on at least two different claims that are more than 30 days apart.[98] Additionally, patients who died at least 1 month after the initiation of chemotherapy were assigned as having all-cause mortality using date of death which is available in both SEER and Medicare files. Patients were followed-up until incident cardiotoxicity, death, disenrollment, or December 31, 2010, whichever came first.

Covariates

Patient characteristics

We obtained data from the SEER-registry, including age in years of diagnosis, ethnicity/race, metropolitan area, and region. Socioeconomic status was defined as median household income, education level (i.e., high school graduation rates), and poverty level from the census tract variables.[88,99] Further, comorbidities were calculated from the macros for calculation of comorbidity weights provided by the National Cancer Institute (NCI).[98] We used a modified Charlson comorbidity index by Klabunde[101] as suggested by the NCI.[98] The reason is because it includes the diagnoses from the physician claims. Since more patients visit a physician at a physician's office than are hospitalized, incorporating physician claims into the analysis may increase the possibility of identifying more comorbid conditions.[98,101] Comorbidities were extracted from inpatient, outpatient, physician, home health agencies, and hospice Medicare claims for specific ICD-9 and HCPCS codes at any time during 1 year before the breast cancer diagnosis. For physician and outpatient claims, a patient's diagnoses must have appeared on at least two different claims that were more than 30 days apart.[98] Additionally, other potential cardiovascular risk factors, including diagnoses of coronary artery disease, ischemic heart disease, stroke, hypertension, diabetes mellitus, renal failure, arrhythmias, and hyperlipidemia were also included in the analyses (Appendix).

Tumor Characteristics

We retrieved data from the SEER registry, including tumor size, stage, grade, estrogen receptivity, and number of positive lymph nodes.

Treatment variables

Treatments, including surgery and radiation, were extracted for the period of 12 months after time of breast cancer diagnosis using ICD-9 and HCPCS codes in the Medicare claims and/or the SEER database (Appendix).

Statistical analyses

Baseline patient and tumor characteristics were compared using the chi-square test for categorical variables and t-test for continuous variables across chemotherapy and hormone groups. Time to cardiotoxicity and time to all-cause mortality were calculated in months from the date of breast cancer diagnosis to the date of the first cardiotoxicity claim and to the date of death, respectively. Hazard Ratios (HRs) and 95% confidence intervals (CIs) of cardiotoxicity episodes or all-cause mortality at a given time were compared across chemotherapy groups, using multivariate Cox proportional hazards models with stepwise selection process, with hormone therapy as the reference group. The models were adjusted for covariates, including patient demographics, tumor characteristics, socioeconomic status, pre-existing cardiovascular conditions, chemotherapy, radiation, surgery, and comorbidities. Cumulative incidence rates of cardiotoxicity and all-cause mortality were also compared across groups, adjusting for baseline covariates. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). This study was approved under expedited review by the institutional review board at Auburn University.

Matching

A propensity scoring technique was used to reduce a potential selection bias that affects both the treatment and the outcome of interest. Specifically, the approach was used to estimate the probability (or propensity) that an individual patient received a

particular treatment (e.g., trastuzumab and/or anthracyclines). Matching variables for the propensity score included a patient's baseline covariates: patient characteristics, socioeconomic status, tumor characteristics, diagnosis year, modified Charlson comorbidity index, pre-existing cardiovascular conditions, and breast cancer treatment.

Results

Cohort characteristics

Figure 1 displays the CONSORT diagram of the 138,320 SEER-Medicare female patients aged 66 and over who had a primary diagnosis of stage I to IV breast cancer. The final study population size included 12,168 patients. Table 1 describes the cohort characteristics of the final study population. Overall, 511 were treated with trastuzumab-based, 220 trastuzumab and anthracycline-based, 2,693 anthracyclines-based, 842 taxane-based, and 1,818 other chemotherapy. Hormones were prescribed in 6,084 patients. Median follow-up was 44 and 48 months for cardiotoxicity and all-cause mortality, respectively. The proportion of patients who received chemotherapy or hormone varied across the study period. Generally, most patients across groups were white, younger than age 76 years, and in the West SEER region. Comparing among treatment regimens, the majority of patients appeared to be healthy with a low comorbidity score. Similarly, there was no difference among some pre-existing cardiovascular conditions (i.e., diabetes, coronary artery disease, and hyperlipidemia). Regarding socioeconomics, there was no difference in terms of median income and education among patients who received any chemotherapy or hormone. In terms of tumor characteristics, patients treated with chemotherapy or hormone were more likely to have advanced breast cancer (e.g., higher stage, higher grade). The hormone group was more likely to have ER-positive disease.

Regarding treatment, patients receiving anthracyclines-based treatment had a slightly higher proportion having surgery or radiation compared with other treatment regimens. The differences in cohort characteristics between the two groups were balanced after we adjusted for propensity score weights (data not shown).

Multivariate Cox model analyses adjusted for covariates examined factors associated with all-cause mortality and cardiotoxicity (Table 2). Only significant factors were presented in the final models after stepwise selection approach. In terms of cardiotoxicity, patients receiving chemotherapy had a statistically significant higher risk of developing cardiotoxicity compared with hormone therapy. Specifically, the trastuzumab and anthracycline-based group had the highest risk of developing cardiotoxicity (adjusted hazard ratio (HR), 2.02; 95% confidence interval (CI) 1.62 to 2.51), followed by trastuzumab-based (adjusted hazard ratio (HR), 1.45; 95% confidence interval (CI) 1.24 to 1.69), and anthracyclines-based groups (adjusted hazard ratio (HR), 1.28; 95% confidence interval (CI) 1.14 to 1.44). In addition, those who were diagnosed with breast cancer after 2001 had lower risk of developing cardiotoxicity.

In terms of patient sociodemographics and tumor characteristics, factors associated with a higher risk of cardiotoxicity include those older (>70 vs ≤70 years), being African-American, living in the West region (vs Northeast), having lower median income, living in higher poverty level, having a higher comorbidity score, having history of pre-existing cardiovascular condition (i.e., hypertension, diabetes, coronary artery disease, renal failure, and atrial fibrillation) and having advanced stage, including higher stage, poorer grade, and more positive lymph nodes.

Regarding all-cause mortality, patients who received taxane-based treatment had a higher risk for all-cause mortality (HR, 1.49; 95%CI 1.38 to 1.62) compared with hormone treatment whereas other therapies, including trastuzumab-based as well as trastuzumab and anthracycline-based regimens, were not associated with different risks compared with hormone. Similar to cardiotoxicity, sociodemographics and tumor characteristics were also associated with a higher risk of all-cause mortality, including being African-American, older age (> 70 vs ≤70 years), living in the South region (vs Northeast), having lower median income, having lower graduation rates, having higher comorbidity scores, having history of pre-existing cardiovascular condition (i.e., hypertension, renal failure, and atrial fibrillation), and having advanced stage, including higher stage, higher-grade tumor and numbers of positive lymph nodes, and ER-negative disease.

The adjusted cumulative incidence of all-cause mortality among chemotherapy and hormones increased with increasing follow-up time (Figure 2). Overall, at 5 years of follow-up, patients who received taxane-based chemotherapy had higher risk of all-cause mortality compared with other therapies and hormones. Specifically, there was a greater risk of all-cause mortality in patients receiving taxane-based (cumulative incidence =34.2%, 95% CI=32.7% to 35.6%) whereas patients with anthracycline-based (cumulative incidence =22.5%, 95% CI=21.5% to 23.5%) and other chemotherapy had the lower risk of all-cause mortality at 5 years of follow-up (cumulative incidence =22.3%, 95% CI=21.3% to 23.2%).

The 5-year adjusted cumulative incidence of cardiotoxicity associated with chemotherapy and hormones increased with increasing time (Figure 3).Typically, five

years after diagnosis from breast cancer, patients who received chemotherapy were more likely to develop cardiotoxicity compared with patients who received hormone. That is, the-5 year cumulative incidence of cardiotoxicity associated with chemotherapy was highest in patients who received trastuzumab and anthracycline-based (cumulative incidence =21.2%, 95% CI=17.7% to 24.6%) and trastuzumab-based treatment (cumulative incidence =16.1%, 95% CI=14.3% to 17.8%), whereas those who received anthracycline-based, taxane-based, or other chemotherapy had similar incidence of cardiotoxicity. Additionally, patients who received hormones had the lowest incidence of developing cardiotoxicity at 5 years of follow-up (cumulative incidence =11.7%, 95% CI=10.9% to 12.5%).

Discussion

In this large cohort of patients who received chemotherapy and hormonal therapy for breast cancer, we found substantial individualization of chemotherapy and hormone administration depending on patient or tumor characteristics. Further, the results suggest treatment regimens account for risk of cardiotoxicity and all-cause mortality. Specifically, as compared to hormones, the risk of cardiotoxicity was statistically significantly higher among patients treated with combination regimens of trastuzumab and anthracycline-based, trastuzumab-based, anthracycline-based, other chemotherapy, and taxane-based regimens, respectively. Consistently, the findings of the 5-year cumulative incidence of cardiotoxicity also indicate that the risk was statistically increased among patients treated with trastuzumab and/or anthracycline regimens.

Our results are consistent with existing evidence demonstrating that trastuzumab- and/or anthracycline-based regimens are associated with risk of cardiotoxicity.

Specifically, the risk was most pronounced for combination regimens of trastuzumab and anthracyclines.[13,48,53,83,88,97,137,138] For instance, Chen et al reported that breast cancer patients treated with trastuzumab and anthracycline-based chemotherapy had significantly increased risk of heart failure (RR, 4.27; 95% CI 2.75 to 6.61), as compared to patients who received non-anthracycline chemotherapy RR = 2.42, 95% CI 0.36 to 6.19).[88] However, it should be noted that our study focuses on use of chemotherapy and hormonal therapy in breast cancer with stage I-IV which may reflect more treatment regimens, whereas Chen et al included stage I-III.

Similarly, our findings are in line with previous studies that reported that the risk of cardiotoxicity increased gradually over follow-up time. For example, Bowles et al reported that breast cancer patients treated with trastuzumab and anthracycline-based chemotherapy had significantly higher cumulative risk of cardiotoxicity (20.1%) at 5-year follow-up, as compared to those treated with trastuzumab alone (12.1%).[83] We found that the incidence rate of cardiotoxicity obtained from this study was higher than prior reports from clinical trials.[53,137] For example, symptomatic heart failure, including severe cardiotoxicity, occurred in 1.73% of patients treated with trastuzumab in Piccart-Gebhart's study.[137] Although we acknowledge that the definition of cardiotoxicity may vary among studies, one of our possible explanations could be that clinical trials typically enrolled patients under restricted conditions (e.g., younger patients, few pre-existing cardiovascular conditions) and typically had shorter follow-up.

In addition, we found that socioeconomics, demographics, and tumor characteristics also have an impact on the risk of cardiotoxicity and all-cause mortality. Similar to previous studies, being older, African-American, lower socioeconomic status

(i.e., lower income and education level, and high poverty level), comorbidity, and advanced cancer (e.g., higher stage, grade, or ER-negative) were associated with an increased risk of developing cardiotoxicity.[48,139,140] This might be partially explained by evidence that African-American women are more likely to be diagnosed with advanced stage disease.[140]

With regard to all-cause mortality, our results are similar to previous studies that indicate that factors such as receipt of chemotherapy as well as patient and tumor characteristics (e.g., age, comorbidity, estrogen receptor) are associated with all-cause mortality.[44,141-145] For instance, Elkin et al[143] reported that chemotherapy was associated with an all-cause mortality of approximately 15%. It is noteworthy that, despite increased risk of cardiotoxicity in patients treated with trastuzumab and/or anthracycline-based regimens, our findings support previous evidence that these therapies improved survival in breast cancer woman.[44,49,53,54,57,59]

Additionally, our findings are also concordant with previous studies, indicating that pre-existing cardiovascular conditions, such as hypertension, stroke, renal failure and atrial fibrillation were also associated with higher incidence of cardiotoxicity and/or mortality.[97,142,146] For instance, Chen et al reported that cardiovascular conditions, such as hypertension and stroke, were associated with incidence rate ratio (IRR) of cardiotoxicity, particularly atrial fibrillation (IRR: 2.35) and renal failure (IRR: 1.88).[97]

A number of limitations and strengths of our study should be noted. First, an observational study may introduce some issues, including selection bias or unmeasurable confounding factors. For instance, we were not able to measure other factors potentially associated with mortality such as smoking or genetic biomarkers that might affect a

provider's decision regarding treatment modality.[134] Second, the nature of registry and claims data might introduce some biases. For example, there may be an issue of ascertainment of cardiotoxicity outcomes, including under-diagnosis. However, diagnosis and procedure codes reflecting cardiotoxicity have been well documented in previous studies.[48,83,88,136,139,145] Third, our scope is limited to nondisabled Medicare beneficiaries who are ≥66 years of age in SEER geographic areas; therefore our results may not be generalized to other populations and other types of insurance. In addition, we only included patients diagnosed with breast cancer as the initial primary tumor. This method help reduce confounding of cardiotoxicity and mortality bias from patients who underwent chemotherapy for prior cancer, but limits generalizability.

Our study has a number of strengths. First, our study fills a research gap in understanding chemotherapy-induced cardiotoxicity by providing new information regarding potential predictive factors and includes other non-anthracycline-based regimens (e.g., taxane-based and hormone) besides trastuzumab and anthracyclines. We also examined risk of all-cause mortality among chemotherapy and hormonal therapy and across cancer stages. A better understanding of patient's demographics, socioeconomics, tumor characteristics, and treatment factors contributing to risk of cardiotoxicity and all-cause mortality may lead to practice and policy change that can reduce risk of cardiotoxicity events and improve overall survival. Second, our population-based study includes patients with heterogeneous characteristics such as pre-existing cardiovascular conditions, while generally these patients are excluded from clinical trials.[20,88,92,94] Therefore, our findings are more generalizable to breast cancer patients in general clinical practice than existing RCTs. Finally, given the favorable results that trastuzumab and/or

anthracycline therapy were not associated with increased risk of all-cause mortality, our study highlights the need for interdisciplinary practice models that team cardiologists and oncologists to reduce cardiac risk while maintaining treatment benefits of chemotherapy. This approach may allow treatment regimens to be continued without compromising cardiac function.

In conclusion, our study indicates that among female Medicare beneficiaries aged 66 and older with breast cancer undergoing cancer therapy, chemotherapy, including trastuzumab and/or anthracycline-based regimens are associated with increased risk of cardiotoxicity and all-cause mortality. Other predictors include patient's characteristics, tumor characteristics, concomitant treatment, and comorbidity.

