Is the Continuity of Care for Comorbidities among Breast Cancer Patients Related to Treatment Adherence and Survival Outcomes?

by

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Abstract

Background: Breast cancer patients with comorbidities need to see multiple healthcare providers. These patients often need to take multiple medications, have frequent health care service utilization and high costs, and have a high mortality rate.

Objective: To examine the association of continuity of care (COC) and the health outcomes (the risk of mortality, medication adherence, and health care service utilization and costs) for breast cancer patients with comorbidities.

Methods: A series of retrospective cohort studies of newly diagnosed female breast cancer patients with comorbidities (hypertension, hyperlipidemia, and diabetes) were identified from the SEER-Medicare data (2006-2014). The primary outcomes were (1) all-cause mortality (assessed annually for up to 5 years); (2) medication adherence (hormone therapy (HT), antihypertensives, hyperlipidemia medications, diabetes medications) which will equal to 1 with proportion of days covered (PDC)≥80% and 0 with PDC<80% (assessed annually for up to 4 years); (3) health care service utilization and costs (assessed annually for up to 4 years). The COC Index, a validated measure accounting for both the frequency and dispersion of healthcare provider visits, was measured yearly with a scale of 0 (dispersed) to 1 (concentrated) and in two ways: Specialty (unique specialist groups: Primary Care Physicians (PCP), Oncologists, and Other specialists (Other)) and Individual (all individual providers regardless of specialty) COC Indices. Cox proportional hazards models estimated the hazard ratio (HR) of all-cause mortality that was associated with the COC Index. Mixed-effects logistic regression models analyzed the associations of the COC Index and medication adherence to hormone therapy, antihypertensives, hyperlipidemia medications, and diabetes medications. Two-stage models including a mixed-effects logistic regression model and a mixed-effects linear regression model (with a log linked and a gamma distribution) were used to determine the association of the COC Index and health care service (emergency department (ED), inpatient) utilization and costs after HT initiation.

Results: Patients who received high continuity of care based on the Specialty COC Index (4th vs. 1st quartile, HR 1.34, 95%CI 1.29-1.40) had higher risks of mortality compared with those who received low continuity of care. However, patients who received high continuity of care based on the Individual COC Index (4th vs. 1st quartile, HR 0.53, 95%CI 0.51-0.54) had lower risks of mortality compared to those who received low continuity of care. Patients with higher levels of Specialty COC Index had less medication adherence to antihypertensives (4th vs. 1st quartile, Odd Ratio (OR) 0.86, 95%CI 0.76-0.96) and hyperlipidemia medications (4th vs. 1st quartile, OR 0.81, 95%CI 0.70-0.94). Patients with higher levels of Individual COC Index had higher medication adherence to hyperlipidemia (4th vs. 1st quartile, OR 1.17, 95%CI 1.01-1.36) and diabetes medications (4th vs. 1st quartile, OR 1.51, 95%CI 1.12-2.00). Patients with intermediate levels of Specialty COC Index were more likely to have ED or inpatient visits (significant in 2nd vs. 1st and 3rd vs. 1st quartile) for all conditions. However, patients with high levels of Individual COC Index were less likely to have ED or inpatient visits (significant in 2nd vs. 1st, 3rd vs. 1st, and 4th vs. 1st quartile) for all conditions. Accordingly, high levels of Specialty COC Index were associated with increased inpatient costs (all-cause-, hypertension-, hyperlipidemia-, and diabetes-related p<0.05). High levels of Individual COC Index were

associated with decreased ED cost (all-cause related $p<0.05$) and inpatient costs (all-cause-, hypertension-, and diabetes-related $p<0.05$).

Conclusion: This study examined the association between COC Indices and health outcomes for breast cancer patients. We found mixed associations of COC Indices and health outcomes. Higher continuity of care based on visits to individual providers could protect patients from all-cause mortality, medication non-adherence, and health service utilization and costs. In contrast, higher continuity of care based on visits to specialty groups could be associated with a high risk of mortality, non-adherence to medication, and more health service utilization and higher costs in patients. Thus, COC should be considered carefully based on different definitions when building the models of continuity and coordination of care and may help to improve the health outcome for cancer survivorship.

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List of Abbreviations

ACEI Angiotensin-Converting Enzyme Inhibitors

ACO Accountable Care Organizations

AI Aromatase Inhibitors

ARB Angiotensin Receptor Blocker

ASCO American Society of Clinical Oncology

ASCVD atherosclerotic cardiovascular disease

CCB Calcium-Channel Blockers

CCI Charlson Comorbidity Index

CDK Chronic kidney disease

COC Continuity of Care

CMS Centers for Medicare & Medicaid Services

DBP Diastolic Blood Pressure

HbA1C Hemoglobin A1c

HR Hazard Ratio

HT Hormone Therapy

GLP-1-RA Glucagon-like peptide-1 receptor agonists

LDL-C low-density lipoprotein cholesterol

OR Odds Ratio

PCP Primary Care Provider

PDC Proportion of Days Covered

SBP Systolic Blood Pressure

SCP Survivorship Care Plan

CHAPTER 1 INTRODUCTION

1.1 Overview

Health care management for cancer patients with comorbidities can be complicated, often involving multiple treatments and coordination of multiple health care providers.[1] Previous research found that the average number of physician visits for cancer patients is 32 during their entire cancer treatment period.[2] However, these specialists might not communicate adequately during the follow-up care of cancer patients with comorbidities.[1] Plus, poor coordination and continuity of care among providers have been observed between primary care providers (PCP) and oncologists along the spectrum of acute cancer treatment and survivorship care.[3,4] Thus, health care providers are challenged with the need for communication and coordination of patients' treatments across different providers.[5-7] Surgeons and oncologists are less likely to recommend curative treatment for cancer patients with comorbidities regardless of clinical guidelines.[4,6-9] Therefore, cancer patients with comorbidities are often under-treated for their cancer and comorbidities following cancer diagnoses,[4,8,9] which can negatively influence cancer patients' health care management and outcomes.[10-15 16-22] Strategies are needed to address these problematic issues during cancer survivorship care.

The definition of COC is the "degree to which a series of discrete healthcare events are experienced as coherent and connected and consistent with the patient 's medical needs and personal context".[23] And according to American Academy of Family Physicians, the definition of COC is the cooperation of one patient and his/her physician or care team during the process of health care management aiming at delivering high quality and cost-effective medical care to the patient.[24,25] There are three types of COC including information continuity, relational continuity, and management continuity.[23-25] Continuity of care can be measured by the Bice-Boxerman COC Index, which counts for patients' discrete and concentrated provider visits.[26]. COC is

significantly associated with patients' satisfaction, quality of care, and their health outcomes including medication adherence, health care service utilization, health care costs, and mortality.[16-22]

Although the five-year survival rate for female breast cancer patients reached 89% in 2012, breast cancer is still the second deadliest cancer for women in the U.S.[27,28] A large proportion of cancer patients has comorbidities. For example, approximately 68.7% of cancer patients have at least one chronic comorbidity and 32.6% of cancer patients have more than two chronic comorbidities.[29] The mortality rate is higher for cancer patients with chronic comorbidities compared to those without comorbidities.[30,31] In fact, 60% of breast cancer survivors die from causes unrelated to cancer.[32] Comorbidities can complicate the acute and maintenance treatment of cancer and negatively influence long-term clinical management.[33] Several studies found that patients with comorbidities were under-treated for their comorbidities following cancer diagnoses, which can increase mortality.[10-14] These under-treatments were often caused by poor continuity and coordination of care.[4,8,9] Patients with higher COC were more likely to have a lower risk of mortality.[16,34-36] For example, elderly adults patients who had continuity of care with a primary care physician (PCP) had lower mortality risk (HR=0.84, 95%CI 0.77-0.91) compared with those who didn't.[34] A study focused on elderly diabetes patients found that patients with higher COC based on PCPs could lead to a 10% lower mortality risk compared to those with lower COC.[16] However, these studies only focused on non-cancer patients. Still, little is known about the association between COC and survival rate within breast cancer patients who have comorbidities.

Medication adherence can be affected by health care provider visits and consequently be associated with the clinical outcomes of chronic disease management.[15,37] Patients with multiple health care provider visits were more likely to have poor medication adherence.[15] After controlling for the number of comorbidities, as the number of health care provider specialties

increases so does medication nonadherence.[38] This is believed to be even more problematic when patients with multiple chronic conditions are faced with a cancer diagnosis.[9,39] Cancer patients with comorbidities often have to take complex medication regimens and receive care from multiple provider specialties for both cancer and other chronic conditions.[3,33] A minimum of 5 years of hormone therapy has been recommended by clinical guidelines for patients with positive hormone receptors (ER+ and/or PR+).[40] Previous research showed that 5 years of adjuvant tamoxifen treatment in breast cancer patients significantly reduced the annual mortality rate by 31%.[41] In fact, the risks of discontinuing hormone therapy were 23-41% higher in breast cancer patients with comorbidities than in those without comorbidities.[42-45] By the end of their second-year hormone therapy, patients' adherence rates for antihypertensives, statins, and oral diabetes medications were 62%, 61%, and 24% respectively.[37] Multiple factors contribute to non-adherence, one of them is the fragmented health care system in the United States,[46] which is closely connected with continuity of care.[18,47-49] Limited studies have been done for the association of COC and cardiometabolic medications adherence. Mixed effects of COC on medication adherence were reported. For example, patients with higher COC had higher adherence to diabetes medication (OR=3.37, 95%CI 3.15-3.60)[18] and statins (OR=6.1, 95%CI: 5.9-6.3) [47]. However, no significant association of COC and medication adherence were found in the usage of antihypertensives.[48,49] To the best of our knowledge, no research has been done for the association of COC and medication adherence within breast cancer patients who had comorbidities. Therefore, understanding the impact of continuity of care in medication adherence is important to improving the survivorship care of breast cancer patients with comorbidities.

Health care service utilization and costs of breast cancer patients with comorbidities are affected by their health care provider visits. Patients can be under-treated for their comorbidities following a cancer diagnosis, which may lead to poor coordination of care between oncologists

and PCPs.[4,8,9,50] This suboptimal comorbidity management following a cancer diagnosis may increase health care costs and service utilization.[10-14] The percentages of Medicare beneficiaries who had inpatient admission were 13%, 30%, and 63% for patients with two to three, four to five, and more than six comorbidities.[51] The additional medical cost for cancer survivors during the 6-month follow-up were $4,584, $13,369, and $25,739 for patients with one, two, and more than three comorbidities.[52] For patients with cardiometabolic conditions, even after controlling for the number of comorbidities, it is known that the risk of emergency department (ED) visits and hospitalizations increases with the number of health care provider specialties.[53] Multiple health care provider visits related to poor continuity of care,[23] which could influence patients' health outcomes.[16,18,19,54] Higher COC would significantly reduce health care cost and service utilization in patients with chronic conditions.[18,19,54,55] For example, a study of senior patients with multiple comorbidities found high COC was associated with less inpatient and ED visits (OR<1, 95%CI<1).[54] Another study of patients with diabetes found, for every 0.1-unit increase in COC, patients had significantly lower chances of inpatient and ED visit (OR<1, 95%CI<1), and lower health care cost ($p<0.05$).[19] However, these studies were focused on non-cancer patients. To our knowledge, there is no systematic quantitative examination regarding health care service utilization and costs focused on breast cancer patients with comorbidities along with their continuity of care. Thus, research is needed for improving health care service utilization and reducing the cost of breast cancer patients with comorbidities.

Limited research has been done for the continuity of care during breast cancer survivorship, especially for breast cancer patients with comorbidities. Therefore, it is important to fill this knowledge gap by estimating the association of COC with health outcomes to provide empirical evidence and inform policymakers to improve health outcomes in breast cancer patients with comorbidities.

Objectives:

The objective of this study is to measure the continuity of care received by breast cancer patients with comorbidities and the corresponding health outcomes.

1.2 Specific Aims

Using data from the 2006-2014 Surveillance, Epidemiology and End Results (SEER) registry linked with Medicare claims, this study addressed the following specific aims:

<u>Specific Aim 1</u>: To examine patterns of continuity of care and the risk of mortality for breast cancer patients with comorbidities for up to five years of cancer survival.

The continuity of care (COC) is the cooperation of one patient and his/her physician or care team during the process of health care management.[24,25] COC Index measures continuity of care based on an individual's total number of visits for one episode of disease or a certain time period to a single provider or a group of specific providers.[25] The health care provider specialties was categorized into primary care providers (PCP), oncologist (Oncologist), and other specialists (Other). COC Index was estimated yearly in two different ways including the Specialty COC Index (unique specialist groups: PCP, Oncologists, and Other) and Individual COC Index (all individual providers regardless of specialty). Comorbidities refer to cardiometabolic diseases including hypertension, hyperlipidemia, and diabetes. Descriptive analyses and Chi-Square test were used for patients' characteristics. ANCOVA analysis was used for COC Indices comparison among groups in different cancer stages or numbers of comorbidities. Kaplan-Meier Curves were plotted for patients' crude mortality rate among groups in different cancer stages or numbers of comorbidities. Cox proportional hazards models estimated the hazard ratio (HR) of all-cause mortality that was associated with the COC Index.

<u>Specific Aim 2</u>: To determine hormone therapy adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care among breast cancer patients with cardiometabolic diseases.

The proportion of days covered (PDC) was calculated per patient yearly after hormone therapy (HT) initiation for each therapeutic group independently. The therapeutic groups

included in this study are hormone therapy (HT), HT plus antihypertensives, HT plus hyperlipidemia medications, and HT plus diabetes medications groups. The primary outcome was medication adherence which equaled to 1 when PDC≥80% and 0 when PDC<80%. Descriptive analyses were used for patients' characteristics for different therapeutic groups (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Logistic regression models analyzed the associations of COC Indices (Specialty and Individual) and medication adherence to hormone therapy, antihypertensives, hyperlipidemia medications, and diabetes medications.

Specific Aim 3: **To examine the associations between continuity of care with patient's outcomes including health care service utilization and costs.**

Health care services utilization and costs were estimated per patient per observation year, including patients' inpatient and ED visits. Descriptive analyses were used for patients' characteristics. Mean COC Indices (Specialty and Individual) were estimated for patients stratified into overall, inpatient, and ED visits. Two-stage models including a logistic regression model and a linear regression model (with a log linked and a gamma distribution) were used to determine the association between COC indices and health care service (emergency department (ED), inpatient) utilization and costs after HT initiation.

1.3 Impact of the proposed research

Continuity of care plays an important role in the health care management of breast cancer patients, especially for those with comorbidities. Breast cancer patients with comorbidities might have to visit multiple health care providers in different specialties for treating breast cancer and other chronic conditions. Theoretically, the health care management of breast cancer patients with comorbidities should involve multiple treatments for both breast cancer and comorbidities, which will require continuity of care and further coordination of multiple health care providers. Nevertheless, the care of patients with multiple comorbidities is rarely coordinated and poorly continued.[1,56] Poor coordination and continuity of care among providers has been observed between primary care providers (PCP) and oncologists along the spectrum of acute cancer treatment and survivorship care.[3,4] In fact, health care providers face several challenges for health care management of cancer survivors: lack of knowledge for cancer survivorship care, each specialist has different roles and responsibilities, no common understanding of their roles, and no sufficient communication during health care management.[1] Although the cancer survivorship care plan (SCP) was recommended to cancer survivorship care, only limited effects of SCP on health outcomes were found by researchers.[57] Previous studies found, cancer patients with comorbidities are often under-treated for their comorbidities following cancer diagnoses.[4,8,9] Concerns have been raised for the continuity of care during cancer survivorship care.

Previous studies found that health care provider visits and continuity of care affected patients' risk of mortality.[16,34-36] Patients with multiple health care provider visits were more likely to have poor medication adherence.[15] However, the mixed effects of the association between continuity of care and medication adherence were reported.[18,47-49] Also, cancer patients who visited multiple health care providers were more likely to have hospitalization and ED visits.[53]

Actually, higher COC would significantly reduce health care cost and service utilization in patients with chronic conditions.[18,19,54,55]

Although previous studies provided some evidence on the association of continuity of care and patients' risk of mortality,[16,34-36] this association within breast cancer patients who had cardiometabolic comorbidities is not well understood. Estimating the patterns of COC Indices (Specialty and Individual COC) distributions based on different scopes of medical disciplines and evaluating the association of COC Indices and patients' risk of mortality after breast cancer diagnoses are highly needed. This information would provide empirical evidence for policymakers and practitioners to improve healthcare delivery and enhance survivorship care for breast cancer patients.

Few studies have evaluated the effect of continuity of care on medication adherence find mixed effects,[18,47-49] and none of them have been focused on breast cancer patients with cardiometabolic comorbidities. Poor continuity of care could become an obstacle for medication adherence since it could cause barriers for treatment decision making and care management. Thus, it is important to conduct a thorough study that will evaluate the influences of continuity of care on medication adherence of breast cancer patients with comorbidities.

Moreover, limited research has assessed the impact of continuity of care on health care service utilization and costs. No previous study has been focused on breast cancer patients with comorbidities. Systematic quantitative analyses about the association of continuity of care as well as health care service utilization and costs for breast cancer patients with comorbidities are highly needed. Such analysis could help provoke the need to optimize continuity of care during the survivorship care for breast cancer patients with cardiometabolic comorbidities, which will further improve the health care management of these patients.

In this study, we performed analyses of Surveillance, Epidemiology and End Results (SEER) linked Medicare data. This nationally comprehensive real-world data provided reliable estimations of the patterns and impacts of continuity of care for breast cancer patients with comorbidities. Moreover, with the large sample size and up to five years study period, the findings of this study could provide evidence for future studies of the general U.S population.

First, we examined patterns of continuity of care for breast cancer patients with multiple comorbidities for up to five years of breast cancer survival. To describe the patterns of continuity of care, we estimate the yearly average COC Index for two types of COC Indices (Specialty and Individual COC) across breast cancer survival. Additionally, we estimate the association of continuity of care and mortality risk for breast cancer patients with comorbidities. These findings will fill the knowledge gap of understanding 1) patterns of continuity of care and 2) the association of continuity of care and mortality risk for breast cancer patients with comorbidities.

Second, we determined medication adherence to different therapeutic groups (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Our findings can inform breast cancer patients as well as health care providers of the likelihood of medication adherence expected from different levels of continuity of care. In addition, the study suggested factors which were associated with medication adherence of breast cancer patients. More importantly, medication adherence could serve as a proxy for poor management across providers.