Figure 1: CONSORT Diagram: Chemotherapy and Hormonal Therapy

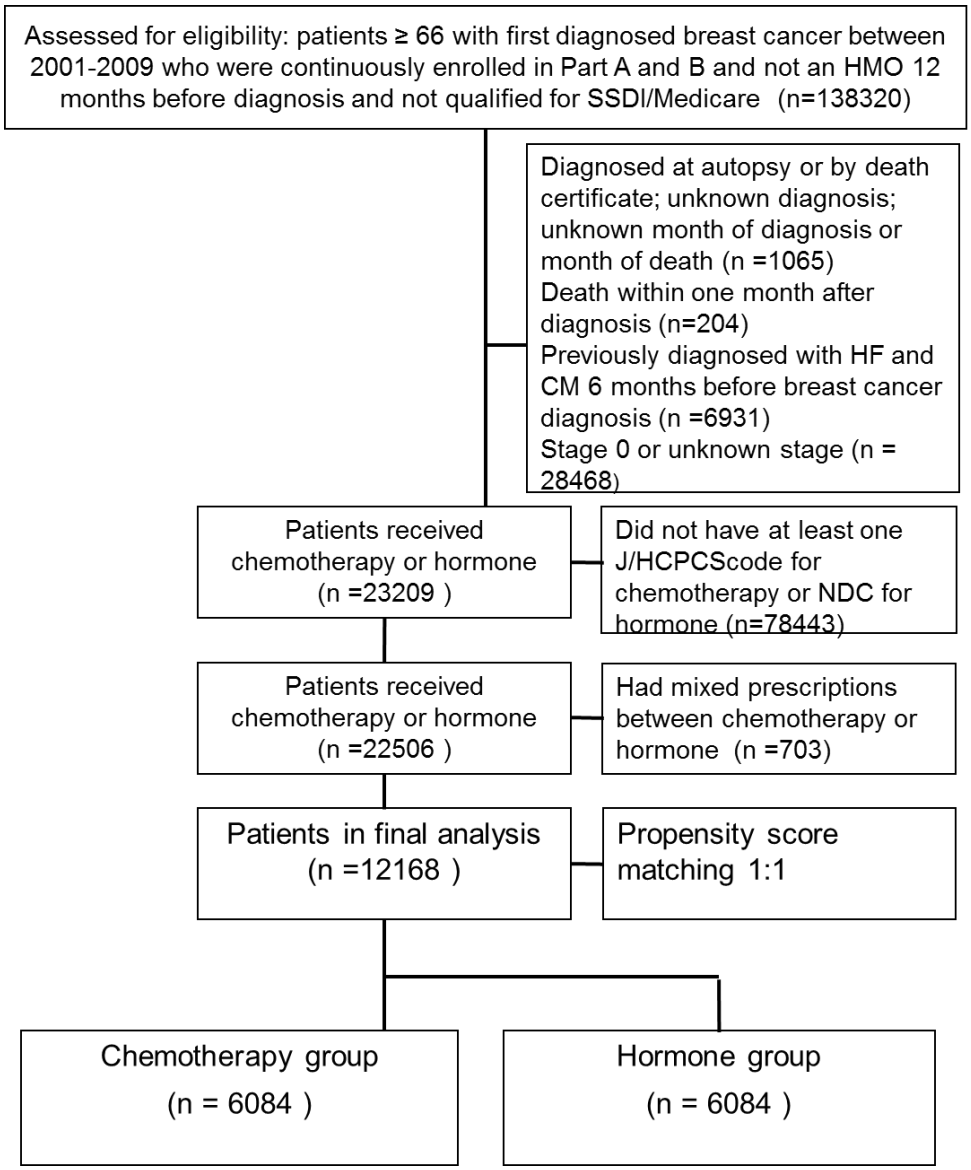


Table 1 Patient characteristics by chemotherapy or hormonal therapy

Factor	Trastuzumab-based (n=511) %	Trastuzumab +Anthracycline-based (n=220) %	Anthracyclines-based (n=2693) %	Taxane-based (n=842) %	Other± (n=1818) %	Hormone (n=6084) %	*P* value
Year of diagnosis							
2001	6.07	7.27	12.44	7.6	18.54	0.51	<.0001
2002	3.91	5.45	14.67	6.41	17.55	0.99	
2003	5.28	7.27	15.26	8.91	15.02	0.82	
2004	7.05	10.45	16.64	7.72	13.04	0.99	
2005	14.09	21.82	14.37	7.6	11.72	0.82	
2006	17.81	23.64	13.92	13.42	11.11	0.61	
2007	12.72	11.82	5.05	12.83	4.73	33.81	
2008	18.79	9.09	4.31	18.76	4.79	31.84	
2009	14.29	3.18	3.34	16.75	3.52	29.62	
Age at diagnosis							
66-70	24.66	50.45	45.64	29.93	22.77	34.52	<.0001
71-75	29.75	31.36	32.64	29.93	24.97	28.29	
76-80	15.85	10.00	15.08	19.83	22.33	18.18	
>80	29.75	8.18	6.65	20.31	29.92	19.02	
Race/ethnicity							
White	84.34	80.45	83.25	83.73	86.19	83.38	0.0026
Black	6.65	9.55	8.1	9.62	5.89	7.43	
Other	4.34	2.08	21.98	5.28	13.58	52.74	
Stage							
I	37.96	27.73	20.61	26.84	44.88	32.87	<.0001
II	32.29	44.55	54.81	35.99	44.61	46.1	
III	16.63	21.36	21.24	18.65	6.82	14.69	
IV	13.11	6.36	3.34	18.53	3.69	6.33	
Grade							
Well differentiated	5.68	1.36	14.93	10.69	21.18	15.58	<.0001
Moderately differentiated	35.42	34.09	45.15	39.55	43.56	45.12	
Poorly and undifferentiated	48.73	60.91	33.53	39.55	27.06	31.72	
Unknown	10.18	3.64	6.39	10.21	8.2	7.58	
Estrogen-receptor status							
Positive	74.76	74.55	86.56	81.83	91.14	90.71	<.0001

Negative	25.24	25.45	13.44	18.17	8.86	9.29	
Tumor size							
<2 cm	49.51	43.64	43.82	41.92	60.29	50.46	<.0001
2-5 cm	35.03	43.18	44.37	39.79	33.83	39.23	
>5 cm	9.00	8.64	9.43	11.16	4.4	7.54	
Diffuse and unknown	6.46	4.55	2.38	7.13	1.49	2.76	
No. positive lymph nodes							<.0001
0	54.01	46.36	36.8	40.86	58.36	47.98	
1-3	14.48	24.55	36.58	23.04	24.53	27.81	
>3	11.74	18.18	19.79	14.85	7.48	13.3	
Unknown	19.77	10.91	6.83	21.26	9.63	10.91	
Marital status							
Not married	51.08	39.55	43.33	47.51	50.99	47.95	<.0001
Currently married	45.01	56.36	52.51	48.81	45.82	48.88	
Unknown	3.91	4.09	4.16	3.68	3.19	3.17	
SEER region							
Northeast	23.68	22.73	19.9	23.04	21.23	17.82	<.0001
Midwest	12.72	24.09	25.18	18.17	14.52	12.00	
South	25.05	25.00	26.77	27.55	21.89	26.89	
West	38.55	28.18	28.15	31.24	42.35	43.29	
Median income							
1 (lowest)	23.68	22.27	26.44	25.06	25.41	25.36	0.829
2	23.48	24.09	26.14	26.84	25.36	25.51	
3	28.18	29.09	24.32	24.47	25.19	24.95	
4 (highest)	24.66	24.55	23.1	23.63	24.04	24.18	
Education (high school graduation rates)							
1 (lowest)	24.85	20.91	25.51	27.43	23.65	26.79	0.051
2	26.22	28.64	27.29	23.63	24.64	24.97	
3	24.85	24.55	24.51	27.08	27.12	24.34	
4 (highest)	24.07	25.91	22.69	21.85	24.59	23.9	
Poverty (living below poverty level)							
1 (lowest)	27.01	33.64	26.7	24.23	24.75	23.55	0.025
2	23.68	21.36	25.25	25.89	26.68	25.26	
3	24.07	19.09	22.95	25.42	23.82	24.67	

4 (highest)	25.24	25.91	25.1	24.47	24.75	26.51	
Surgery							
None	20.16	12.73	7.54	22.09	6.16	9.98	<.0001
Breast conserving	40.7	45.91	43.41	41.33	52.7	47.76	
Mastectomy	39.14	41.36	49.05	36.58	41.14	42.26	
Radiation therapy							
No radiation	46.18	39.09	36.06	41.33	44.99	40.4	<.0001
Radiation	53.82	60.91	63.94	58.67	55.01	59.6	
Comorbidity score							
0	67.71	73.64	72.37	65.56	70.46	69.95	0.001
1	21.53	20.00	21.54	25.65	21.95	22.34	
≥2	10.76	6.36	6.09	8.79	7.59	7.71	
Pre-existing cardiovascular conditions							
Hypertension	72.6	65.00	68.88	75.77	69.36	70.51	0.001
Diabetes	29.55	25.45	25.7	29.69	25.63	26.97	0.118
Coronary artery disease	4.7	2.27	4.27	5.94	5.12	4.9	0.177
Stroke and transient ischemic attack	9.39	9.09	6.54	10.57	8.31	7.76	0.003
Renal failure	5.28	3.64	2.71	4.28	2.64	3.07	0.011
Atrial fibrillation/ flutter	5.18	0.76	14.66	9.1	19.09	51.2	<.0001
Hyperlipidemia	65.17	63.64	62.27	66.51	61.39	63.36	0.134

±Other chemotherapy includes antimetabolites, alkylating agents, and others

Table 2 Factors associated with all-cause mortality and cardiotoxicity in breast cancer received chemotherapy or hormonal therapy

Factor	Mortality	95% CI	Cardiotoxicity	95% CI
Treatment	**HR**		**HR**	
Trastuzumab-based	1.05	0.95-1.17	1.45	1.24-1.69
Trastuzumab and anthracyclines-based	1.09	0.92-1.30	2.02	1.62-2.51
Anthracycline-based	0.79	0.73-0.85	1.28	1.14-1.44
Taxane-based	1.49	1.38-1.62	1.25	1.09-1.44
Other±±	0.77	0.71-0.84	1.27	1.13-1.43
Hormone	REF		REF	
Year of diagnosis				
2001	REF		REF	
2002	0.99	0.90-1.08	0.91	0.95-1.17
2003	0.92	0.84-1.01	0.65	0.92-1.30
2004	0.91	0.82-1.00	0.76	0.73-0.85
2005	0.91	0.82-1.00	0.67	1.38-1.62
2006	0.93	0.84-1.04	0.47	0.71-0.84
2007	0.86	0.78-0.95	0.53	0.95-1.17
2008	0.97	0.88-1.08	0.37	0.92-1.30
2009	0.98	0.88-1.10	0.22	0.73-0.85
Age at diagnosis				
66-70	REF		REF	
71-75	1.08	1.01-1.15	1.15	1.05-1.26
76-80	1.44	1.35-1.53	1.51	1.37-1.65
>80	2.19	2.07-2.33	1.78	1.62-1.95
Race/ethnicity				
White	REF		REF	
Black	1.15	1.08-1.24	1.28	1.15-1.42
Other	0.80	0.74-0.87	0.75	0.67-0.85
Stage				
I	REF		REF	
II	1.02	0.93-1.12	1.13	1.03-1.23
III	1.43	1.28-1.60	1.27	1.11-1.46
IV	3.65	3.27-4.06	1.35	1.16-1.58
Grade				
Well differentiated	REF		REF	
Moderately differentiated	1.08	1.01-1.16	1.20	1.10-1.31

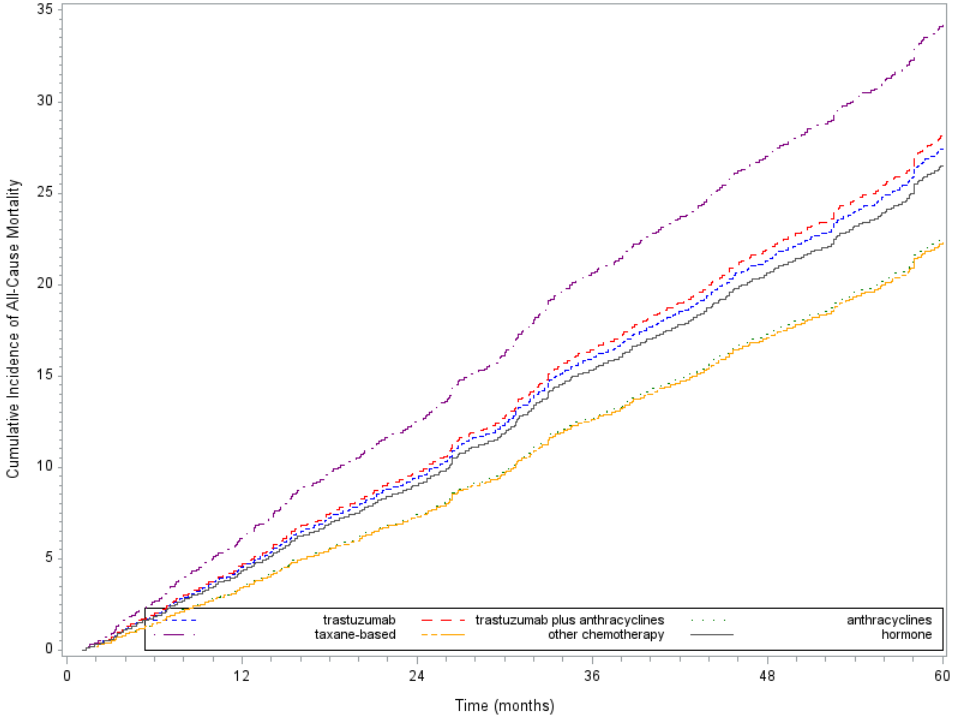
Poorly and undifferentiated	1.63	1.51-1.75	1.25	1.14-1.38
Unknown	1.35	1.23-1.48	1.28	1.12-1.47
Estrogen-receptor status				
Positive	REF		REF	
Negative	1.95	1.85-2.06		
Tumor size				
<2 cm	REF		REF	
2-5 cm	1.34	1.26-1.44		
>5 cm	1.57	1.44-1.71		
Diffuse and unknown	1.80	1.64-1.99		
No. positive lymph nodes				
0	REF		REF	
1-3	1.39	1.29-1.49	1.10	1.00-1.21
>3	1.84	1.69-2.01	1.44	1.26-1.64
Unknown	2.58	2.41-2.77	1.13	1.01-1.27
Marital status				
Not married	REF		REF	
Currently married	0.87	0.83-0.91	0.83	0.78-0.89
Unknown	0.67	0.59-0.77	0.75	0.63-0.91
SEER region				
Northeast	REF		REF	
Midwest	0.91	0.84-0.98	1.07	0.96-1.19
South	1.14	1.07-1.22	0.94	0.86-1.04
West	1.04	0.97-1.11	1.10	1.01-1.21
Median income				
1 (lowest)	REF		REF	
2	0.89	0.82-0.95	1.02	0.93-1.13
3	0.86	0.79-0.93	1.05	0.93-1.18
4 (highest)	0.78	0.70-0.87	0.75	0.65-0.87
Education (high school graduation rates)				
1 (lowest)	REF		REF	
2	1.08	1.01-1.15		
3	0.82	0.76-0.88		
4 (highest)	0.85	0.78-0.93		
Poverty (living below poverty level)				
1 (lowest)	REF		REF	
2	0.96	0.89-1.03	1.05	0.95-1.17

3	0.87	0.80-0.94	1.13	1.00-1.28
4 (highest)	0.86	0.78-0.96	1.33	1.15-1.54
Surgery				
None	REF	REF		
Breast conserving	0.74	0.69-0.80	0.84	0.75-0.93
Mastectomy	0.92	0.86-0.99	0.79	0.71-0.88
Radiation therapy				
No radiation	REF		REF	
Radiation	0.83	0.80-0.87	0.86	0.80-0.92
Comorbidity score				
0	REF		REF	
1	1.42	1.36-1.49	1.34	1.24-1.45
≥2	1.71	1.58-1.84	1.46	1.30-1.64
Pre-existing cardiovascular conditions				
Hypertension	1.09	1.04-1.15	1.16	1.08-1.25
Diabetes			1.35	1.25-1.46
Coronary artery disease	1.09	0.99-1.19	1.53	1.37-1.71
Stroke and transient ischemic attack				
Renal failure	1.32	1.19-1.47	1.44	1.25-1.67
Atrial fibrillation/flutter	1.41	1.31-1.51	2.51	2.31-2.72
Hyperlipidemia	0.84	0.80-0.88		

± Only significant factors were presented in the models after stepwise selection approach. All models were adjusted for covariates.