Third, we compared the health care service utilization (inpatient visits and ED visits) and their related costs for breast cancer patients with different levels of continuity of care. Our findings provided information about the association of continuity of care with health care service utilization and costs. The information could help improve health care management for breast cancer patients with comorbidities.

In conclusion, this study addressed our long-term goal of improving continuity of care for patients who have complex treatment needs, therefore improving health outcomes and reducing costs. The potential impact of this study is reflected by quantitative data analyses of breast cancer survivors. Furthermore, this study would promote the quality of medication treatments and care management across cancer treatments and survivorship years.

CHAPTER 2 BACKGROUND AND LITERATURE REVIEW

2.1 Breast Cancer

2.1.1 Prevalence

Breast cancer is the most common cancer among women in the United States.[27] Statistics show that approximately 12.4% of women are diagnosed with breast cancer at some point during their lifetime.[58] In 2016, 246,660 women were diagnosed with breast cancer, and 40,450 women died from breast cancer.[27] Due to advances in cancer treatments, the five-year, ten-year, and fifteen-year survival rates for female breast cancer patients have reached 89%, 83%, and 78% respectively in 2012.[27,28]

Breast cancer begins in the parts of breast tissue that fulfill the functions of milk production (lobules) and transportation (ducts).[59] Most breast cancer cases are detected by screening before any symptoms are observed, or detected by the patient or health care provider by noticing a lump.[59] Several different ways are used to classify breast cancer. The most common way to classify breast cancer is based on tumor size, nodal involvement, and metastases. [60] In this case, breast cancer could be classified into stages 0, I, II, III, and IV.[60] Another way to classify breast cancer is by the histopathological characteristics of cancer. With this approach, breast cancer could be classified into in situ carcinomas and invasive carcinomas.[60] The third way to classify breast cancer is based on the type of predictive markers of breast cancer. Currently, three predictive markers have been found in breast cancer, which are the estrogen-receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2).[61-63] Thus, breast cancer could be classified into hormone receptor-positive, HER2 receptor positive, or triple negative breast cancer.[61,62]

Cancer stage and type are associated with the prevalence of breast cancer. According to the Surveillance Epidemiology and End Results (SEERs) program cancer statistic review, the

distributions of breast cancer among stages are 61% for localized cancer, 31% for regional cancer, 6% for distant cancer, and 2% for unstaged cancer.[28] In addition, the prevalence of breast cancer varies among different predictive marker statuses. Previous research found that the proportions of ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR- breast cancer are 63%, 13%, 3%, and 20% respectively.[64]

The effect of risk factors in the prevalence of breast cancer is also notable. These risk factors include female gender, age, family history, early menarche, late menopause, postmenopausal obesity, use of combined estrogen and progestin menopausal hormones, alcohol consumption, and breastfeeding.[59] Among all the above risk factors, the most critical risk factor for breast cancer is gender. Breast cancer has a higher incidence rate in women than men. In fact, 99% of breast cancer happens in women,[65] and 29% of newly diagnosed cancers in women are breast cancer.[58] The second critical risk factor for breast cancer is age. Age is closely related to the morbidity and mortality of breast cancer. Previous research of female breast cancer demonstrated that from 2010-2014, the median age at diagnosis was 62 and the median age at death was 68.[58] Moreover, 75% of breast cancer is diagnosed in women older than 50 years of age.[63] The morbidity rates of breast cancer for different age groups are: 23.4% for age 65-74, 13.8% for age 75-84, and 5.6% for age >84.[58] Accordingly, the mortality rates of breast cancer for different age groups are: 21.9% for age 65-74, 19.9% for age 75-84, and 16.9% for age >84.[58] Family history is the third critical risk factor for breast cancer. Women with a family history of breast cancer may have a significantly high risk of developing breast cancer.[66] For example, 5-8% of female breast cancer cases occur in patients from high-risk families.[63] Several germline mutations could significantly contribute to the family history of breast cancer. One such mutation happens in breast cancer susceptibility genes BRCA1 and BRCA2, which are transmitted through maternal or paternal lines.[63] Other hereditary germline mutations occur in the p-53 tumor suppressor gene and the PTEN gene.[63]

2.1.2 Treatment

Treatment options for breast cancer are surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy.[67] The first line treatment option for breast cancer is surgery. Surgery is used to remove cancer tissue and diagnose the stage of cancer. Three types of surgeries are applied for the treatment of breast cancer: breast-conserving surgery (BCS), total mastectomy, and modified radical mastectomy.[63] The second treatment option is radiation therapy. Radiation therapy is considered a local treatment, which uses high energy particles or beams to shrink the tumor size and kill cancer cells.[67] External radiation therapy and internal radiation therapy are two subtypes of radiation therapy.[67] The combination of radiation therapy and surgery reduces the five-year recurrence rate by about 20% and the fifteen-year mortality rate by about 6% compared to surgery only.[68] The third treatment option for breast cancer is chemotherapy. Chemotherapy inhibits cancer growth by using chemo agents to kill or prevent cancer cells from dividing.[67] The benefits of chemotherapy change with age at breast cancer diagnosis. After six months of anthracycline-based polychemotherapy, the annual mortality rates drop by 38% for age group <50, but only by 20% for age group 50-69.[41] The fourth treatment option for breast cancer is hormone therapy, which is also known as endocrine therapy. Hormone therapy is a type of cancer treatment given to hormone receptor positive (ER+/PR-, ER-/PR+, or ER+/PR+) breast cancer patients. This therapy can reduce estrogen levels or block the effects of estrogen on breast cancer cell growth. Great treatment benefits have been brought to breast cancer patients through hormone therapy. A five-year adjuvant tamoxifen treatment has been shown to reduce the mortality rate in ER+ breast cancer patients by 31%.[69] The fifth treatment option for breast cancer is targeted therapy, which mostly refers to anti-HER2 therapy. Anti-HER2 therapy uses multiple medications to target and blocks the HER2 protein. Early studies show that the combination of anti-HER2 monoclonal antibody and

chemotherapy helped to reduce the three-year recurrence rate by 12% and the mortality rate by 33%.[70]

In general, treatment strategies are adjusted according to breast cancer stages. For early stages of breast cancer (stage 0, stage I and stage II), local treatments (surgery, radiation therapy) and adjuvant systemic therapies (hormone therapy, anti-HER2 therapy, chemotherapy) are recommended.[63,67] For stage III breast cancer, the treatment strategies are dependent on cancer subtypes. Recommendations for stage IIIA and operable stage IIIC are local treatments and adjuvant systemic therapies.[67] For stage IIIB and non-operable stage IIIC breast cancer, local treatments should be used with caution.[67] Recommendations for stage IV breast cancer are hormone therapy, chemotherapy, and biological agents.[63,67] Among different treatment options for breast cancer, hormone therapy plays an important role in each treatment strategy.

2.1.3 Hormone therapy

Nearly 80% of breast cancer cases have positive hormone receptors (ER+ and/or PR+).[64,71] For these breast cancer cases, hormone therapy can greatly improve the outcomes of breast cancer treatment. Based on the American Society of Clinical Oncology clinical practice guidelines, a minimum of five years of hormone therapy has been recommended for this group of patients.[40] Previous research showed that five years of adjuvant tamoxifen treatment in breast cancer patients significantly reduced the annual mortality rate by 31%.[41]

Hormone treatment algorithms change with breast cancer stage.[63,72] For early-stage breast cancer with positive hormone receptors, adjuvant therapy is often applied after surgery.[63,72] After surgery, breast cancer patients with ER+ and/or PR+ are recommended adjuvant hormone therapy with or without adjuvant chemotherapy.[63,72] For later stage breast cancer with ER+ and/or PR+, which refers to metastatic or recurrent cancer, hormone therapy is recommended without surgery.[63,72] Based on comorbid conditions of breast cancer patients,

some are treated with hormone therapy plus chemotherapy,[63,72] while others are treated with hormone therapy plus anti-HER2 therapy.[72] Another strategy is the neoadjuvant treatment for breast cancer with positive hormone receptors.[72] The hormone therapy shrinks the tumor size and then surgery is used to remove the tumor cells.[72,73] The algorithm for early-stage breast cancer hormone therapy is summarized in Figure 2.1.[74] The algorithm for advanced hormone therapy is summarized in Figure 2.2.[63]

Figure 2.1 Hormone therapy for early-stage breast cancer algorithm[74]