±±Other chemotherapy includes antimetabolites, alkylating agents, and others

Figure 2 Adjusted cumulative incidence of all-cause mortality

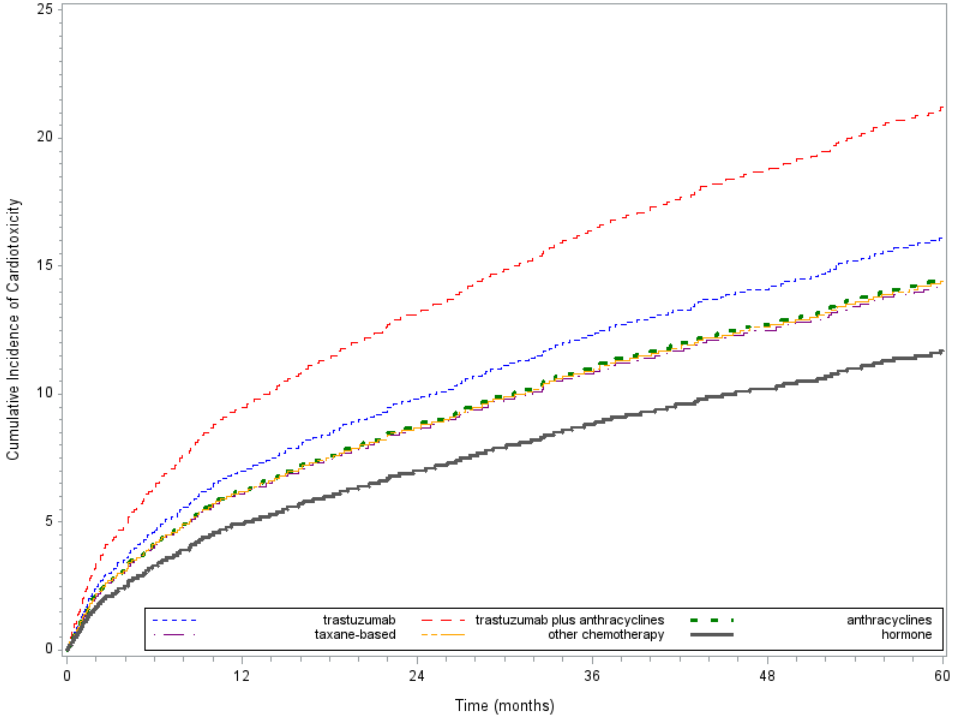


Time (months)	Trastuzumab-based		Trastuzumab and anthracycline-based		Anthracycline-based		Taxane-based		Others±		Hormone	
	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI
0												
12	4.5	4.1-4.9	4.6	3.9-5.3	3.4	3.2-3.7	6.1	5.7-6.5	3.4	3.1-3.6	4.3	4.0-4.5
24	9.4	8.7-10.1	9.7	8.4-11.1	7.4	6.9-7.8	12.5	11.8-13.2	7.3	6.8-7.7	9.0	8.7-9.4

36	15.9	14.9-17.0	16.4	14.3-18.4	12.7	12.1-13.4	20.6	19.6-21.6	12.6	11.9-13.2	15.3	14.8-15.8
48	21.4	20.0-22.7	22	19.4-24.4	17.3	16.5-18.1	27.1	25.8-28.3	17.1	16.3-17.9	20.6	19.9-21.3
60	27.4	25.8-29.1	28.1	25.1-31.1	22.5	21.5-23.5	34.2	32.7-35.6	22.3	21.3-23.2	26.5	25.7-27.3

Adjusted cumulative incidence of all-cause mortality for chemotherapy and hormones. Values are % (per 100 patients). Covariates adjusted for were patient characteristics, socioeconomics, cancer characteristics, and treatments. Plotted at their mean values.
±Other chemotherapy includes antimetabolites, alkylating agents, and others

Figure 3 Adjusted cumulative incidence of cardiotoxicity



Time (months)	Trastuzumab -based		Trastuzumab and anthracycline-based		Anthracycline-based		Taxane-based		Others±		Hormone	
	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI	Cumulative incidence	95% CI
0												
12	7.0	6.1-7.8	9.5	7.7-11.2	6.2	5.8-6.7	6.1	5.4-6.8	6.2	5.7-6.6	4.9	4.6-5.3
24	9.8	8.7-10.9	13.2	10.8-15.5	8.8	8.2-9.4	8.6	7.7-9.5	8.7	8.1-9.3	7.0	6.5-7.5

36	12.3	10.9-13.7	16.4	13.5-19.2	11	10.3-11.8	10.8	9.7-11.9	10.9	10.2-11.7	8.8	8.2-9.4
48	14.1	12.6-15.7	18.7	15.5-21.8	12.7	11.9-13.5	12.5	11.2-13.7	12.6	11.8-13.4	10.2	9.5-10.9
60	16.1	14.3-17.8	21.2	17.7-24.6	14.5	13.6-15.4	14.2	12.8-15.6	14.4	13.4-15.3	11.7	10.9-12.5

Adjusted cumulative incidence of cardiotoxicity for chemotherapy and hormones. Values are % (per 100 patients). Covariates adjusted for were patient characteristics, socioeconomics, cancer characteristics, and treatments. Plotted at their mean values.
±Other chemotherapy includes antimetabolites, alkylating agents, and others

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Aim 3

Abstract

Objectives: The purpose of this study was to examined the effect of angiotensin-converting enzyme inhibitors and/or β blockers (ACEIs/BBs) on prevention of trastuzumab and anthracycline-induced cardiotoxicity compared with those who were not exposed to ACEIs/BBs

Methods: A retrospective, population-based cohort study of 142,990 women (≥66 years of age) newly diagnosed with breast cancer from 2001-2009 was conducted using the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database. The ACEI/BB exposure was defined as a filled prescription at any time before or during 12 months after the initiation of trastuzumab and/or anthracyclines. The non-exposed group was defined as those who had never been prescribed ACEIs/BBs during the observed treatment period. Cumulative rates of cardiotoxicity and all-cause mortality were estimated and marginal structural Cox models were used to determine factors associated with cardiotoxicity and all-cause mortality adjusting for baseline covariates and use of chemotherapy, through stabilized weights.

Results: The final sample included a total of 6,542 women. Compared with the non-exposed group, the exposed group had higher comorbidities and more advanced disease and the adjusted hazard ratio (HR) for cardiotoxicity and all-cause mortality were 0.77 (95% CI, 0.62 to 0.95) and 0.79 (95% CI, 0.70-0.90), respectively. Additionally, starting ACEIs/BBs ≤ 6 months after the initiation of trastuzumab/anthracyclines and having exposed duration ≥ 6 months were also associated with decreased risk of cardiotoxicity and all-cause mortality. Certain baseline characteristics, including age, non-Hispanic black, advanced cancer, region, comorbidity, pre-existing cardiovascular conditions,

lower socioeconomic status, and concomitant treatment were significantly associated with an elevated risk of all-cause mortality and/or cardiotoxicity (all $P<0.05$).

Conclusions: ACEIs/BBs appear to prevent cardiotoxicity and improve survival in female breast cancer patients undergoing trastuzumab/anthracycline treatment. Practitioners should further evaluate treatment and patient characteristics for risk mitigation strategies.

Introduction

Despite the benefits of anti-neoplastic agents for decreasing mortality from breast cancer, these favorable effects are also associated with adverse effects, particularly cardiotoxicity. Anti-neoplastic agents, including conventional chemotherapy (i.e., anthracyclines) and targeted therapy (i.e. trastuzumab), have become increasingly recognized for risk of cardiotoxicity, including heart failure (HF) and cardiomyopathy (CM).[12,13,59,97,135] For example, a study using the Surveillance, Epidemiology and End Results (SEER) database demonstrated a 38.4% incidence of heart failure in women at 10 years after completion of anthracycline-based therapy.[13,48] Likewise, the incidence of cardiac dysfunction was 0.5-34% of patients in the clinical trials of trastuzumab.[14-16] In terms of combination regimens, anthracyclines in combination with or followed by trastuzumab resulted in high incidence of cardiotoxicity, compared with non-trastuzumab therapy.[34,83] Chemotherapy-induced cardiotoxicity may cause serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis.[17] This cardiac adverse event may compromise the clinical effectiveness of chemotherapy and eventually lead to premature death.[17-19]

To date, there is no specific guideline to manage cancer therapy-related cardiotoxicity. Nevertheless, the existing evidence has supported the benefit of angiotensin-converting enzyme inhibitors (ACEIs) or β-blockers (BBs) in patients with chemotherapy-induced cardiotoxicity.[12,16,22-30] Indeed, ACEIs and BBs appear to be associated with long-term improvement in left ventricular systolic function by reducing ventricular remodeling.[26-28,31-33] This may eventually delay or slow clinical progression to heart failure in patients undergoing chemotherapy.[26,28,33]

Despite promising results from clinical studies, little is known about using ACEIs/BB in prevention of cardiotoxicity in real-world settings. Specifically, randomized clinical trials (RCTs) may have some limitations, including restrictive inclusion and exclusion criteria or short follow-up which may lead to generalizability issues. Hence, patients in RCTs may not be representative of the population nor reflect patients in routine practice. Therefore, there is a need for studies that apply to diverse populations in heterogeneous health care settings. In this study, we examined the effect of ACEIs/BBs on prevention of trastuzumab and anthracycline-induced cardiotoxicity compared with those who were not exposed to ACEIs/BBs using large population-based data sources.

Patients and Methods

Data Source and Study Population

We used the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer claims data from the Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database from 2000-20010 The SEER program is a population-based cancer registry which collects clinical data (e.g., cancer site, stage, comorbidities), demographics, and cause of death. The Medicare program provides claims data which cover health care services from the time of a person's Medicare eligibility (individuals aged ≥65 and those who received Social Security Disability Insurance (SSDI)) until death. Detailed information on the SEER-Medicare database is published and available at http://appliedresearch.cancer.gov/seermedicare/.

Female who were continuously enrolled in the Medicare fee-for-service Part A or Part B during 6 months before diagnosis of breast cancer (i.e., the index date) and ≥66 years of age at first diagnosis from 2001 to 2009 were included in the study. Beneficiaries 65 years of age were excluded in order to ensure adequate period of Medicare claims data were available for defining comorbidities, and 2010 data was reserved for outcome assessment among those deemed eligible towards the end of eligibility time. Patients were excluded if: 1) not continuously enrolled in the SEER-Medicare data 12 months after the index date or 1 month after the index date if patients died after diagnosis; 2) qualified for SSDI or had dual-eligibility for Medicare and Medicaid, 3) previously diagnosed with HF and CM within the preceding 6 months of breast cancer diagnosis and/or before trastuzumab or anthracyclines containing regimen initiation,[83,97] 4) breast cancer was diagnosed at autopsy or not the initial primary tumor diagnosis; 5) missing or unknown cancer stage; 6) no receipt of anthracyclines or trastuzumab (refer to figure 1 CONSORT diagram).

ACEIs/BBs exposure

Assignment to the exposed group, referred to as ACEI/BB users, included a filled prescription defined as either 1) at least one prescription of ACEIs/BBs at any time before the initiation of trastuzumab and/or anthracyclines (i.e., the index date) or 2) at least one prescription of ACEIs/BBs within 12 months after the initiation of anthracyclines or trastuzumab therapy, which ever came first. Additionally, exposed participants who started ACEIs/BBs during the pre-index period were required to have at least one prescription of ACEIs/BBs during12 month-post index period. ACEIs/BBs were extracted from pharmacy claims from the Part D event (PDE) file. Time of first ACEI/BB

prescription fill was considered time zero. The duration between time zero and the first initiation of anthracyclines or trastuzumab was assessed and classified in the following categories; ≤6 months, 6-12 months, or >12 months. In addition, the duration from time zero to the end of study or to the first cardiotoxicity event or all-cause mortality, whichever came first, was assessed and classified by the following categories: ≤6 months, 6-12 months, or >12 months. The non-exposed group was defined as patients with breast cancer who had never been prescribed any ACEIs/BBs before/after the initiation of anthracyclines or trastuzumab. An artificial time zero was randomly assigned and matched to the non-exposed group based on the overall distribution of time zero of the exposed group.[104-106] Both the ACEI/BB exposed and non-exposed groups were followed to cardiotoxicity event, death, or the end of the study follow-up, whichever came first.

Matching

To reduce bias from treatment selection affected by presence of time-dependent covariates (i.e., use of anthracycline/trastuzumab) and loss to follow-up that may confound the treatment effect, we have used Robins' marginal structural models (MSMs)[108] which are casual models based on inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs) to create a pseudo-population that is adjusted for time-dependent covariates and censoring. The MSM approach has been used in previous studies.[108-114] Specifically, the numerator of the IPTWs was obtained from patient's probability of having ACEIs/BBs treatment given the patient's baseline covariates and both the baseline and time-dependent covariates were included in the denominator using regression models. Likewise, the numerator of the IPCWs was obtained from patient's probability of censoring given the patient's baseline

covariates and both the baseline and time-dependent covariates were included in the denominator, using regression models. Then we have created stabilization weights (SWs) for each patient by multiplying the above weights (i.e., IPTWs*IPCWs).

Covariates

Baseline patient characteristics were defined as age in years at breast cancer diagnosis, ethnicity/race, and region. Census tract data and zip code data were used to estimate socioeconomic status using median household income, education (i.e., high school graduation rates), and poverty levels.[88,99,100] Tumor characteristics, including stage, grade, size, estrogen receptor status, and number of positive lymph nodes were measured in the cancer registry. Comorbidity burden was calculated using a modified Charlson comorbidity index by Klabunde,[101] as suggested by the NCI. Comorbid ICD-9 and HCPCS codes at any time during 6 months before the breast cancer diagnosis were captured in inpatient, outpatient, physician, home health agencies, and hospice Medicare claims.[98] For physician and outpatient claims, a patient's diagnoses must have appeared on at least two different claims that were more than 30 days apart.[98] Other cardiovascular comorbidities during the 6 months before breast cancer diagnosis, including coronary artery disease, ischemic heart disease, stroke, hypertension, diabetes mellitus, renal failure, arrhythmias, and hyperlipidemia were also included. Further, concomitant or combination chemotherapies during 12 months after breast cancer diagnosis were also included, including taxane-based, alkylating agents, and others (e.g., anti-metabolites, hormones, and other chemotherapies). Radiation, surgery, and antihypertensive medications (i.e., calcium channel blockers (CCBs), diuretics, and angiotensin receptor blockers (ARBs)) also were captured (Appendix).

Cardiotoxicity and all-cause mortality outcomes

The primary outcomes were cardiotoxicity, defined as HF and CM, and all-cause mortality. Cardiotoxicity episodes were identified using to the following ICD-9-CM codes: HF (402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, 428.x) or CM (425.x).[48,97] Data were retrieved from Medicare inpatient, outpatient, physician/supplier files, and nursing home data. Patients with ICD-9-CM diagnosis codes of cardiotoxicity that appeared in at least 1 inpatient claim or at least two different outpatient or physician claims more than 30 days apart[98] after the initiation of chemotherapy were assigned as having chemotherapy-induced cardiotoxicity. Additionally, patients who died at least 1 month after the initiation of chemotherapy were assigned as having all-cause mortality using date of death which is available in both the SEER and Medicare files. Patients were followed until the end of study or until the first event, which ever came first (Appendix).

Statistical analyses

Patient characteristics, socioeconomic, and tumor characteristics were compared using the chi-square test for categorical variables and t-test for continuous variables. Time to cardiotoxicity and time to all-cause mortality were calculated in months from the date of breast cancer diagnosis to the date of the first cardiotoxicity claim and to the date of death, respectively. Marginal structural Cox models (i.e., a Cox proportional hazards model with stabilized weights) with stepwise selection process were conducted to examine the treatment effect on cardiotoxicity or all-cause mortality, adjusting for use of chemotherapy (anthracyclines/trastuzumab) as a time-dependent variable. Additional covariates included year of diagnosis, patient and geographical characteristics,

socioeconomics, tumor characteristics, surgery, radiation, comorbidity (modified Charlson scores and other cardiovascular comorbidities), use of other chemotherapy, and use of other antihypertensive medications. Cumulative incidence rates of cardiotoxicity and all-cause mortality were also compared across groups, adjusting for baseline covariates. All analyses were performed using SAS statistical software (version 9.3; SAS Institute, Inc., Cary, NC, USA) and the significance level was set at 0.05. We performed sensitivity analyses to examine the robustness of our findings across 1) ACEI/BB dose (low, average, and high) and 2) combination ACEIs/BBs on impact of risk of cardiotoxicity or all-cause mortality. Additionally, we also performed two sensitivity analyses by limiting data to those who had trastuzumab/anthracycline initiation after 2007, given the possibility of measurement bias introduced by incomplete capture of drug use during the earlier years of the study (i.e., pre-2006 or before Part D plan).This study received expedited approval by the institutional review board at Auburn University.

Results

Cohort characteristics

Table 1 displays cohort characteristics, of 142,990 patients aged 66 and over with a primary diagnosis of stage I to IV breast cancer. Of the 6,542 patients receiving anthracycline/trastuzumab regimens, 508 were exposed to ACEIs/BBs and 6,034 were not exposed to ACEIs/BBs. The median follow-up time was 55 and 62 months for cardiotoxicity and all-cause mortality, respectively. Generally, most patients in both groups were white, younger than age 76 years, and living in the West SEER region. Compared to the non-exposed group, the exposed group was less likely to be healthy, including having higher comorbidity score and higher proportion of pre-existing

cardiovascular conditions. Regarding socioeconomics, the exposed group was more likely to have lower median income, lower graduation rates, and lived in higher poverty areas. In terms of tumor characteristics, both groups were more likely to have advanced breast cancer and the exposed group was more likely to have ER-negative disease. Regarding treatment, the exposed group had a slightly higher proportion having surgery than the non-exposed group. Additionally, the exposed group had higher proportions receiving trastuzumab-based or trastuzumab and anthracycline-based chemotherapy, ARBs, CCBs, and diuretics. The differences in cohort characteristics between the two groups were balanced after we adjusted for stabilized weights (data not shown).

Marginal structural Cox model analyses adjusted for covariates examined factors associated with survival and cardiotoxicity (Table 2). Only significant factors were presented in the final models after stepwise selection approach. In terms of cardiotoxicity, patients who were exposed to ACEIs/BBs had a statistically significant 23% lower risk of developing cardiotoxicity (adjusted hazard ratio (HR), 0.77; 95% confidence interval (CI) 0.62 to 0.95). Specifically, those who had longer exposed duration (> 6 months vs ≤ 6 months) and those who started ACEI/BB use closer to the initiation of anthracyclines/trastuzumab (pre-index to 6 months vs ≥6 months) had lower risk of developing cardiotoxicity. Regarding patient sociodemographics, factors associated with a higher risk of cardiotoxicity include those who lived in the Midwest SEER region (vs Northeast), had lower education level, had a higher comorbidity score, and had history of pre-existing cardiovascular conditions (i.e., hypertension, diabetes, stroke, and atrial fibrillation). With regard to treatment, risk of cardiotoxicity was higher for trastuzumab-based (HR, 1.23; 95%CI, 1.04 to 1.44), and trastuzumab plus anthracyclines (HR, 1.76;

95%CI, 1.47 to 2.11) compared with other treatments. Other treatments, particularly radiation (HR, 1.21; 95%CI, 1.08-1.35), alkylating agent-based (HR, 1.55; 95%CI 1.31 to 1.83), and concomitant use of angiotensin receptor blockers and diuretic were also associated with a higher risk of cardiotoxicity.

Likewise, in terms of all-cause mortality, those who were exposed to ACEIs/BBs had a statistically significant 21% lower risk of all-cause mortality (HR, 0.79; 95%CI 0.70 to 0.90). Similar to predictors of cardiotoxicity, those who had longer exposed duration (> 6 months vs ≤ 6 months) had a lower risk of developing all-cause mortality. Regarding patient sociodemographics and tumor characteristics, factors associated with a higher risk of all-cause mortality include African-American race, age older than 70 (vs ≤70), residence in the South region (vs Northeast), unmarried (vs married), lower socioeconomic status (income and poverty), history of pre-existing cardiovascular condition (i.e., hypertension, stroke, renal failure, and atrial fibrillation), and advanced stage (i.e., higher-grade tumor, higher numbers of positive lymph nodes, and ER-negative disease).

With regard to treatment, risk of all-cause mortality increased with other chemotherapy; whereas mortality risk decreased with use of trastuzumab-based (HR, 0.62; 95%CI, 0.57 to 0.67), trastuzumab and anthracycline-based (HR, 0.79; 95%CI, 0.73 to 0.86) and combination of taxane-based (HR, 0.93; 95%CI 0.88 to 0.99) and radiation therapy (HR, 0.85; 95%CI 0.80 to 0.90). Lower mortality risk also was found with use of ARBs (HR, 0.73; 95%CI 0.61 to 0.86) and diuretics (HR, 0.73; 95%CI 0.65 to 0.81).

The adjusted cumulative incidence of all-cause mortality among ACEIs/BBs exposure and ACEIs/BB non-exposure increased with increasing follow-up time (Figure

2). Overall, during years of follow-up, patients who were exposed to ACEIs/BBs were less likely to develop all-cause mortality compared with the non-exposed group. At 5 years of follow-up, we observed differences of 3.9% in the rates of all-cause mortality between the ACEIs/BBs exposed group and unexposed group. Specifically, there was a greater risk of all-cause mortality in the non-exposed group (cumulative incidence =50.5%, 95% CI=49.5% to 51.6%) compared with ACEIs/BB exposure (cumulative incidence =46.6%, 95% CI=44.0% to 49.0%) at 5 years of follow-up.

The 5-year adjusted cumulative incidence of cardiotoxicity associated with ACEI/BB exposure and non-exposure increased with increasing time (Figure 3). Five years after diagnosis from breast cancer the ACEIs/BBs non-exposure were more likely to develop cardiotoxicity compared with the ACEIs/BB exposure group. At 5 years of follow-up, we observed differences of 3.4% in the rates of cardiotoxicity between the ACEIs/BBs exposure group and non-exposure group. Specifically, the-5 year cumulative incidence of cardiotoxicity was higher in the ACEIs/BB non-exposure group (cumulative incidence =19.8%, 95% CI=18.9% to 20.7%) compared with the ACEIs/BB exposure group (cumulative incidence =16.4%, 95% CI=14.4% to 18.3%).

Our sensitivity analyses suggests no differences among ACEIs/BBs dosage intensities or the combination between two drug classes in developing risk of cardiotoxicity. Consistently, the combination of two drug classes did not affect risk of mortality. However, those receiving low-dose ACEIs or BBs had higher mortality risk than those with average-dose daily (data not shown.) Additionally, the two sensitivity analyses after limiting data to 2007 and beyond provide consistent results in terms of prevention of cardiotoxicity and mortality. Specifically, the point estimates are similar in

direction in both analyses. Nevertheless, given the smaller sample size after limiting the data, the mortality confidence interval becomes very wide and is not statistically significant (data not shown).

Discussion

In this large population-based study, we observed a favorable effect of ACEIs/BBs in prevention of cardiotoxicity and mortality in breast cancer patients treated with trastuzumab and/or anthracycline regimens, with a 23% decrease in cardiotoxicity a 21% decrease in all-cause mortality. Specifically, those who had early treatment with ACEs/BBs (≤ 6 months after the initiation of trastuzumab/anthracycline) and longer duration of ACEI/BB use (>6 months) have lower risk of cardiotoxicity and all-cause mortality. We also observed lower cumulative rates in both cardiotoxicity and all-cause mortality in ACEI/BB exposed compared with unexposed patients. Although the ACEI/BB exposure group was more likely to have advanced cancer and more pre-existing cardiovascular conditions.

Our findings are consistent with clinical trials[20,92,94,104,147] as well as cancer registry studies[148,149] reporting that ACEIs/BBs can prevent cardiotoxicity. For example, Bosch et al evaluated the efficacy of enalapril and carvedilol in patients undergoing chemotherapy. The results suggested that compared to nonusers, the enalapril and carvedilol users had a lower incidence of the combined event of death or heart failure (6.7% vs. 22%).[20] In addition, Keyhan et al reported that women exposed to ACEIs had lower mortality (HR 0.80, 95%CI 0.76 to 0.85).[104]

Socioeconomics, demographics, geographical area, and tumor characteristics also have an impact on the risk of all-cause mortality and/or cardiotoxicity. Our results are

similar to previous studies that reported factors such as receipt of chemotherapy and patient or tumor characteristics (e.g., age, comorbidity, estrogen receptor) were associated with all-cause mortality.[104,141-145,150] For example, our results are consistent with a previous meta-analysis which reported an approximate 20% reduction in all-cause mortality among breast cancer patients 50-69 years of age treated with chemotherapy.[150] Similarly, comorbid cardiovascular conditions, such as hypertension, stroke, diabetes, and atrial fibrillation were also associated with higher incidence of cardiotoxicity and mortality.[104,142,146] Notably, we also found that certain factors, including race, older age, or tumor characteristics are not associated with increased risk of cardiotoxicity, despite the increased risk in all-cause mortality. For instance, we found lower risk of cardiotoxicity in patients diagnosed at age ≥80 as compared to those diagnosed at≤70 which might be a result of competing risk, and this is concordant with previous study using SEER-Medicare.[139]

Treatment regimens also contribute to risk of cardiotoxicity and all-cause mortality. Our results are consistent with existing evidence demonstrating that trastuzumab and/or anthracycline regimens are associated with high risk of cardiotoxicity. Specifically, the risk of cardiotoxicity was higher with trastuzumab-based than anthracycline-based regimens and the risk was most pronounced for combination trastuzumab and anthracycline-based regimens.[13,34,53,83,88,97] For instance, Chen et al reported that breast cancer patients treated with trastuzumab and anthracycline-based chemotherapy had significantly increased risk of heart failure (RR, 4.27; 95% CI 2.75 to 6.61), as compared to patients who received non-anthracycline chemotherapy RR = 2.42, 95% CI 0.36 to 6.19).[88] Similar to previous evidence, we also found that a combination

use of alkylating agents with trastuzumab/or anthracycline-based chemotherapy significantly increases the risk of cardiotoxicity in breast cancer patients while a combination of taxane-based regimen with those two agents appears to have favorable results (e.g., did not increase the risk of cardiotoxicity).[34]

Although increased risks of cardiotoxicity were found in those who had concomitant use of ARBs or diuretics, our findings demonstrate lower risks of all-cause mortality among these two drug classes. Our study is similar to Keyhan and colleague in terms of ARBs. Contrastingly, our findings did not support existing evidence that ARBs may play a role in prevention of cardiotoxicity.[12,31] Further studies on ARBs and cardiotoxicity may help determine if the use of ARBs has an impact on cardiotoxicity or outweigh the risk of cardiotoxicity. Interestingly, the finding that early anti-hypertensive treatment after the initiation of chemotherapy is associated with lower risk of cardiotoxicity and mortality is consistent with previous studies both in human and animal models.[16,92,148,151] For instance, results from Olivia indicate that ACEI/BB use during the first 3-months of a trastuzumab regimen are associated with a decrease in cardiotoxicity.[148]

The findings from our sensitivity analyses suggests no differences among ACEIs/BBs dosage intensities or the combination between two drug classes in developing risk of cardiotoxicity. This findings is consistent with previous clinical studies.[148,152] For instance, Olivia et al found that the combination of two drug classes was not associated with trastuzumab-induced cardiotoxicity. Similarly, Dandona et al demonstrated that low-dose of BBs still has treatment benefits.[152]

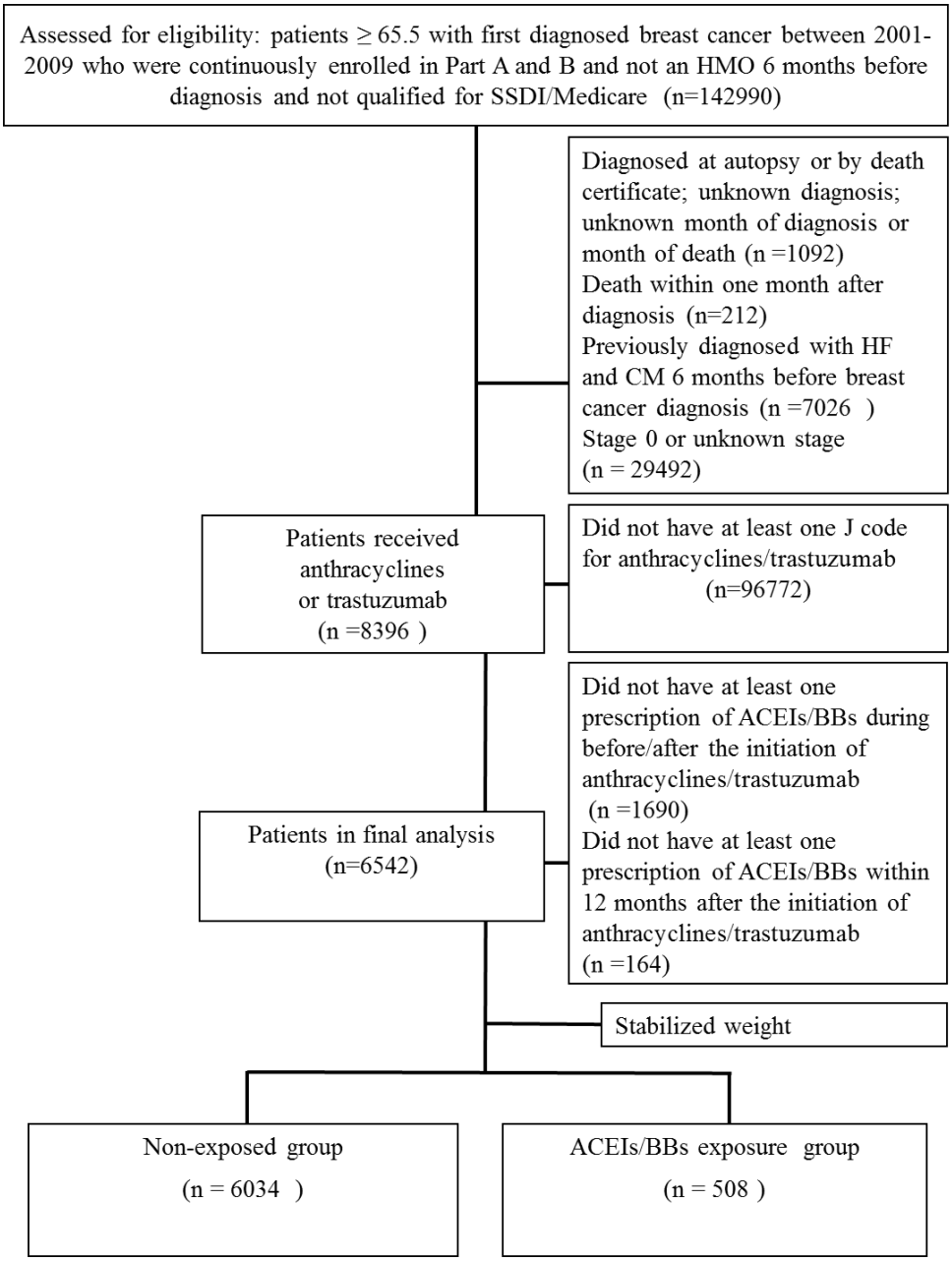
A number of limitations and strengths of our study should be noted. First, an observational study may introduce some issues, including selection bias or unmeasurable confounding factors. For instance, we were not able to measure other factors potentially associated with mortality such as smoking or genetic biomarkers that might affect a provider's decision regarding treatment modality.[134] A related issue is the small sample size of the exposure cohort. However, we used MSM and stabilized weight models adjusting for baseline covariates and confounding issue of treatment effect to preserve sample size and ensure that the distribution of confounding factors is similar among groups. This approach has been used in existing studies on anti-hypertensive medications and it is supported in that it provides estimates that are consistent with clinical trials.[111,113,114] Second, the nature of registry and claims data might introduce some biases. For example, there may be an issue of ascertainment of cardiotoxicity outcomes, including under-diagnosis. However, diagnosis codes and procedure of cardiotoxicity as well as other variables are generally accepted based on previous studies.[48,83,88,136,139,145] Third, incomplete capture of drug use during pre-2006 or before Part D plan may introduce measurement bias. However, we addressed this issue by conducting sensitivity analyses, as well as including timing of diagnosis in the models. Future studies should consider using additional newer years of data to address this limitation. Finally, our scope is limited to nondisabled Medicare beneficiaries who are ≥65 years of age in SEER geographic areas; therefore, results may not be generalized to other populations.