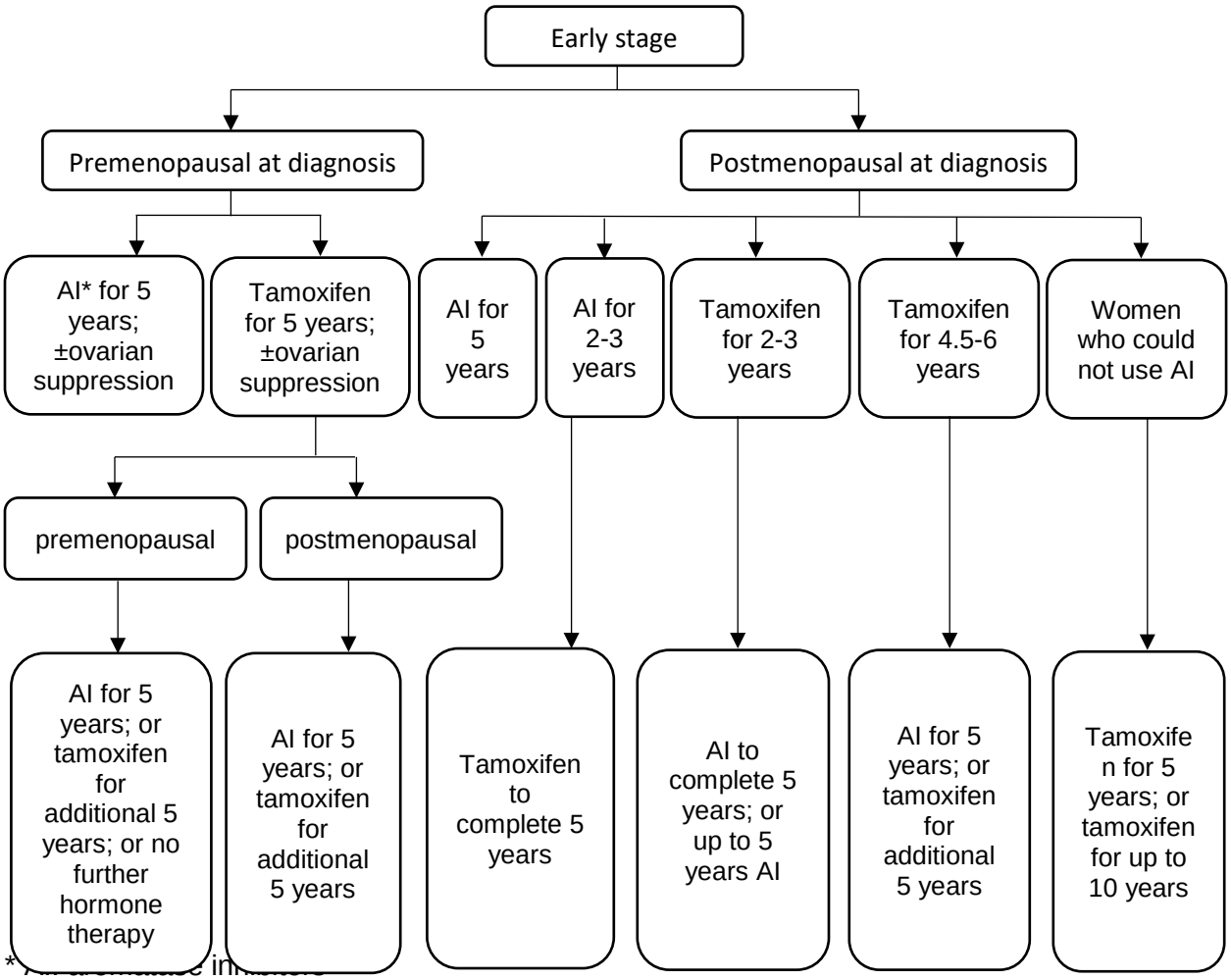

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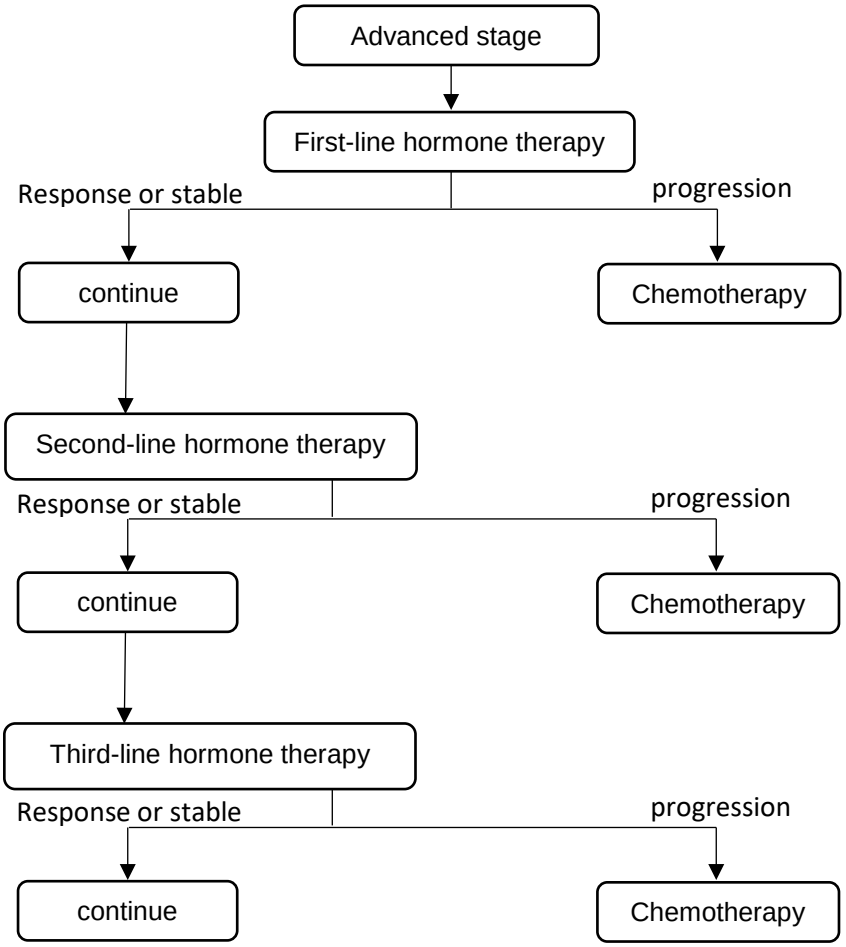
Figure 2.2 Hormone therapy for advanced-stage breast cancer algorithm[63]



Several medications have been used for hormone therapy of ER+ and/or PR+ breast cancer. According to pharmacological functions, these hormone therapies can be divided into four classes: anti-estrogen therapy, aromatase inhibitors (AIs), anti-androgen therapy, and others.[72] Anti-estrogen therapy includes selective estrogen-receptor modulators (SERMs) and selective estrogen-receptor downregulators (SERDs). SERMs and SERDs both reduce the effects of estrogen by binding to estrogen receptors.[75] SERMs block the estrogen effect,[75] while SERDs act as estrogen antagonists.[75] AIs are a newer class of drugs developed after SERMs and SERDs. These drugs block the production of estrogen by inhibiting the function of aromatase enzymes.[72,75] These enzymes are used by the body to produce estrogen in ovaries,

breast tissues, and other tissues.[72,75] Anti-androgen therapy work by suppressing ovarian functions and inhibiting estrogen production.[72,75] Table 2.1 presents different classes of hormone therapy based on the current treatment strategies.[63,72,75,76]

2.1.4 Survival and recurrence

Due to the early detection by screening mammography and the widespread use of adjuvant systemic therapy, the five-year survival rate for breast cancer has been increased from 75% in 1978 to 89% in 2012.[27,28,63]. Likewise, the overall mortality rate of breast cancer decreased 36% from 1989 to 2012.[27]

The survival rates of breast cancer vary among cancer stages and race groups. Previous research showed, in 2016, the five-year breast cancer survival rates for earlier stages (100% for stage 0 and I, 93% for stage II) were much higher than later stages (72% for stage III, 22% for stage IV).[58] From 2005 to 2011, the five-year survival rates for non-Hispanic whites was 89%, for non-Hispanic blacks it was 80%, for Hispanics it was 88%, and for Asians it was 92%.[59]

The mortality rate and recurrence rate for each treatment strategy are different. Patients who only receive surgery have high mortality rates and recurrence rates compared to other treatment strategies. Statistics show that the fifteen-year mortality rates for breast cancer patients treated with BCS and mastectomy were 31-55% and 28-55%, respectively.[68] Additionally, the five-year recurrence rates for BCS and mastectomy were 23-41% and 6-23%, respectively.[68] Radiotherapy could significantly reduce the mortality rates and recurrence rates. Combined with surgery, radiotherapy can reduce the mortality and recurrence rates by 5% and 20% respectively.[68] Chemotherapy is an effective treatment option for breast cancer. Previous research demonstrated that chemotherapy reduced the annual mortality rate of breast cancer by 38% for women age <50 and by 20% for women age 50-60 respectively.[41] Five years of adjuvant hormone therapy reduced the annual mortality rate of breast cancer by 31%.[41] Each

type of hormone therapy has different treatment effects on breast cancer. The recurrence rates for AIs are 5.0-9.6%, while for tamoxifen it is 8.1-12.6%. Similarly, the mortality rate for AIs are 1.7-4.8%, but for tamoxifen, it is 2.4-5.9%.[77]

Although the survival rate has been greatly improved, breast cancer is still the second most deadly among all cancer types.[27] Multiple factors contribute to the high death rate of breast cancer, which include comorbidities, poor medication adherence, and the challenges in the management of cancer treatment and survivorship care across the health system.