Our study has a number of strengths. To our knowledge, this is the first population-based study examining the relationship of ACEI/BB treatment in prevention of trastuzumab and/or anthracycline-induced cardiotoxicity and all-cause mortality. We

included patients with pre-existing cardiovascular conditions, while generally RCTs have excluded this population.[20,88,92,94] Besides pre-existing cardiovascular conditions, we were also able to examine how demographics, geographic region, socioeconomics, and concurrent use of treatment regimens might affect risk of cardiotoxicity. A better understanding of patient and tumor characteristics, treatment factors, as well as geographic region contributing to risk of cardiotoxicity and all-cause mortality may lead to development of strategies to reduce cardiotoxicity events and improve overall breast cancer survival. Finally, given the favorable results of promptly starting (i.e., ≤ 6 months) ACEIs/BBs after the initiation of trastuzumab and/or anthracycline-based regimens, these findings underscore the importance of an early assessment and start of ACEIs/BBs treatment for achieving a significant prevention in cardiotoxicity and survival benefits. Consequently, our study emphasizes the need for an interdisciplinary approach between cardiologists and oncologists to assess and monitor for cardiotoxicity when starting these regimens. This approach may allow treatment regimens to be continued without compromising cardiac function.

In conclusion, our study indicates that among female Medicare beneficiaries aged 66 and older with breast cancer receiving trastuzumab and/or anthracyclines chemotherapy, treatment with ACEIs/BBs is associated with reduction in cardiotoxicity and all-cause mortality.

Figure 1 CONSORT Diagram: Angiotensin-converting enzyme inhibitors and/or β-blockers (ACEIs/BBs) exposure and non-exposure groups



CM: cardiomyopathy; HF: heart failure

Table 1 Patients characteristics by angiotensin-converting enzyme inhibitors and/or β-blockers (ACEIs/BBs) exposure

Variable	Exposed group	Non-exposed group	*P* value
	(n=508)	(n=6034)	
Year of diagnosis			
2001	1.18	13.41	<.0001
2002	1.57	13.81	
2003	2.76	12.96	
2004	3.94	13.72	
2005	5.51	13.85	
2006	38.19	11.97	
2007	20.28	7.82	
2008	16.14	7.42	
2009	10.43	5.04	
Age at diagnosis			
66-70	41.54	48.19	0.0037
71-75	34.25	30.08	
76-80	12.8	13.64	
>80	11.42	8.09	
Race/ethnicity			
White	79.13	83.43	0.0092
Black	8.86	8.42	
Other	12.01	8.15	
Stage			
I	20.67	17	0.0141
II	44.49	50.81	
III	27.36	23.68	
IV	7.48	8.5	
Grade			
Well differentiated	5.12	7.34	<.0001
Moderately differentiated	27.36	33.11	
Poorly and undifferentiated	63.19	51.94	
Unknown	4.33	7.61	
Estrogen-receptor status			
Positive	46.46	65.16	<.0001
Negative	53.54	34.84	
Tumor size			
<2 cm	39.57	38.2	0.0154
2-5 cm	45.67	43.59	
>5 cm	11.22	10.86	
Diffuse and unknown	3.54	7.36	
No. positive lymph nodes			
0	39.57	31.32	0.0010
1-3	26.97	32.81	

>3	23.82	24.54	
Unknown	9.65	11.32	
SEER region			
Northeast	18.11	19.14	0.2769
Midwest	12.01	12.26	
South	30.51	26.53	
West	39.37	42.06	
Marital status			
Not married	51.38	40.98	<.0001
Currently married	46.26	55.82	
Unknown	2.36	3.20	
Median income			
1 (lowest)	33.27	21.79	<.0001
2	23.23	25.34	
3	23.03	26.86	
4 (highest)	20.47	26	
Education (high school graduation rates)			
1 (lowest)	33.27	21.33	<.0001
2	22.44	26.35	
3	25.59	26.17	
4 (highest)	18.7	26.15	
Poverty (living below poverty level)			
1 (lowest)	20.87	27.93	<.0001
2	23.43	25.46	
3	23.43	25.04	
4 (highest)	32.28	21.58	
Surgery			
None	14.17	9.65	0.0023
Breast conserving	34.25	38.81	
Mastectomy	51.57	51.54	
Radiation therapy			
No radiation	40.35	35.03	0.0161
Yes	59.65	64.97	
Comorbidity score			
0	72.83	85.71	<.0001
1	22.05	11.67	
≥2	5.12	2.62	
Pre-existing cardiovascular conditions			
Hypertension	73.43	47.51	<.0001
Diabetes	32.87	17.04	<.0001
Coronary artery disease	3.74	2.10	0.0266
Ischemic stroke and transient ischemic attack	5.51	3.43	0.0243

Renal failure	4.33	1.29	<.0001
Atrial fibrillation/flutter	5.91	3.10	0.0007
Hyperlipidemia	58.86	43.77	<.0001
Treatment			
Anthracyclines-based	50.59	75.89	<.0001
Trastuzumab and Anthracycline-based	15.94	9.15	
Trastuzumab-based	33.46	14.97	
Alkylating agent-based	65.35	81.32	<.0001
Taxane-based	69.49	63.13	0.004
Other regimens±	35.83	33.48	0.28
Angiotensin receptor blockers	21.85	3.33	<.0001
Calcium channel blockers	37.60	5.30	<.0001
Diuretics	62.01	7.94	<.0001

±Other regimens included anti-metabolites, hormones, and others

Table 2 Factors associated with survival and cardiotoxicity in breast cancer received trastuzumab and/or anthracyclines±

Factor	All-cause mortality		Cardiotoxicity	
	HR	**95% CI**	**HR**	**95% CI**
ACEIs/BBs non-exposed	REF		REF	
ACEIs/BBs exposed	0.79	0.70-0.90	0.77	0.62-0.95
Baseline characteristics and comorbidities				
Year of diagnosis				
2001	REF		REF	
2002			0.81	0.67-0.98
2003			0.91	0.75-1.10
2004			0.68	0.55-0.83
2005			0.83	0.68-1.02
2006			0.94	0.76-1.16
2007			1.08	0.85-1.36
2008			1.21	0.95-1.54
2009			0.87	0.63-1.20
Age				
66-70	REF		REF	
71-75	1.39	1.30-1.48	0.93	0.82-1.05
76-80	1.39	1.29-1.51	1.05	0.90-1.21
>80	1.91	1.75-2.07	0.77	0.63-0.93
Race/ethnicity				
White	REF		REF	
Black	1.23	1.13-1.34		
Other	0.89	0.80-1.00		
Stage				
I	REF			
II	1.25	1.11-1.41		
III	1.59	1.40-1.82		
IV	2.28	1.99-2.61		
Grade				
Well differentiated	REF		REF	
Moderately differentiated	1.19	1.05-1.35	0.98	0.79-1.23
Poorly and undifferentiated	1.88	1.66-2.12	0.80	0.65-0.99
Unknown	1.16	1.01-1.33	1.00	0.76-1.31
Estrogen-receptor status				
Positive	REF			
Negative	1.55	1.46-1.64		
No. positive lymph nodes				
0	REF			
1-3	1.28	1.16-1.42		
>3	1.94	1.75-2.15		
Unknown	2.92	2.61-3.27		

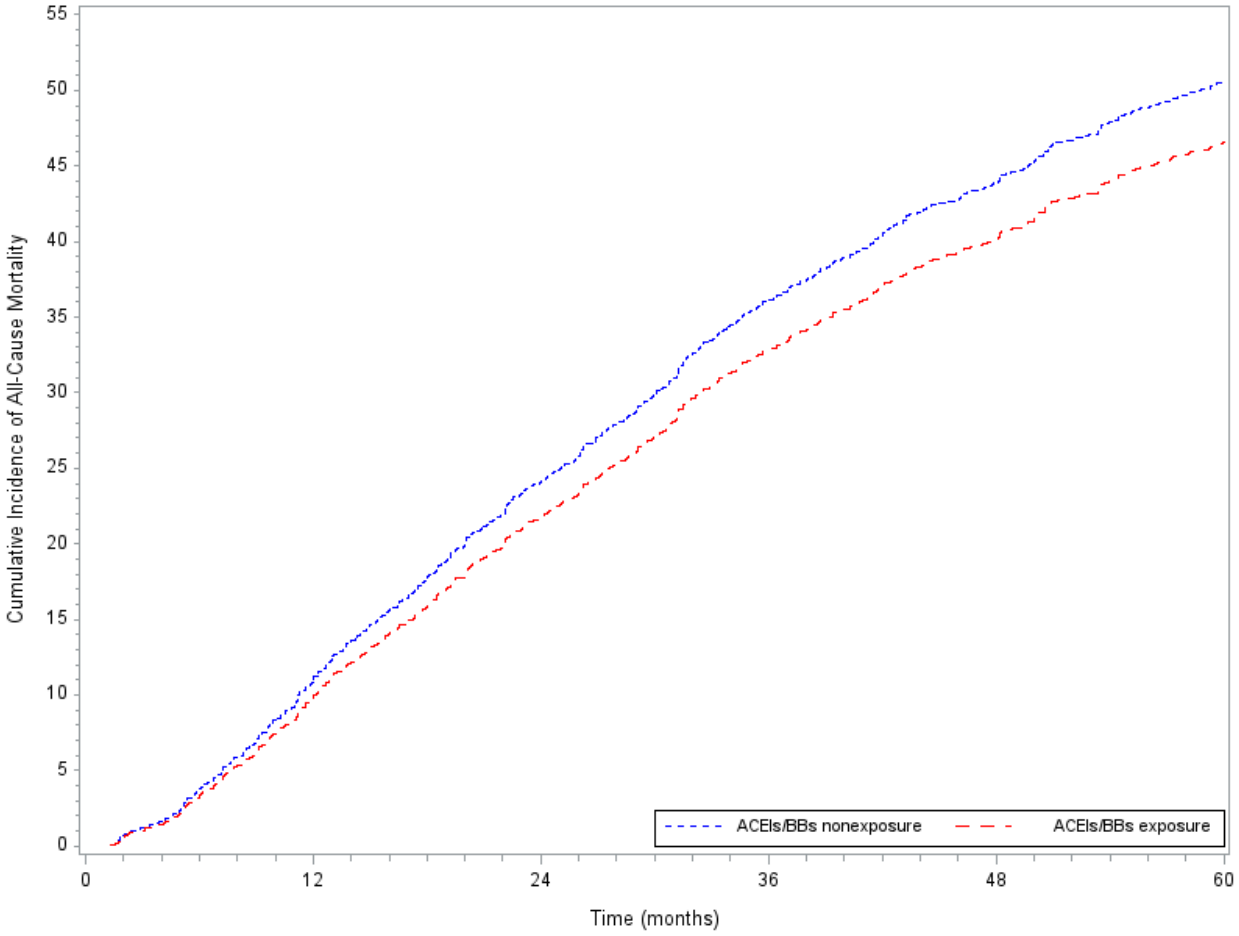
SEER region				
Northeast	REF		REF	
Midwest	0.72	0.65-0.79	1.23	1.03-1.47
South	1.09	1.00-1.19	0.85	0.72-1.00
West	0.88	0.81-0.95	1.00	0.86-1.15
Marital status				
Not married	REF		REF	
Currently married	0.86	0.82-0.91	0.90	0.81-1.01
Unknown	1.04	0.90-1.21	0.57	0.39-0.82
Median income				
1 (lowest)	REF			
2	0.83	0.75-0.92		
3	1.06	0.94-1.20		
4 (highest)	0.95	0.83-1.10		
Education (high school graduation rates)				
1 (lowest)	REF		REF	
2	1.02	0.90-1.15	0.86	0.73-1.00
3	0.93	0.84-1.03	0.97	0.84-1.13
4 (highest)	0.92	0.84-1.01	0.88	0.76-1.03
Poverty (living below poverty level)				
1 (lowest)	REF			
2	1.07	0.98-1.17		
3	1.36	1.21-1.52		
4(highest)	1.38	1.19-1.61		
Surgery				
None	REF			
Breast conserving	0.76	0.69-0.84		
Mastectomy	0.84	0.77-0.92		
Radiation therapy				
No radiation	REF		REF	
Yes	0.85	0.80-0.90	1.21	1.08-1.35
Comorbidity score				
0			REF	
1			1.07	0.92-1.26
≥2			1.37	1.08-1.74
Pre-existing cardiovascular conditions				
Hypertension	1.33	1.26-1.41	1.20	1.07-1.35
Diabetes			1.43	1.24-1.64
Coronary artery disease	0.71	0.59-0.84		
Ischemic stroke and transient ischemic attack	1.34	1.18-1.53	1.36	1.10-1.68
Renal failure	2.31	1.91-2.79		
Atrial fibrillation/flutter	1.74	1.53-1.98	2.14	1.81-2.54
Hyperlipidemia	0.81	0.76-0.86		
Treatment				

Anthracyclines-based	REF		REF	
Trastuzumab and Anthracycline-based	0.79	0.73-0.86	1.76	1.47-2.11
Trastuzumab-based	0.62	0.57-0.67	1.23	1.04-1.44
Alkylating agent-based			1.55	1.31-1.83
Taxane-based	0.93	0.88-0.99	0.90	0.80-1.00
Other regimens±±	1.49	1.40-1.59	0.77	0.69-0.87
Angiotensin receptor blockers	0.73	0.61-0.86	1.41	1.15-1.74
Diuretics	0.73	0.65-0.81	1.42	1.20-1.69
Exposed duration				
≤6 months	REF		REF	
6-12 months	0.87	0.82-0.94	0.63	0.55-0.72
≥ 12 months	0.27	0.25-0.29	0.22	0.02-0.22
Exposed timing at the initiation of anthracyclines/trastuzumab				
Before	REF		REF	
After	0.76	0.72-0.81	0.52	0.46-0.59
Exposed timing at the initiation of anthracyclines/trastuzumab				
Within 6 months			REF	
6-12 months			1.17	1.04-1.31
≥12 months			2.01	1.62-2.50

± Only significant factors were presented in the models after stepwise selection approach. All models were adjusted for covariates.

±± ±Other regimens included anti-metabolites, hormones, and others

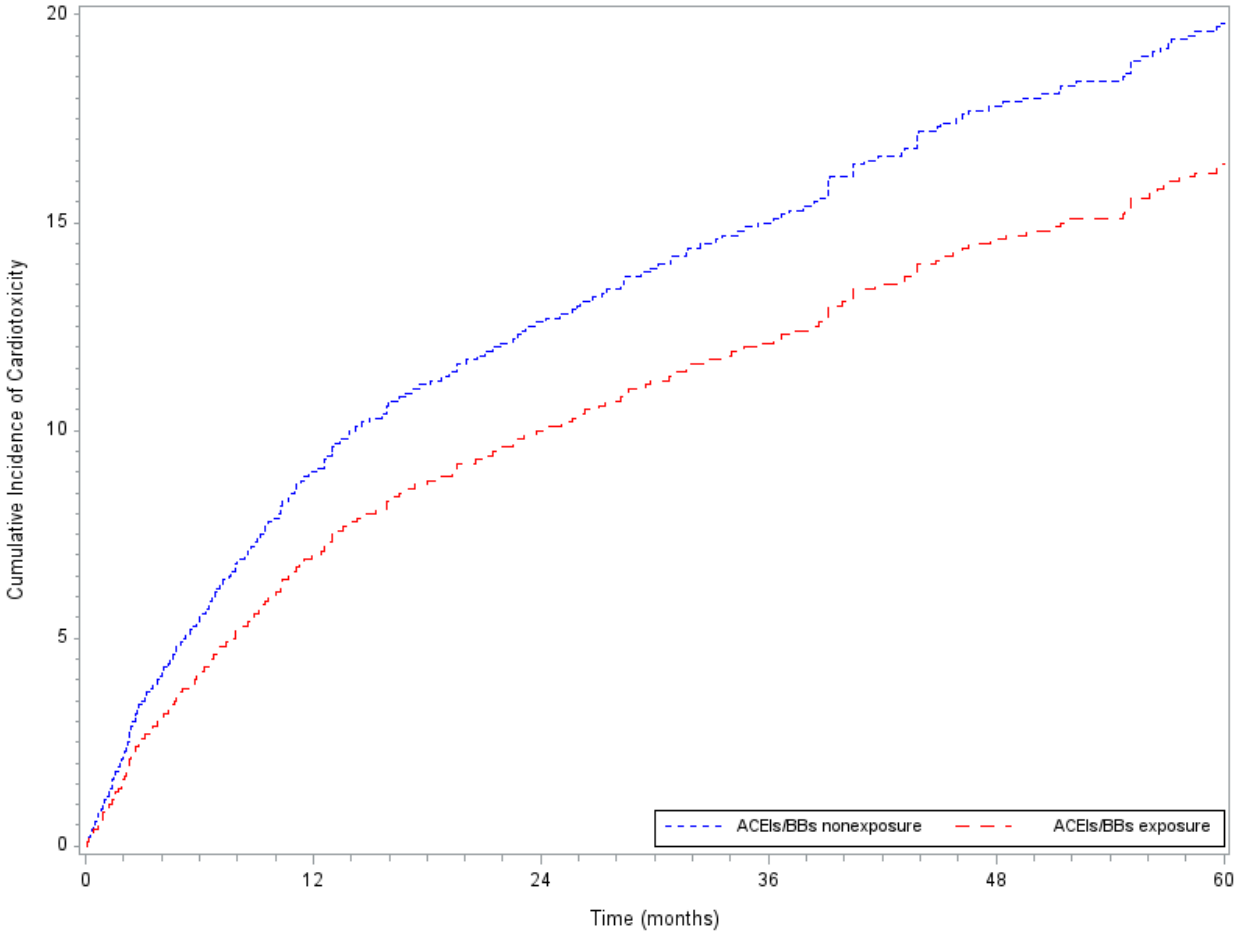
Figure 2 Adjusted cumulative incidence of all-cause mortality



Time (months)	Non-exposed group		Exposed group	
	Cumulative incidence	95% CI	Cumulative incidence	95% CI
0				
12	10.8	10.2-11.4	9.7	8.9-10.5
24	24.1	23.3-25.0	21.8	20.2-23.3
36	36.1	35.1-37.1	32.9	30.8-34.9
48	43.9	42.9-44.9	40.2	37.8-42.5
60	50.5	49.5-51.6	46.6	44.0-49.0

Adjusted cumulative incidence of all-cause mortality for chemotherapy and hormonal therapy. Values are % (per 100 patients). Covariates adjusted for were patient characteristics, socioeconomics, cancer characteristics, and treatments. Plotted at their mean values.

Figure 3 Adjusted cumulative incidence of cardiotoxicity



Time (months)	Non-exposed group		Exposed group	
	Cumulative incidence	95% CI	Cumulative incidence	95% CI
0				
12	9	8.5-9.5	7	5.9-8.1
24	12.6	12-13.2	10	8.5-11.4
36	15	14.3-15.7	12.1	10.5-13.7
48	17.8	17-18.6	14.6	12.7-16.4
60	19.8	18.9-20.7	16.4	14.4-18.3

Adjusted cumulative incidence of cardiotoxicity for chemotherapy and hormonal therapy. Values are % (per 100 patients). Covariates adjusted for were patient characteristics, socioeconomics, cancer characteristics, and treatments. Plotted at their mean values.

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Chapter 5

Discussion and Conclusions

Breast cancer is the most common cancer among women in the United States and remains the second leading cause of cancer death among women regardless of race and ethnicity.[1] Substantial evidence supports the benefits of breast cancer treatment, but there is some concern regarding treatment disparities which might affect long-term outcomes and eventually patient survival.[3] Although there were some population-based studies examining breast cancer treatment patterns, there is a current knowledge gap in evaluating treatment patterns and factors associated with treatment using data which are representative across different population groups, characteristic of health care settings, or geographical location. Additionally, despite the shift in chemotherapy administration from hospital settings to ambulatory settings, little is known about patterns of and factors-related to breast cancer treatment in ambulatory settings.

Evidence indicates improvements in survival and declines in mortality in breast cancer over the last two decades; [1,4] however, it remains an issue for patients undergoing chemotherapy because the incidence of chemotherapy-induced cardiotoxicity, especially with anthracyclines (0.9%-48%)[5] and trastuzumab (0.5-34%),[6] has become increasingly recognized.[5] Cardiotoxicity such as heart failure in breast cancer patients may cause serious consequences and may compromise the clinical effectiveness of chemotherapy and eventually lead to premature death.[7] To date, there is no specific guideline for cancer

therapy-related cardiotoxicity. Nevertheless, an increasing amount of evidence has supported the benefit of angiotensin-converting enzyme inhibitors (ACEIs) or β-blockers (BBs) in patients with chemotherapy-induced cardiotoxicity.[8-10] This may eventually delay or slow clinical progression to heart failure in patients undergoing chemotherapy.[8,10,11] Therefore, using ACEIs and/or BBs as a prophylactic or concurrent regimen in breast cancer patients treated with trastuzumab and/or anthracyclines therapy may be beneficial in the prevention of cardiotoxicity. However, available evidence to support the potential benefits of using ACEIs and/or BBs in prevention of cardiotoxicity is currently insufficient, particularly in real world data.

The overall goal of this study was to 1) examine treatment patterns of anti-neoplastic agents prescribed to breast cancer patients, 2) estimate the incidence of and identify factors associated with adjuvant chemotherapy-induced cardiotoxicity and all-cause mortality among breast cancer patients, and 3) compare the effect of ACEIs and/or BBs in prevention of trastuzumab- and anthracycline-induced cardiotoxicity and all-cause mortality. The underlying hypothesis of the proposed study is that breast cancer patients who were exposed to ACEIs and/or BBs (i.e., ACEI/BB users) during or before trastuzumab and/or anthracycline therapy will have a lower incidence of cardiotoxicity compared with breast cancer patients who were unexposed to ACEIs and/or BBs (i.e., ACEI/BB nonusers).

This chapter summarizes the overall findings and the implications of the findings, as well as provides recommendations for future research.

Overall findings for aim 1

The results suggest that the proportion of visits in which breast cancer patients received anti-neoplastic agent(s) in ambulatory settings remained stable across time and patients appear to receive treatment concordant with standard guidelines. Next, the finding demonstrate that treatment patterns differ among breast cancer patients. Among anti-neoplastic agents, hormones were commonly prescribed, followed by mitotic inhibitors, and human epidermal growth factor receptor2 inhibitors. Further, the findings provide information regarding factors predicting type of treatment, particularly patient demographic and socioeconomics (e.g., age, race/ethnicity, type of insurance, cancer stage, and certain comorbidities). For instance, those with advanced stage were more likely than patients with in situ stage to receive treatment, particularly chemotherapy and targeted therapy. Similarly, those with older age, being minorities, co-morbid depression, and having Medicaid insurance had a lower likelihood of receiving targeted therapy. In addition to demographic and socioeconomics, ambulatory care characteristics also play a role in treatment patterns. Specifically, patients seen in hospital-based settings and settings located in metropolitan areas were more likely to receive chemotherapy.

Overall findings for aim 2

In this population-based study, we found that women with breast cancer aged 66 and older who were treated with adjuvant chemotherapy, particularly trastuzumab and/or anthracycline-based regimens, had a statistically significant increase in the risk of cardiotoxicity compared with hormonal therapy. At 5-years of follow-up, the cumulative incidence of cardiotoxicity was increased among women treated with combination of

trastuzumab and anthracyclines, followed by trastuzumab-based and anthracycline-based regimens. We also found that the incidence rate of cardiotoxicity in our study was higher than reports from RCTs. In terms of all-cause mortality, the findings indicate improvement in survival in those who received trastuzumab and/or anthracycline-based regimens, despite the risk of cardiotoxicity. Additionally, risk of all-cause mortality was higher in patients treated with taxane-based regimens compared with hormone. Similarly, the cumulative risk of all-cause mortality among adjuvant and hormonal therapy increased gradually over the follow-up period. In addition to types of adjuvant chemotherapy, the findings indicate that factors including patient demographics, socioeconomics, pre-existing cardiovascular comorbid conditions, as well as tumor characteristics were associated with risk of cardiotoxicity and all-cause mortality in women with breast cancer.

Overall finding for aim 3

The results of this population-based study demonstrate that use of ACEIs/BBs in patients undergoing adjuvant trastuzumab and/or chemotherapy is associated with decreased risk of cardiotoxicity, as well as improved all-cause mortality. We also found that timeliness and duration of ACEIs/BBs have a significant impact on risk of cardiotoxicity and all-cause mortality. Specifically, promptly starting ACEIs/BBs after the initiation of trastuzumab and/or anthracyclines (≤ 6 months) and having longer exposed duration (≥ 6 months) were associated with decrease in risk of cardiotoxicity and all-cause mortality. Certain patient characteristics (e.g., age, non-Hispanic black), cancer characteristics (e.g., advanced cancer and ER-positive), lower socioeconomic status (e.g., lower education and higher poverty levels), region, comorbidity, pre-existing

cardiovascular conditions, region, and concomitant treatment (e.g., combination of trastuzumab and anthracycline-based) were associated with a significant elevation in risk of all-cause mortality and/or cardiotoxicity.

Implications of the finding and future research for aim 1

The study based on encounter level data (i.e., visits to ambulatory settings) provides a number of clinical and public health implications. First, findings may help to understand practice variation and the effectiveness of practice guideline dissemination. A better understanding of geographic variability in practice may result in better treatment outcomes in breast cancer patients. Second, the study underscores that treatment disparities exist among the ambulatory U.S. breast cancer population, specifically in terms of race/ethnicity, age, type of insurance, and metropolitan areas. Hence, the findings may provide evidence to policy makers in order help achieve the American Cancer Society (ACS) 2015 challenge goals for eliminating cancer disparities across diverse cancer populations in the U.S. Third, factors associated with receipt of treatment should be considered when assessing breast cancer patients in ambulatory settings in order to help identify potentially undertreated patients. Overall, treatment rates and the types of treatment patterns were expected to be relatively consistent across population subgroups. However, given the variation in the clinical practice patterns relative to newer more expensive drugs, this is likely evidence of treatment differences related to certain factors such as physician preferences. Further research is needed to investigate these treatment differences

Implications of the finding and future research for aim 2

Findings in this study have a number of implications and fill a research gap. First, our study provides new information regarding potential factors and risk estimates for treatments other than anthracyclines and trastuzumab adjuvant chemotheapy (e.g., taxane-based and hormone). Second, our population-based study includes patients with heterogeneous characteristics such as pre-existing cardiovascular conditions; hence, our findings are more generalizable to breast cancer patients in general clinical practice than RCTs. A better understanding of patient's demographics, socioeconomics, tumor characteristics, and treatment factors contributing to risk of cardiotoxicity and all-cause mortality may lead to reduction in cardiotoxicity events and improve overall survival in real-world settings. Finally, given that trastuzumab and/or anthracycline adjuvant therapy were not associated with increased risk of all-cause mortality, our study highlights the need for interdisciplinary medicine between cardiologists and oncologists to manage the risks and benefits when starting these regimens. This approach may allow treatment regimens to be continued without compromising cardiac functions. Considering the lack of some clinical information, such as HER2 status reported by SEER-Medicare database, further study is needed to examine the impact of biological characteristics or genetic biomarkers using linkage data such as electronic medical record and claims databases.

Implications of the finding and future research for aim 3

Our SEER-Medicare study has a number of implications that reflect real-world practice settings. First and most importantly, our study supports the existing evidence of using cardioprotective agents, particularly ACEIs/BBs in prevention of chemotherapy-

induced cardiotoxicity. Second, given the favorable results of promptly starting (i.e., ≤ 6 months) ACEIs/BBs after the initiation of trastuzumab and/or anthracycline-based regimens, our study underscores the importance of an early assessment and start of ACEIs/BBs treatment for achieving a significant prevention in cardiotoxicity and survival benefits. Consequently, our study emphasizes the need for interdisciplinary medicine between cardiologists and oncologists for the assessment and monitoring of cardiotoxicity when starting these regimens. This approach may allow treatment regimens to be continued without compromising cardiac functions. Finally, our study also provides new information about how demographic, geographic region, socioeconomics, and concurrent use of treatment regimens might affect risk of all-cause mortality and/or cardiotoxicity. A better understanding of patient and tumor characteristics, treatment factors, as well as geographic region contributing to risk of cardiotoxicity and all-cause mortality may lead to reduction in cardiotoxicity events and improve in overall survival. Future research may consider comparing efficacy of cardiotoxicity prevention among cardioprotective agents (e.g., angiotensin-receptor blocker receptors) in this population in order to understand whether cardioprotective agents demonstrate comparable or superior benefits to ACEIs/BBs.