Table 2.1 Hormone therapy medications for breast cancer [63,72,75,76]

Class	Drug generic name	Usual dose(/day)	Usual frequency	Breast cancer stage	Duration	Defined daily dose (DDD)
Anti-estrogen therapy						
Selective estrogen-receptor modulators (SERMs)						
	Tamoxifen*	20mg-200mg	1-2/day	all	5 years and up	20mg
	Toremifene	40mg-60mg	1/day	all	5 years and up	60mg
Selective estrogen-receptor downregulators (SERDs)						
	Fulvestrant*	250mg-500mg	1/month	advanced	until disease progression	8.3mg
Aromatase inhibitors (AI)						
First generation AI**						
	Aminoglutethimide	250mg	4/day	-	-	1g
Second generation AI**						
	Formestrane	-	-	-	-	18mg
	Fadrozole	-	-	-	-	
	Rogletimide	-	-	-	-	
Third generation AI						
	Anastrozole	1mg-10mg	1/day	early	5 years and up	1mg
				advanced	until disease progression	
	Letrozole	2.5mg	1/day	early	5 years and up	2.5mg
				advanced	until disease progression	
	Exemestane	25mg	1/day	early	5 years and up	25mg
				advanced	until disease progression	
Anti-androgen therapy						
	Goserelin	3.6 mg	1/28days	advanced	up to 24 months	0.129mg 60 mcg implant, 1mg, 0.134mg
	Leuprolide	3.75 mg	1/28days	all		
		11.25 mg	1/3months	all		

Other

Megestrol	40 mg	4/day	advanced	at least 2 months

* first line hormone therapy medication

** rarely use now

2.2 Breast cancer comorbidities

2.2.1 Prevalence

For cancer patients, comorbidities refer to any coexisting non-cancer diseases in addition to cancer.[78] Comorbidities can complicate the acute treatment of cancer and negatively influence long-term clinical management.[33] Consequently, comorbidities can worsen cancer treatment response, increase health care service utilization and costs, and reduce the quality of life for cancer patients.[79-81] The mortality rate is higher for cancer patients with chronic comorbidities compared to those without comorbidities.[30,31,82] A randomized clinical trial showed that 60% of breast cancer survivors die from causes unrelated to cancer.[32] Therefore, studies that are focused on breast cancer survivors with comorbidities are highly needed.

The prevalence of cancer comorbidities changes with cancer types, age groups, and race groups. In general, 68.7% of cancer patients have chronic comorbidities; 32.8% of cancer patients have more than two chronic comorbidities.[29] Compared with other cancer types, breast cancer has a lower proportion of patients with comorbidities. From an annual report based on 1975 to 2010 SEER-Medicare data, 32.2% of breast cancer patients have comorbidities, and 10% of them have two or more comorbidities.[82] Age also can affect the prevalence of comorbidities in breast cancer patients. For example, older breast cancer patients have higher risks of getting comorbidities than younger breast cancer patients.[63,83,84] Similarly, race difference could influence the prevalence of comorbidities in breast cancer patients. Cancer patients from minority race groups are more likely to have comorbidities.[85]

Among different comorbidities, the cardiometabolic disease was found to commonly coexistent with breast cancer.[86] Previous research showed that 28% of breast cancer patients had cardiometabolic diseases.[87] The cardiometabolic disease refers to a clustering of disorders which may cause cardiovascular disease.[88] According to the definition of the American Heart Association (AHA), the symptoms of cardiometabolic syndrome include: (1) hypertension, which

refers to systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; (2) elevated fasting glucose, where fasting blood glucose level ≥100 mg/dL; (3) lipid disorders, that is, triglycerides ≥150 mg/ dL or high-density lipoprotein (HDL) cholesterol <50 mg/dL; (4) abdominal obesity, which include patients with waist circumference ≥ 88 cm.[89] The prevalence of breast cancer patients with hypertension, high glucose, lipid disorder, and abdominal obesity are 36%, 30%, 38%, and 34% respectively.[87]

Breast cancer and cardiometabolic disease share common risk factors. The first shared risk factor is older age. Age is considered a critical factor for breast cancer, cardiovascular disease, and type 2 diabetes.[63] Statistics show that 80% of cancer cases occur in patients older than 55 years, and the median age of cancer diagnosis is 66.[78] Sixty percent of patients with hypertension are older than 65.[90] Twenty percent of adult diabetes is diagnosed in patients older than 65,[91] with type 2 diabetes accounting for most diabetes cases.[91] The incidence of cardiovascular disease is higher in senior women. For example, women in the age group 50-64 are associated with a 50% higher risk of cardiovascular disease than women in the age group 25-49.[92] The second shared risk factor for breast cancer and cardiometabolic disease is gender. For women, the common causes of mortality are cancer, cardiovascular disease, and type 2 diabetes.[63] Breast cancer and cardiometabolic diseases are more likely to coexist in older women, leading to high mortality rates. Previous studies found that 99% of breast cancer occurred in women,[65] 70% of women older than 65 have hypertension,[90] and the incidence of cardiovascular disease and diabetes were higher in older women than older men.[91,92]

2.2.2 Treatment

Breast cancer patients with cardiometabolic diseases may need treatments for both cancer and comorbidities. The treatment strategies for breast cancer have been discussed in section 2.1.2 and 2.1.3. This section will only focus on the treatment strategies for cardiometabolic diseases (hypertension, lipid disorders, and type 2 diabetes).

Lifestyle modification and pharmacotherapy are the current treatment strategies for cardiometabolic diseases.[63,93] Lifestyle modification is recommended as an effective treatment for cardiometabolic diseases, which includes dietary adjustment, physical activity, weight control, and tobacco cessation.[63,93] Previous research demonstrated that for patients with hypertension, lifestyle modification could decrease blood pressure by 11/7 mmHg.[94] For patients with lipid disorder, lifestyle modification can help reduce 10% of serum cholesterol levels and 20% of coronary heart disease risks.[63] For patients with type 2 diabetes, lifestyle modification could help weight loss by 8.6%, improve diabetes control, and reduce cardiovascular disease risk factors.[95] Although lifestyle modification showed significant benefits in treating cardiometabolic diseases, it needs to be accompanied with pharmacotherapy for effective lifelong treatment.[63]

Pharmacotherapy is the cornerstone of effective therapy for cardiometabolic diseases. Previous research showed, for the treatment of hypertension in older adult patients, five years of antihypertensive drug usage could significantly reduce cardiovascular morbidity and mortality rates.[96] For the treatment of lipid disorder, statin drugs can reduce low-density lipoprotein (LDL) level by 24-50%, reduce triglyceride level by 10-29%, and increase HDL level by 6-12%.[97] Moreover, statins can decrease the incidence rate of coronary artery disease by 25-60%, and lower the mortality rate for all causes by 30%.[97] For the treatment of type 2 diabetes, ten years of sulfonylurea-insulin or metformin treatment could reduce glucose levels by 5-17 mg/dl and reduce glycated hemoglobin (HbA1c) levels by 0.5-0.6%.[98] Consequently, these medications can decrease the risk of myocardial infarction by 15-33% and all-cause mortality rate by 13-27%.[98] The recommended medications for treating hypertension, lipid disorders and type 2 diabetes are listed in Table 2.2, Table 2.3, and Table 2.4.[63,76]

2.2.3 Pharmacotherapy Guidelines for Cardiometabolic Diseases

Pharmacotherapy is recommended to most patients with hypertension, lipid disorder, or type 2 diabetes. Different clinical guidelines are recommended for each cardiometabolic disease. For hypertension, the Eighth Joint National Committee (JNC-8) clinical guidelines were widely used around the country before 2017.[99] By the end of 2017, the Ninth Joint National Committee (JNC-9) clinical guidelines were published.[100] Since this study will use a retrospective cohort before 2017, we will focus on JNC-8. For lipid disorder, the guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) are recommended by the American College of Cardiology (ACC) / American Heart Association (AHA).[101] For type 2 diabetes, the pharmacologic therapy guidelines are developed by the American Diabetes Association (ADA).[102] The details of the clinical guidelines on medication treatments for selected cardiometabolic diseases are summarized in Figures 2.3, Figure 2.4, and Figure 2.5.[99,101,102]

2.2.4 Burden

Comorbidities place a heavy burden on breast cancer treatment. The mortality rate is higher for cancer patients with chronic comorbidities compared to those without comorbidities.[30,31] Previous research showed that 60% of breast cancer survivors die from causes unrelated to cancer.[32] Comorbidities can complicate the acute treatment of cancer and negatively influence long-term treatment management.[33] Likewise, the diagnosis of breast cancer can significantly affect the treatment management of patients who already have chronic conditions.[1]

Comorbidities may also expand the burden on health care expenditures for breast cancer. In the United States, the total direct medical spending for breast cancer reached $87.8 billion in 2014, where 58% was for hospital outpatient visits and doctor visits, and 28% was for

hospitalization.[103] Similarly, the total direct cost of cardiovascular disease in the U.S. was $189.7 billion in 2012.[104] Given the high prevalence of cardiometabolic diseases in breast cancer patients, the medication costs for these patients could be a significant economic burden to the United States. Previous research found that cancer patients with more comorbidities could have higher health care expenditures and more health care service utilization.[105]

The above burdens could be addressed by improving health care management for both breast cancer and comorbidities.