Appendix

Appendix A

Table A1. The incidence of cardiotoxicity profile of chemotherapeutic agents (adapted from Zambelli; Svoboda; Shaikh and colleagues; Floyd and colleagues)[12,17,76,84]

Class	Drug	Target receptors	Cardiomyopathy	Clinical features	Incidence
Antibiotics					
Anthracyclines					
	Doxorubicin	-	Yes	Left ventricular dysfunction	3-48%
	Epirubicin	-	Yes	Left ventricular dysfunction	0.9-3.3%
	Idarubicin	-	Yes	Left ventricular dysfunction	5-18%
	Liposomal doxorubicin	-	Yes	Left ventricular dysfunction	6-13%
Anthraquinones					

	Bleomycin	-	No	Pericarditis; myocardial ischemia/infarction	
	Mitoxantrone	-	No	Arrhythmias	
	Mitomycin	-	No	Heart failure	
Alkylating agents					
	Busulfan	-	No	Endocardial fibrosis	
	Cyclophosphamide	-	No	Left ventricular dysfunction: perdicardial effusion, myopericardisis, heart failure	7-28% CHF risk is increased with cumulative dose or high dose (e.g., bone marrow transplantation), in elderly, after chest XRT, or after prior anthracyclines

	Ifosphamide	-	No	Left ventricular dysfunction: perdicardial effusion, myopericardisis, heart failure	17% CHF risk is increased with cumulative dose, prior anthracyclines
Platinums					
Cisplatin		-	No	Arrhythmias, heart block, heart failure, myocardial ischemia/infraction; thromboembolism	Thromboembolism: 8.5% majority of cardiac toxicity is seen in combination chemotherapy
Taxanes					
	Docetaxel	-	No	Bradycardia/AV block; atrial and ventricular arrhythmias; heart failure; myocardial ischemia	Heart failure: 2.3-8% Heart failure mostly occurred when used in combination with doxorubicin.[76]

	Paclitaxel	-	No	Bradycardia	Bradycardia: 0.1-31%; Trimble and colleague reported grade 1 asymptomatic bradycardia at 76%
Antimetabolites					
	Clofarabine	-	No	Transient left ventricular dysfunction	27%
	Fluorouracil	-	No	Cardiac failure; atrial or ventricular ectopy; myocardial ; myocardial ischemia/infarction	Ischemic syndrome 1.1-4.5%; silence ischemic changes were reported up to 68% in patients 24 hours after the initiation of administration.[76]

	Capecitabine	-	No	Ischemic syndrome; angina; ischemic infarction	Mostly ischemic syndrome but less cardiac toxic than fluorouracil
	Methotrexate	-	No	Arrhythmias; myocardial ischemia/infraction	Rarely[76]
	Fludarabine	-	No	Hypotension; angina	Rarely if used as a single agent; however, cardiotoxicity has been reported in study using fludarabine and melphalan as regimen for bone marrow transplantation.[76]
	Cytarabine	-	No	Angina; pericardial effusion	

Biologic response modifiers					
	Interferons		No	Atrial and ventricular arrhythmias; AV block; heart failure; myocardial ischemia/infraction	Arrhythmias: 20% ; Cardiomyopathy usually reversible after termination of interferons.
	Interleukin-2		No	Arrhythmias; heart failure; myocardial ischemia/infraction	Arrhythmias: 6%
Hormone therapies					
	Tamoxifen		No	Deep vein thrombosis; pulmonary embolism; and stroke	Deep vein thrombosis: 1.34 per 10000 women (RR, 1.60: 95% CI 0.91 to 2.86) Pulmonary embolism: 0.69 per 1000 women

					(RR, 3.01: 95% CI 1.15 to 9.27) Stroke: 1.45 per 1000 women per year (RR, 1.59: 95% CI 0.93 to 2.77)[79]
	Letrozole		No		Thromboembolism: 1.5% (less than tamoxifen); Cardiac events (ischemic heart disease, heart failure): 2.1% (higher than tamoxifen)[153]
	Diethylstilbestrol		No	Vasospasm	Cardiotoxicity at dose 1 mg/day: less

	(seldom used as cancer treatment nowadays)				significant; cardiotoxicity has been reported at high-doses ≥ 5 mg/day
Targeted therapies					
mAb					
	Trastuzumab (Herceptin)	HER2	Yes, moderate	Dilate cardiomyopathy, heart failure	Heart failure: 0.5-19%[85] LVEF depression: 1.5-16% Arrhythmias/tachy cardia: 3-12%
	Bevacizumab (Avastin)	VEGF-A	Yes, moderate	Pathologic remodeling due to pressure over load; heart failure; thromboembolism	Heart failure: 1.6% Hypertension: grade ¾: 5-18%

					(can be up to 30-80%)
	Rituximab	Anti CD20	Rare	No long-term cardiotoxicity	Arrythmias and angina <1%; Severe hypotension and angioedema: 1%[26]
Tyrosine kinase inhibitors (TKIs)					
	Lapatinib (Tyverb)	EGFR, HER2	No	Low incidence of HF or other adverse cardiac effects than trastuzumab; QT prolongation	LVEF depression: 1.3%
	Sorafenib (Nexavar)	VEGFR2-3, KIT	Yes, low	Pathologic remodeling due to pressure over load	Heart failure: n/a Hypertension: Grade ¾: 2-3%

					Myocardial ischaemia (MI): 2.9%
	Sunitinib (Sutent)	VEGFR1-2-3, KIT	Yes, moderate	Pathologic remodeling due to pressure over load	Heart failure: 8% Hypertension grade3/4: 13% LVEF depression: 11% MI: <0.1% QT prolong: <0.1%
	Imatinib (Gleevec)	Bcr-Abl1, KIT	Very low	Fluid retention	Heart failure <0.2-1.7%
	Dasatinib (Sprycel)	Bcr-Abl1, KIT	Very low	Fluid retention	Heart failure: 2% QT prolong: <1%

					Pleural effusion: 14-43%[85]
	Nilotinib (Tasigna)	Bcr-Abl1, KIT	Very low	Fluid retention	Heart failure: 1% QT prolong: <1%
Proteasome inhibitors					
	Bortezomib		Low	Heart failure; left ventricular ejection fraction (LVEF);fluid retention	Heart failure 2-5% Cardiomyopathy: reversible
Histone Deacetylase inhibitors (HIDAC)					
	Vorinostat		Low	No major cardiotoxic events were reported	Most common events: tachycardia[85]

	Romidepsin		Low	No major cardiotoxic events were reported	Most common events: tachycardia; One case of sudden cardiac death[85]
Mammalian target of rapamycin (mTOR)					
	Temsirolimus		Low		Most common events: hypertension
	Everolimus		Low		Most common events: hypertension;

					tachycardia and congestive heart failure have been reported (infrequency)
Miscellaneous agents					
	All-trans-retinoic acid		No	Myocardial ischemia/infarction; pericardial effusion	10-26% retinoic acid syndrome[26]
	Arsenic trioxide		No	Prolonged QT; Torsades de pointes	>50%
Radiation therapy					
Radiotherapy				Acute or chronic: Mainly due to progression of coronary atherosclerosis	Disease of heart coronary arteries, valves, and myocardium;

					conduction system diastolic dysfunction All cardiovascular diseases: mortality ratio of 1.10; 95% CI: 1.03 to 1.18]; Ischemic heart disease: morality ratio of 1.13; 95% CI:1.03 to1.25[80]

mAbs: Monoclonal antibodies; TKIs: tyrosine kinase inhibitors

Appendix B

Table B1. Recent studies related to the proposed study

	Cardinale and colleagues[92]
Objective	Evaluate the effect of enalapril (ACEI) treatment on the prevention of cardiotoxicity in cancer patients undergoing high-dose chemotherapy
Study design	A prospective, randomized clinical study Enalapril user =56 (undergoing high-dose chemotherapy and use enalapril within 1 month after the end of the last cycle of high dose chemotherapy and treatment was continued for 1 year) vs Control = 58 (had high dose chemotherapy and never used statin)
Population	Cancer patients with high-dose chemotherapy (e.g., breast cancer, non-Hodgkin's lymphoma, leukemia) and had a plasma troponin I concentration >0.07 ng/mL Exclusion criteria: had uncontrolled hypertension, presence of ischemic, hypertensive heart disease, left ventricular function <50%, age ≥65 years, abnormal renal or hepatic function, ongoing therapy with b-blocking agents, ACEIs, ARBII, systolic blood pressure <90.
Matching	No
Database	Clinical trial
Outcome and definition	Primary endpoint: decrease in left ventricular ejection fraction (LVEF)>10%

	Secondary endpoint: cardiac events (e.g., death, heart failure)
Statistical analyses	-Chi-square or Fisher's exact test for comparing categorical variables at baseline between two groups -Kaplan-Meier survival analysis (log-rank tests) for the primary and secondary endpoints between two groups -Multivarite Cox proportional hazards regression analysis adjusting for age, gender, hypertension, diabetes, ratiotherapy, total dose of anthracyclines, and ventricular volumes and of LVEF , and number of chemotherapies administered for Hazard Ratio
Sensitivity analysis	No
Covariates	age, gender, hypertension, diabetes, radiation therapy, total dose of anthracyclines, and ventricular volumes and of LVEF , and number of chemotherapies administered
Results	-The incidence of the primary end points was significantly higher in enalapril nonusers than in the enalapril users (43% vs 0%; $p<0.001$). Similar to the secondary and combined end points ($p<0.001$).
Conclusions	In high-dose chemotherapy-treated patients, early treatment with enalapril seems to prevent the development of late cardiotoxicity
Limitations	-lack of placebo -lack of prespecified and rigorously defined clinical end points and the several oncological diseases and chemotherapeutic regimens

	Kalay and colleagues[94]

Objective	To determine the protective effect of carvedilol in anthracycline (ANT)-induced cardiomyopathy (CMP)
Study design	Prospective randomized, single-blind, and placebo-controlled trial. In the treatment group, 12.5 mg once-daily oral carvedilol was started before anthracyclines and maintained for 6 months/cycles (a mean of every 3 weeks/cycle).
Population	25 patients diagnosed with breast cancer, lymphoma, and other malignancies and planned anthracyclines therapy (doxorubicin or epirubicin)
Exclusion criteria	The exclusion criteria were earlier chemotherapy (CT) or radiotherapy, presence of congestive heart failure symptoms or established dilated or restrictive CMP, coronary arterial disease history, presence of moderate or severe mitral or aortic valve disease in baseline echocardiograph, any contraindication to carvedilol, bundle branch block, thyroid function disorder, or another comorbid disease.
Matching	Randomized
Database	Clinical trial
Outcome and definition	The primary end point: systolic functions Definition: the mean changes in left ventricular ejection fraction (EF) and systolic and diastolic diameters
Statistical analyses	Descriptive analysis (mean± SD) and t-tests

Sensitivity analysis	N/A
Covariates	N/A
Results	The mean EF of the carvedilol group was similar at baseline and control echocardiography (70.5 vs. 69.7, respectively; p =0.3) In the control group, the mean EF at control echocardiography was significantly lower (68.9 vs. 52.3; p = 0.001). Both systolic and diastolic diameters were significantly increased compared with basal measures in the control group.
Conclusions	Prophylactic use of carvedilol in patients receiving anthracyclines may protect both systolic and diastolic functions of the left ventricle.
Limitations	Small number of participants. The study timeline was 6 months; therefore, it only evaluated the protective effect of carvedilol only on early cardiotoxic effects of anthracyclines and could not evaluate late-term effects of anthracyclines.

	Bosch and colleagues[20]
Objective	This study sought to evaluate the efficacy of enalapril and carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction (LVSD) in patients with hematological malignancies.
Study design	A randomized, controlled tiral study. Patients were randomly assigned to a group receiving enalapril and carvedilol or to a control group 6 months.

	Enalapril and carvedilol was started simultaneously at least 24 h before the first cycle of chemotherapy. The initial dose of enalapril was 2.5 mg and can be titrated up to 5 mg and 10 mg twice daily. The initial dose of carvedilol was 6.25 mg twice daily and can be titrated up to12.5 mg and 25 mg twice daily.
Population	90 patients diagnosed with acute leukemia, lymphoma, multiple myeloma, or who underwent stem cell transplantation
Exclusion criteria	Patients with history of left ventricular dysfunction myocardial infarction, presence of heart failure, renal failure, hepatocellular insufficiency or grade III to IV increase of liver enzymes not secondary to tumoral liver infiltration; ongoing or expected need to be treated with ACEI, angiotensin II receptor blockers (ARB), or beta-blockers; prior allergy to ACEI or ARB; systolic blood pressure (SBP) lower than 90 mm Hg; asthma; atrioventricular block or sinus bradycardia (heart rate lower than 60 beats/min); persistent atrial fibrillation
Matching	randomized
Database	Clinical trial
Outcome and definition	The absolute change from baseline to 6 month follow-up in LV ejection fraction (LVEF).
Statistical analyses	Descriptive analysis (mean±SD) and t-tests

Sensitivity analysis	Yes. A sensitivity analysis had been performed for missing values.
Covariates	N/A
Results	At 6 months, LVEF did not change in the intervention group but significantly decreased in controls. Compared to controls, patients in the intervention group had a lower incidence of the combined event of death or heart failure (6.7% vs. 22%, p ¼ 0.036) and of death, heart failure, or a final LVEF <45% (6.7% vs. 24.4%, p ¼ 0.02).
Conclusions	Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy.
Limitations	Limited number of patients. Need longer administered doses of enalapril and carvedilol

	Chen and colleagues[88]
Objective	To estimate heart failure (HF) and cardiomyopathy (CM) rates after adjuvant trastuzumab therapy and chemotherapy in a population of older women with early-stage breast cancer.
Study design	Retrospective Patients were assigned for the following mutually exclusive treatment groups: 1) trastuzumab (with or without nonanthracycline chemotherapy); 2) anthracycline plus trastuzumab; 3) anthracycline (without trastuzumab and with or without nonanthracycline

	chemotherapy); 4) other nonanthracycline chemotherapy, or no adjuvant chemotherapy or trastuzumab therapy
Population	45,537 women diagnosed with breast cancer
Exclusion criteria	Patients were excluded if: 1) breast cancer was not the initial primary tumor diagnosis reported to SEER, or Medicare claims indicated any cancer diagnosis in Medicare claims within 2 years **before** the index diagnosis of breast cancer; 2) the source of diagnosis was autopsy or death certificate; 3) tumor histological examination was not of epithelial origin or stage was unknown; 4) month of diagnosis was missing or the patient died during the month of diagnosis; 5) patients did not have continuous Medicare Part A or Part B coverage or at least 1 nondenied Medicare claim during the 2 years before diagnosis through the end of the study period; 6) chemotherapy or trastuzumab therapy was initiated more than 9 months after breast cancer surgery; 7) prior inpatient HF or CM Medicare claim or with 2 or more HF or CM outpatient or physician claims more than 30 days
Matching	YES. Breast cancer patients with cancer-free Medicare patients were matched 1:1 with breast cancer patients. Those cancer-feee patients were assigned selected a random index date within the same calendar year as the diagnosis of cancer of the matched SEER patient based on 1) region; 2) 2) age quartile; 3) number of comorbidities; (any vs. none); and 4) quartile of total Medicare costs during the year preceding cancer diagnosis (or the year preceding index date for cancer-free individuals).

Database	Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) data from 2000 through 2007
Outcome and definition	3-year incidence rates of HF or CM
Statistical analyses	Baseline patient characteristics were compared across the adjuvant therapy groups using the chi-squared test. Poisson regression was used to quantify risk of HF or CM, adjusting for sociodemographic factors, cancer characteristics, and cardiovascular conditions.
Sensitivity analysis	No
Covariates	Cancer characteristics (e.g., stage, grade, tumor size, and number of positive lymph nodes), comorbidities (identified from inpatient, outpatient, and physician Medicare claims for specific ICD-9-CM codes at any time during the 2 years before the breast cancer diagnosis. Cardiovascular risk factors, including: coronary artery disease, ischemic stroke or transient ischemic attack, hypertension, diabetes mellitus, renal failure, atrial fibrillation or atrial flutter, and hyperlipidemia), socioeconomic status, breast cancer treatment
Results	Adjusted 3-year HF or CM incidence rates were higher for patients receiving trastuzumab (32.1 per 100 patients) and anthracycline plus trastuzumab (41.9 per 100 patients) compared with no adjuvant therapy (18.1per 100 patients, $p < 0.001$). Adding trastuzumab to anthracycline therapy added 12.1, 17.9, and 21.7 HF or

	CM events per 100 patients over 1, 2, and 3 years of follow-up, respectively.
Conclusions	HF or CM are common complications after trastuzumab therapy for older women, with higher rates than those reported from clinical trials.
Limitations	HF and CM events and comorbidities were ascertained on the basis of administrative codes and were not confirmed clinically. Clinical data on left ventricular systolic function were not available; hence, severity could not be evaluated.

Appendix C

Table C1. Diagnosis codes used to identify breast cancer and cardiovascular events in medical claims

Disease	**ICD-9 code**
Breast cancer	174-175
Breast cancer surgery	Refer to appendix C. Table C5
Cardiotoxicity events[48,83,88]	
Heart failure	402.01, 402.11, 402.91, 404.1, 404.91, 404.93, 428.x
Cardiomyopathy	425.x
Comorbidities[83,88]	
Atrial Fibrillation / Flutter	427
Coronary heart disease	410-414
Angina	413
Other form of heart disease	420-429
Hypertension	401-405
Cerebrovascular disease (stroke)	430-438
Disease of arteries, arterioles, and capillaries	440-448
Disease of veins and lymphatics and other diseases	451-459
Congenital cardiovascular anomalies	745-747
Disease of pulmonary circulation	415-417

Renal failure	403-404, 588, V42.0, V45.1, 585.x, 586.x, V56.x
Hyperlipidemia	272.x

Table C2. Comparative dose classification of angiotensin-converting enzymes (ACEIs) inhibitors

Class	Generic name	Usual Dosage Range (mg/day)[a]	Three-level Dose Classification [b]		
			Low	Median	High
Short acting	Captopril	25-100	<43.75	43.75-81.25	>81.25
Intermediate acting	Benazepril	10-40	<17.5	17.5-32.5	>32.5
	Enalapril	5-40	<13.75	13.75-31.25	>31.25
	Moexipril	7.5-30	<13.125	13.125-24.375	>24.375
	Quinapril	10-80	<27.5	27.5-62.5	>62.5
	Ramipril	2.5-20	<6.875	6.875-15.625	>15.625

Long acting	Fosinopril	10-40	<17.5	17.5-32.5	>32.5
	Lisinopril	10-40	<17.5	17.5-32.5	>32.5
	Perindopril	4-8	<5	5-7	>7
	Trandolapril	1-4	<1.75	1.75-3.25	>3.25

[a] The dose classification is based on the dosing ranged provided in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[103]

[b] Low: Quartile Q1; Medium: Quartile Q2; High: Quartile Q3

Table C3. Comparative dose classification of beta-blockers

Class	Generic name	Usual Dosage Range (mg/day)[a]	Three-level Dose Classification [b]		
			Low	Medium	High
	Atenolol	25-100	<43.75	43.75-81.25	>81.25
	Betaxolol	5-20	<8.75	8.75-16.25	>16.25
	Bisoprolol	2.5-10	<4.375	4.375-8.125	>8.125
	Metoprolol	50-100	<62.5	62.5-87.5	>87.5
	Metoprolol extended release	50-100	<62.5	62.5-87.5	>87.5
	Nadolol	40-120	<60	60-100	>100
	Propranolol	40-160	<70	70-130	>130
	Propranolol long-acting	60-180	<90	90-150	>150
	Timolol	20-40	<25	25-35	>35

BBs with intrinsic sympathomimetic activity	Acebutolol	200-800	<350	350-650	>650
	Penbutolol	10-40	<17.5	17.5-32.5	>32.5
	Pindolol	10-40	<17.5	17.5-32.5	>32.5
BBs with alpha blocking activity	Carvedilol	12.5-50	<21.875	21.875-40.625	>40.625
	Labetalol	200-800	<350	350-650	>650

[a] The dose classification is based on the dosing ranged provided in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[103]

[b] Low: Quartile Q1; Medium: Quartile Q2; High: Quartile Q3

Table C.4 Definitions of breast cancer chemotherapy codes[67]

Chemotherapy Agent Codes
Code Description
C1167 epirubicin, hcl, 2 mg
C9115 zoledronic acid, 2 mg
C9120 injection, fulvestrant
C9127 paclitaxel, protein bound
C9214 injectino, bevacizumab
C9399 unclassified drugs or biologics
C9411 pamidronate disodium, brand
C9415 doxorubicin hcl, brand
C9420 cyclophosphamide
C9421 cyclophosphamide, lyophilized, brand
C9430 leuprolide acetate inj, brand
C9431 paclitaxel, inj, brand
C9432 mitomycin inj, brand
C9440 vinorelbine tar, brand
G0356 hormonal anti-neoplastic
G8371 chemotherapy not received for stage 3 colon cancer
G8373 chemo plan doc prio che
G8374 chemo plan not doc prior che
J0207 amifostine
J0640 leucovorin calcium
J1950 leuprolide acetate, 3.75 mg
J7150 prescription oral chemo drug
J8520 capecitabine, oral, 150 mg
J8521 capecitabine, oral, 500 mg
J8530 cyclophosphamide oral, 25 mg
J8610 methotrexate oral, 2.5 mg
J8700 temozolomide
J8999 oral prescription drug, chemo
J9000 doxorubicin
J9001 doxorubicin hcl lipsome
J9035 bevacizumab
J9045 carboplatin
J9070 cyclophosphamide, 100 mg
J9080 cyclophosphamide, 200 mg
J9090 cyclophosphamide, 500 mg
J9093 cyclophosphamide, lyophilized
J9094 cyclophosphamide, lyophilized
J9095 cyclophosphamide, lyophilized

J9096 cyclophosphamide, lyophilized
J9097 cyclophosphamide, lyophilized
J9170 docetaxel
J9175 methotrexate (Elliotts b solution per ml)
J9178 epirubicin, hcl
J9180 epirubicin, hcl
J9190 fluorouracil
J9200 floxuridine
J9202 goserelin acetate implant
J9217 leuprolide acetate suspension
J9218 leuprolide acetate injection
J9219 leuprolide acetate implant
J9250 methotrexate sodium
J9260 methotrexate sodium
J9264 paclitaxel, protein bound
J9265 paclitaxel
J9280 mitomycin, 5 mg
J9290 mitomycin, 20 mg
J9291 mitomycin 40 mg inj
J9293 mitoxantrone hydrochloride
J9295 polyestradiol phosphate inj
J9355 trastuzumab
J9357 valrubicin, 200 mg
J9390 vinorelbine tartrate/10mg
J9395 Fulvestrant, injection
J9999 chemotherapy drug

Chemotherapy Administration codes

Code Description
C8953 Chemotherapy administration, intravenous; push technique
C8954 Chemotherapy administration, intravenous; infusion technique, up to one hour
C8955 Chemotherapy administration, intravenous; infusion technique, each additional hour
(list separately in addition to c8954)
G0355 Chemotherapy administration, subcutaneous or intramuscular non-hormonal antineoplastic
G0359 Chemotherapy administration, intravenous infusion technique; up to one hour, single
or initial substance/drug
G0361 Initiation of prolonged chemotherapy infusion (more than eight hours), requiring use of
a portable or implantable pump
G8371 Chemotherapy documented as not received or prescribed for stage iii colon cancer
patients
G8374 chemotherapy plan not documented prior to chemotherapy administration
Q0081 infusion therapy, using other than chemotherapeutic drugs, per visit

Q0083 chemotherapy administration by other than infusion technique only (eg subcutaneous, intramuscular, push), per visit Q0084 chemotherapy administration by infusion technique only, per visit Q0085 chemotherapy administration by both infusion technique and other techique(s) (eg subcutaneous, intramuscular, push), per visit

Table C5. Definitions of breast cancer surgical codes[67]

Conserving surgery
ICD9 Procedure Codes *Code Code Description* 85.2 Excision Or Destruction Of Breast Tissue 85.20 Excision Or Destruction Of Breast Tissue, Not Otherwise Specified 85.21 Local Excision Of Lesion Of Breast 85.22 Resection Of Quadrant Of Breast **CPT Procedure Codes** *Code Code Description* 19160 Mastectomy, partial (eg lumpectomy, tylectomy, quadrantectomy, segmentectomy) 19162 Mastectomy, partial (eg lumpectomy, tylectomy, quadrantectomy, segmentectomy; with axillary lymphadenectomy) 19120 Excision of cyst, fibroadenoma, or other benign or malignant tumor, aberrant breast tissue, duct lesion, nipple or areolar lesion, open, male or female, 1 or more lesions
Non-conserving surgery
CPT Procedure Codes *Code Code Description* 85.36 Other Bilateral Subcutaneous Mammectomy 85.35 Bilateral Subcutaneous Mammectomy With Synchronous Implant 85.34 Other Unilateral Subcutaneous Mammectomy 85.33 Unilateral Subcutaneous Mammectomy With Synchronous Implant 85.23 Subtotal Mastectomy 85.4 Mastectomy 85.41 Unilateral Simple Mastectomy 85.42 Bilateral Simple Mastectomy 85.43 Unilateral Extended Simple Mastectomy 85.44 Bilateral Extended Simple Mastectomy 85.45 Unilateral Radical Mastectomy 85.46 Bilateral Radical Mastectomy 85.47 Unilateral Extended Radical Mastectomy 85.48 Bilateral Extended Radical Mastectomy **CPT Procedure Codes** *Code Code Description* 19120 Excision of cyst, fibroadenoma, or other benign or malignant tumor, aberrant breast tissue, duct lesion, nipple or areolar lesion, open, male or female, 1 or more lesions 19125 Excision of breast lesion identified by preoperative placement of radiological marker, open; single lesion 19126 Excision of breast lesion identified by preoperative placement of radiological marker, open; each additional lesion separately identified by preoperative radiological marker

19180 Mastectomy, simple, complete
19182 Mastectomy, subcutaneous
19200 Mastectomy, radical, including pectoral muscles, axillary lymph nodes
19220 Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes
(urban type operation)
19240 Mastectomy, modified radical, including axillary lymph nodes, with or without pectoralis minor
muscle, but excluding pectoralis major muscle
19260 Excision of chest wall tumor including ribs
19271 Excision of chest wall tumor involving ribs, with plastic reconstruction; without mediastinal
lymphadenectomy
19272 Excision of chest wall tumor involving ribs, with plastic reconstruction; with mediastinal
19301 Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy)
19302 Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy); with axillary
lymphadenectomy
19303 Mastectomy, simple, complete
19304 Mastectomy, subcutaneous
19305 Mastectomy, radical, including pectoral muscles, axillary lymph nodes
19306 Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes
(urban type operation)
19307 Mastectomy, modified radical, including axillary lymph

Table C6. Definitions of breast cancer radiation codes[67]

ICD-9 procedure codes
Code Code Description 92.21 Superficial Radiation 92.22 Orthovoltage Radiation 92.23 Radioisotopic Teleradiotherapy 92.24 Teleradiotherapy Using Photons 92.25 Teleradiotherapy Using Electrons 92.26 Teleradiotherapy Of Other Particulate Radiation 92.27 Implantation Or Insertion Of Radioactive Elements 92.28 Injection Or Instillation Of Radioisotopes
ICD-9 diagnostic codes
Code Code Description V580 Encounter for radiotherapy (Radiotherapy encounter) V661 Convalescence following radiotherapy (Radiotherapy convalescence) V671 Follow-up examination, following radiotherapy (Radiotherapy follow-up)
CPT procedure codes
Code Code Description 77261 Therapeutic radiology treatment planning; simple 77262 Therapeutic radiology treatment planning; intermediate 77263 Therapeutic radiology treatment planning; complex 77280 Therapeutic radiology simulation-aided field setting; simple 77285 Therapeutic radiology simulation-aided field setting; intermediate 77290 Therapeutic radiology simulation-aided field setting; complex 77295 Therapeutic radiology simulation-aided field setting; 3-dimensional 77299 Unlisted procedure, therapeutic radiology clinical treatment planning 77300 Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician 77301 Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications 77305 Teletherapy, isodose plan (whether hand or computer calculated); simple (1 or 2 parallel opposed unmodified ports directed to a single area of interest) 77310 Teletherapy, isodose plan (whether hand or computer calculated); intermediate (3 or more treatment ports directed to a single area of interest) 77315

Teletherapy, isodose plan (whether hand or computer calculated); complex (mantle or inverted
Y, tangential ports, the use of wedges, compensators, complex blocking, rotational beam, or
special beam considerations)
77321 Special teletherapy port plan, particles, hemibody, total body
77331 Special dosimetry (eg, TLD, microdosimetry) (specify), only when prescribed by the treating
physician
77332 Treatment devices, design and construction; simple (simple block, simple bolus)
77333 Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks,
special bolus)
77334 Treatment devices, design and construction; complex (irregular blocks, special shields,
compensators, wedges, molds or casts)
77336
Continuing medical physics consultation, including assessment of treatment parameters, quality
assurance of dose delivery, and review of patient treatment documentation in support of the
radiation oncologist, reported per week of therapy
77338 Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design
and construction per IMRT plan
77370 Special medical radiation physics consultation
77371 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course
77750 Infusion or instillation of radioelement solution (includes 3-month follow-up care)
77761 Intracavitary radiation source application; simple
77762 Intracavitary radiation source application; intermediate
77763 Intracavitary radiation source application; complex
77776 Interstitial radiation source application; simple
Code Code Description
77777 Interstitial radiation source application; intermediate
77778 Interstitial radiation source application; complex
77789 Surface application of radiation source
77790 Supervision, handling, loading of radiation source
G0173 Stereo radiosurgery, complete
G0174
Intensity modulated radiation therapy (imrt) delivery to one or more treatment areas, multiple
couch angles/fields/arc, custom collimated pencil-beams with treatment setup and verification
images, complete course of therapy requiring more than one session, per session
G0178

Intensity modulated radiation therapy (imrt) plan, including dose volume histograms for target
and critical structure partial tolerances, inverse plan optimization performed for highly conformal distributions, plan positional accuracy and dose verification, per course of treatment
G0242 Multisource photon stero plan
G0243 Multisource photon stero treat
G0251 Linear acc based stero radio
G0338 Linear accelerator stero plan
G0339 Robot lin-radsurg com, first
G0340 Robot lin-radsurg fractx 2–5
61770 Incise skull for treatment
61793 Focus radiation beam
S8049 Intraoperative radiation therapy (single administration)
G8378 Clinician documentation that patient was not an eligible candidate for radiation therapy measure
G8379 Documentation of radiation therapy recommended within 12 months of first office visit
C9726 Placement and removal (if performed) of applicator into breast for radiation therapy
C9728 Placement of interstitial device(s) for radiation therapy/surgery guidance (eg, fiducial markers,
dosimeter), other than prostate (any approach), single or multiple
D5985 Radiation cone locator
D5983 Radiation carrier
D5984 Radiation shield
A4650 Implantable radiation dosimeter, each

Revenue Center codes

Radiation Oncology Indicator Switch
0280 Oncology, general classification
0289 Oncology, other
Therapeutic Radiology Indicator Switch
0330 General classification
0333 Radiation Therapy

SEER radiation delivery variables and codes

Variable Name: rad1-rad10 (Radiation)
Codes Radiation, Yes or No
1-6 Yes
0, 7-9 No
Variable Name: radsurg1-radsurg10 (Radiation sequence with surgery)
Codes Radiation, Yes or No
2-6, 9 Yes
0 No

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