Table 2.2 Hypertension medications [63]

Class	Drug name	Usual dose range (mg/day)	Usual frequency (/day)	Defined daily dose (DDD)
Diuretics*				
Thiazide Diuretics	Chlortalidone	6.25-50	1	25mg
	HCTZ	6.25-51	2	25mg
	Indapamide	1.25-5	1	2.5mg
	Metolazone	2.50-5	1	5mg
Loop Diuretics	Bumetanide	0.50-2	2	1mg
	Ethacrynic acid	25-100	2	50mg
	Furosemide	20-160	2	40mg
	Torsemide	2.50-20	1-2	15mg
Potassium Sparing	Amiloride	5-20	1	10mg
	Eplerenone	25-100	1-2	50mg
	Spironolactone	6.25-400	1-2	75mg
	Triamterene	25-100	1	0.1mg
β-Blockers*				
	Acebutolol	200-800	2	0.4g
	Atenolol	25-100	1	75mg
	Betaxolol	5-20	1	20mg
	Bisoprolol	2.5-20	1	10mg
	Carteolol	2.5-10	1	10mg
	Metoprolol	50-450	2	0.15g
	Metoprolol XL	50-200	1-2	
	Nadolol	20-320	1	0.16g
	Penbutolol	10-80	1	40mg
	Pindolol	10-60	2	15mg
	Propranolol	40-180	2	0.16g
	Propranolol LA	60-180	1-2	
	Timolol	20-60	2	20mg
α-/β-Blockers/Vasodilating β-Blockers				
	Carvedilol	6.25-50	2	37.5mg
	Carvedilol CR	20-80	1	
	Labetalol	200-2400	2	0.6g
	Nebivolol	5-40	1	5mg
Calcium-Channel Blockers (CCB)*				
Dihydropyridines	Amlodipine	2.5-10	1	5mg
	Felodipine	2.5-20	1-2	5mg
	Isradipine CR	2.5-20	2	5mg not for CR
	Nicardipine SR	30-120	2	90mg not for CR
	Nifedipine XL	30-120	1	30mg not for CR
	Nisoldipine	10-40	1-2	20mg
Nondihydropyridines	Diltiazem CD	120-540	1	0.24g not for CD

	Verapamil HS	120-480	1	0.24g not for HS
Angiotensin-Converting Enzyme Inhibitors (ACEI)*				
	Benazepril	10-80	1-2	7.5mg
	Captopril	25-150	2	50mg
	Enalapril	2.5-40	2	10mg
	Fosinopril	10-80	1-2	15mg
	Lisinopril	5-80	1-2	10mg
	Moexipril	7.5-30	1	15mg
	Perindopril	4-16	1	4mg
	Quinapril	5-80	1-2	15mg
	Ramipril	2.5-20	1	2.5mg
	Trandolapril	1-8	1	2mg
Angiotensin Receptor Blocker (ARB)*				
	Candesartan	8-32	1	8mg
	Eprosartan	400-800	1-2	0.6g
	Irbesartan	150-300	1	0.15g
	Losartan	25-100	2	50mg
	Olmesartan	5-40	1	20mg
	Telmisartan	20-80	1	40mg
	Valsartan	80-320	1-2	80mg
Direct Renin Inhibitor				
	Aliskiren	150-300	1	0.15g
α-Blockers				
	Doxazosin	1-16	1	4mg
	Prazosin	1-40	2-3	5mg
	Terazosin	1-20	1	5mg
	Phenoxybenzamine for pheochromocytoma	20-120	2	30mg only phenoxybenzamine
Central Sympatholytics				
	Clonidine	0.2-1.2	2-3	0.45mg
	Clonidine	0.1-0.6	weekly	
	Guanabenz	2-32	2	25mg
	Guanfacine	1-3	1(qhs)	3mg
	Methyldopa	250-1000	2	1g levorotatory, 2g racemic
	Reserpine	0.05-0.25	1	0.5mg
Direct Vasodlators				
	Hydralazine	10-200	2	0.1g
	Minoxidil	2.5-100	1	-
Fixed-dose Combinations				
	Aliskiren/HCTZ	150/12.5-300/25	1	-
	Amiloride/HCTZ	5/50	1	-
	Amlodipine/benazepril	2.5-5/10-20	1	-
	Amlodipine/olmesartan	5/20-10/40	1	-
	Amlodipine/telmisartan	5/20-10/80	1	-

Amlodipine/valsartan	5/160-10/320	1	-
Atenolol/chlorthalidone	50-100/25	1	-
Benazepril/HCTZ	5-20/6.25-25	1	-
Bisoprolol/HCTZ	2.5-10/6.25	1	-
Candesartan/HCTZ	16-32/12.5-25	1	-
Enalapril/HCTZ	5-10/25	1-2	-
Eprosartan/HCTZ	600/12.5-25	1	-
Fosinopril/HCTZ	10-20/12.5	1	-
Irbesartan/HCTZ	150-300/12.5-25	1	-
Losartan/HCTZ	50-100/12.5-25	1	-
Olmesartan/HCTZ	20-40/12.5	1	-
Spironolactone/HCTZ	25/25	1/2-1	-
Telmisartan/HCTZ	40-80/12.5-25	1	-
Trandolapril/verapamil	2-4/180-240	1	-
Triamterene/HCTZ	37.5/25	1/2-1	-
Valsartan/HCTZ	80-160/12.5-25	1	-

*selected for aim 2 and aim 3 analyses[106]

Table 2.3 Hyperlipidemia medications [63,76]

Class	Drug name	Usual dose range (/day)	Usual frequency (/day)	Defined daily dose (DDD)
Statins (HMG-CoA reductase inhibitors) *				
	Simvastatin	20-80 mg	1	30mg
	Atorvastatin	10-80 mg	1	20mg
	Pravastatin	20-80 mg	1	30mg
	Fluvastatin	20-80 mg	1	60mg
	Lovastatin	20-80 mg	1	45mg
	Rosuvastatin	10-40 mg	1	10mg
	pitavastatin	1-4 mg	1	2mg
Nicotinic acid				
	Niacin	1-2 g	3	-
	Niacin ER	1-2 g	1	-
Fibrates				
	Gemfibrozil	1.2 g	1	1.2g
	Fenofibrate	34-200 mg	1	0.2g
Cholesterol absorption inhibitor				
	Ezetimibe	10 mg	1	10mg
Bile acid sequestrants				
	Colesevelam	2.5-3.75 g	1	3.75g
	Colestyramine	4-16 g	1	14g
	Colestipol	2-16 g	1	20g
Fish oil				
	Omega-3-acid ethyl esters	-	-	-

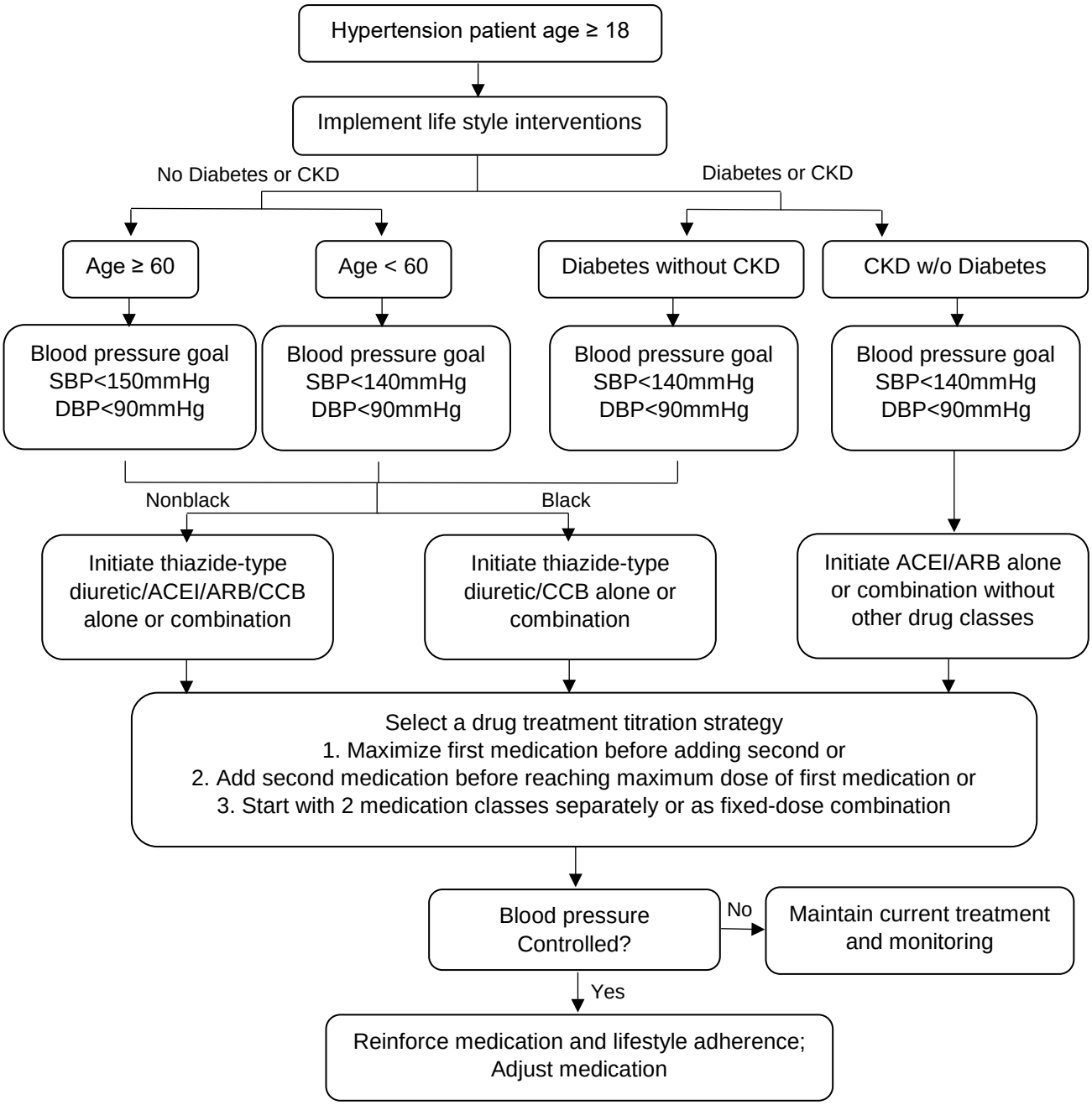
* selected for aim 2 and aim 3 analyses[101,106]

Table 2.4 Diabetes medications [63,76,102]

Class	Drug name	Usual dose range (/day)	Usual frequency (/day)	Defined daily dose (DDD)
Sulfonylureas*				
	First generation			
	Chlorpropamide	100-250 mg, maximum daily dose 750 mg	1	0.375g
	Tolazamide	100-250 mg, maximum daily dose 1 g	1	0.5g
	Tolbutamide	0.25-3 g, maximum daily dose 3 g	1	1.5g
	Second generation			
	Glyburide	1.25-20 mg, maximum daily dose 20 mg	1	-
	Glipizide	2.5-5 mg, maximum (single dose 15 mg, daily dose 40 mg)	1	10mg
	Glimepiride	1-2 mg, maximum daily dose 8 mg	1	2mg
Glinides*				
	Repaglinide	0.5-2 mg, maximum (single dose 4 mg, daily dose 16 mg)	2-4	4mg
	Nateglinide	60-120 mg	3	0.36g
Biguanides*				
	Metformin	500-850 mg, maximum daily dose 2,550 mg	1-3	2g
	Metformin ER	500-2000 mg, maximum daily dose 2,500 mg	1	
Thiazolidinediones*				
	Rosiglitazone	4-8 mg, maximum daily dose 8 mg	1-2	6mg
	Pioglitazone	15-45 mg	1	30mg
α-Glucosidase*				
	Acarbose	25-100 mg	3	0.3g
	Miglitol	25-100 mg	4	0.3g
GLP-1 receptor agonists*				
	Exenatide	5-10 mcg	2	0.286 mg depot inj, 0.15 mcg
	Exenatide ER	2 mg / week		
	Liraglutide	0.6-1.8 mg	1	1.2mg
Amylin mimetics*				
	Pramlintide	60-120 mcg	3	-
DPP-4 inhibitors*				
	Sitagliptin	100 mg	1	0.1g
	Saxagliptin	2.5-5 mg	1	5mg
Bile acid sequestrants				
	Colesevelam	1.875 g x 2/day, 3.75 g /day		3.75g
D2 agonists*				
	Bromocriptine	1.6-4.8 mg	1	40mg

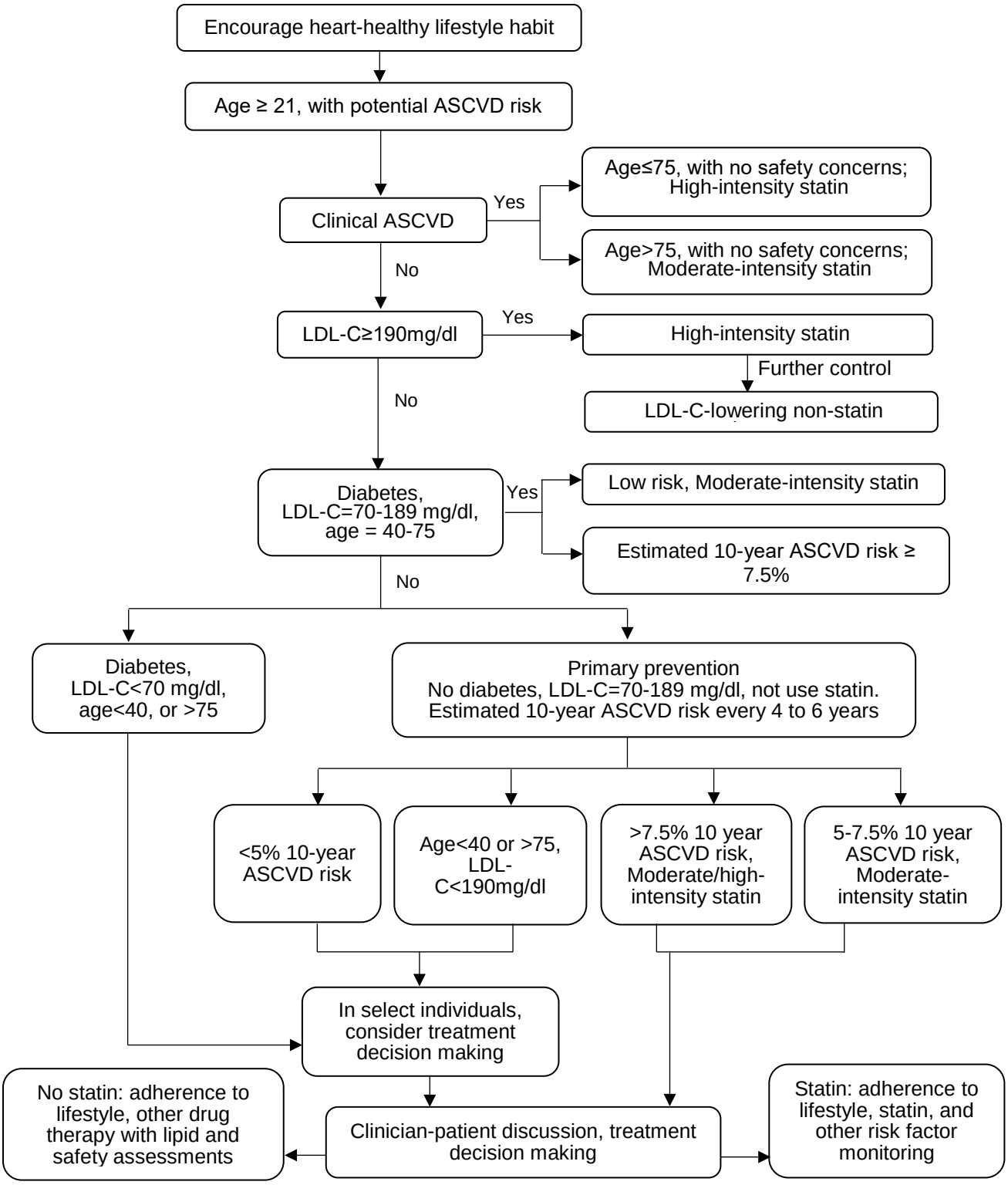
*selected for aim 2 and aim 3 analyses[106]

Figure 2.3 Pharmacotherapy for hypertension algorithm [99]



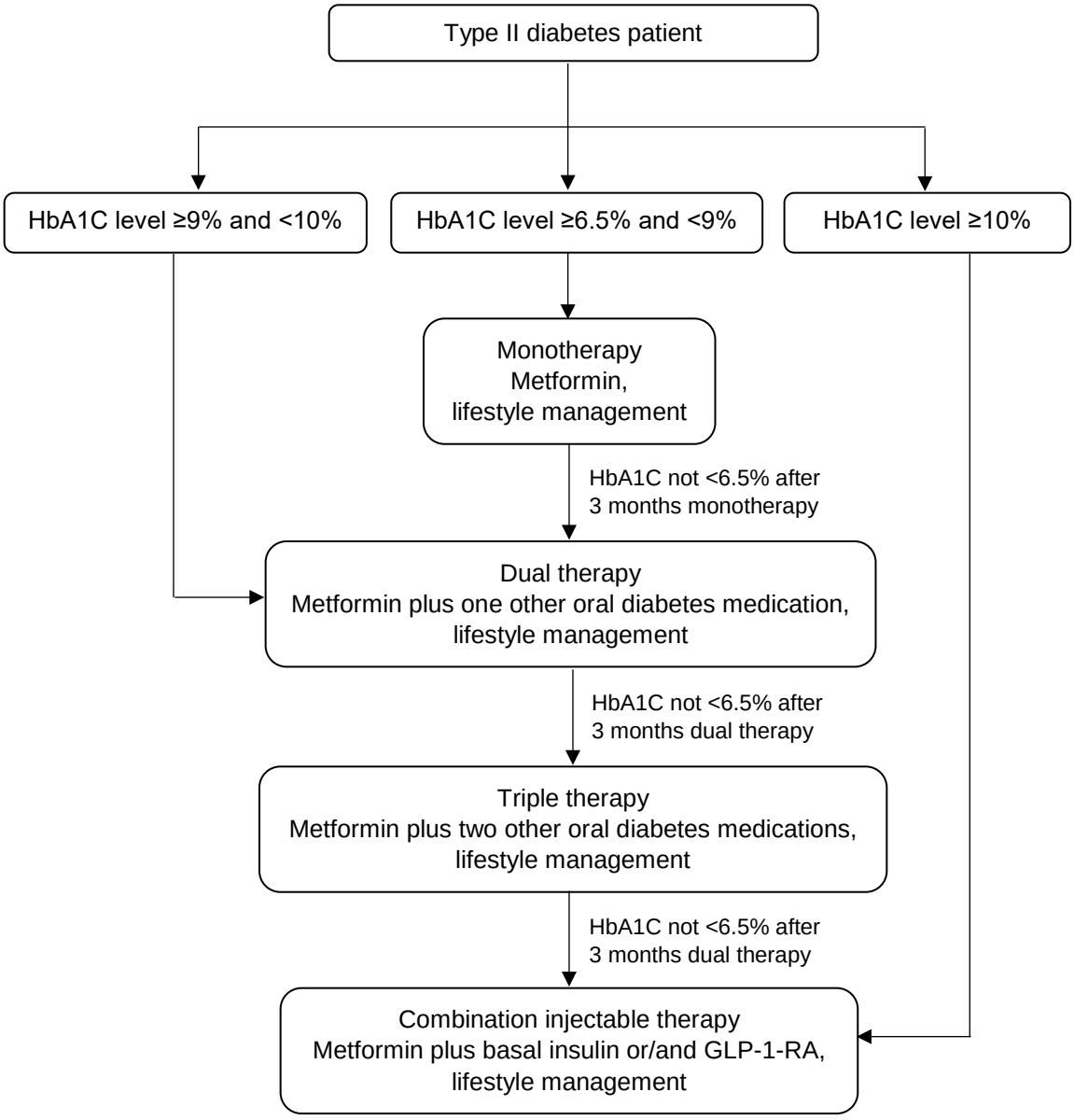
Note: CDK: Chronic kidney disease; ACEI: Angiotensin-Converting Enzyme Inhibitors; CCB: Calcium-Channel Blockers; ARB: Angiotensin Receptor Blocker; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Figure 2.4 Pharmacotherapy for hyperlipidemia algorithm [101]



Note: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Figure 2.5 General pharmacotherapy for type 2 diabetes algorithm [102]



Note: HbA1C, Hemoglobin A1c; GLP-1-RA, Glucagon-like peptide-1 receptor agonists.

2.3 Continuity of Care for Breast Cancer Survivors

Continuity of care (COC) plays an important role in patients' health care management, especially for breast cancer patients with comorbidities. Since continuity of care could influence health care providers' treatment decision making and medication prescribing, it can impact patients' medication adherence, health care service utilization, and health care costs. These factors reflect the treatment of breast cancer and comorbidities. In order to improve health care service utilization and control the health care costs for breast cancer patients with comorbidities, the impact of continuity of care on medication adherence, health care service utilization, and health care costs should be studied thoroughly.

Since COC indicates the relationship between health care provider and patients,[107] it is closely related to patients' health care management.

2.3.1 The health care management for patients with multiple comorbidities

Patients with multiple comorbidities tend to use health care services more frequently and visit health care providers with more diverse specialties. Previous research found that for Medicare beneficiaries, the average number of physicians visited by patients with multiple comorbidities was 3 for less than 2 conditions, 5 for 3 or 4 conditions, 7 for 5 or 6 conditions, and 11 for more than 7 conditions.[108] The numbers of involved health care providers might increase as patients get older. For patients older than 65, the average number of physicians visited by Medicare beneficiaries ranged from 1 to 20 for 0 to 5 chronic conditions respectively.[56] Similarly, cancer patients with multiple comorbidities are often faced with the need to see multiple health care providers in different specialties.[1] One study about the distribution of physician office visits by cancer survivors showed that 32% of the visits were made to primary care physicians (PCPs), 18% of the visits were made to oncologists, 13% of the visits were made to surgeons, and 36% of the visits were made to other specialists.[1] Another study found

that 46% of follow-up care of cancer survivors involved both primary care physicians (PCPs) and oncologists, 37% of follow-up care of cancer survivors involved PCPs only, and 8% of follow-up care of cancer survivors involved oncologists only.[50] Accordingly, the number of physicians visited by cancer survivors could be large. Previous research showed that the minimum number of physicians' office visits by cancer patients was 13, the median was 32, and the maximum was 97.[2] Limited research focused on healthcare provider visit sequences. One study found that oncologists often take over all care for newly diagnosed cancer patients during acute treatment, and then PCP and other specialists may then transition back to the care team after acute cancer treatment is completed.[4] Therefore, the health care management of patients with multiple comorbidities could be challenging.

Although the health care management of patients with multiple comorbidities should involve multiple treatments and coordination of multiple health care providers, the reality is complicated. Patients with multiple comorbidities found that their health care providers rarely coordinated with each other despite patients' complicated health conditions.[1,56] In fact, for cancer survivors with multiple comorbidities, poor coordination among providers was observed between primary care providers (PCP) and oncologists along the spectrum of acute cancer treatment and survivorship care.[3,4] Theoretically, the number of health care provider specialists might increase after cancer diagnoses. However, oncologists and patients are more likely to focus on cancer treatment right after cancer diagnoses.[4] Thus, oncologists could take over all care for newly diagnosed cancer patients during acute treatment, and then PCP and other specialists may then transition back to the care team after acute cancer treatment is over.[4]

Within the fragmented health care delivery system in the U.S., health care providers face several challenges of health care management for cancer survivors. First, health care providers do not have sufficient knowledge of cancer survivorship care.[1] Physicians and other health care providers do not have sufficient training and standard processes for handling and coordination

for cancer survivorship care.[1] Second, specialists and PCPs have different roles and responsibilities for the follow-up care of cancer patients with comorbidities.[1] Specialists most often focus on providing patients with guidance and treatments in their areas of expertise. PCPs provide general as well as cancer-related health care services to patients, often covering all aspects of patient care. They address all physical and mental health needs of their patients by providing general health care services or referring patients to specialists. Third, specialists and PCPs might not have a common understanding of their roles and responsibilities about the follow-up care of cancer patients with comorbidities.[1] This role uncertainty creates a great barrier for the coordination of health care management among different providers.[109,110] Fourth, specialists and PCPs might not communicate adequately during the follow-up care of cancer patients with comorbidities.[1] A previous study suggested that PCPs played an important role in follow-up care of cancer survivors since cancer survivors preferred to visit PCPs rather than other specialists for 90% of conditions.[111] However, specialists might not inform PCPs about their own treatment decisions for cancer survivors.[110] A survey of U.S. physicians found that only 7% of physicians routinely communicate with other physicians.[112]

Since 2010, policymakers launched multiple renovations to improve coordination and communication of care in the U.S. health care system, but limited improvements were found for the health outcomes of cancer patients. For example, from 2010, Medicare fee-for-service beneficiaries could get coordinated care by groups of health care providers through Accountable Care Organizations (ACO).[113] However, research found the Medicare contracted ACO program was not associated with reduced negative health outcomes in cancer patients.[113,114] Although a new cancer Survivorship Care Plan (SCP) was developed by the American Society of Clinical Oncology (ASCO) in 2014 to promote communication and coordination among health providers for cancer survivorship,[115] limited effects of SCP on cancer patients' health outcomes were reported.[57] Since 2016, the Centers for Medicare & Medicaid Services (CMS) issued new

nursing home regulations, which enhanced physician service and promoted communication between pharmacists and physicians.[116] Nevertheless, the element of continuity of care was not mentioned in the regulations.

2.3.2 Impact of fragmented health care management

Visiting multiple health care providers influences treatment decision making and medication prescription for cancer survivors with multiple comorbidities.[5-7] In the U.S., the structure of shared care among multiple health care providers is more parallel than coordinated. Thus, for each provider, the treatment decisions for cancer patients with comorbidities are harder to make than for cancer patients without comorbidities. In general, physicians are more cautious when making treatment decisions for cancer patients with comorbidities than for those without comorbidities.[5-7] For example, surgeons and oncologists are less likely to recommend chemotherapy for colon cancer patients with comorbidities than for those without comorbidities regardless of clinical guidelines.[6,7] One study suggested that better coordination between multiple health care providers' treatment decision-making would be beneficial for patients with multiple comorbidities.[109] Likewise, health care providers might find it challenging to prescribe medication to cancer patients with comorbidities.[5-7] Since these patients have multiple chronic conditions along with cancer, health care providers have more concerns about treatments' toxicity, adverse events, and reducing treatment effects.[5-7] Improved communication and health care coordination could help reduce health care providers' concerns about treatment safety and quality.[109] Continuity of care has been suggested as an important factor for improving patients' quality of care.[21,22]

Moreover, visiting multiple health care providers could impact patients' medication adherence, health care service utilization, and health care costs.[15,105,117] Previous studies reported mixed effects of multiple health care providers on medication adherence. For hypertension treatment, patients with more than four medication prescribers have significantly

lower adherence to antihypertensive medications (odds ratio: 0.69, with 95% CI: 0.59-0.80) than those who have only one medication prescriber.[38] For patients with cardiometabolic diseases, the overall medication adherence decreased when the number of prescribers increased.[118] However, within statin users, the number of prescribers increased medication adherence by 14% in new patients but decreased medication adherence by 24% in prevalent patients.[118] These complex effects on medication adherence related to multiple health care providers are believed to be even more problematic for cancer patients with multiple comorbidities.[9,39] Cancer patients with multiple comorbidities often have to take complex prescription medications and visit multiple health care providers for both cancer and other chronic conditions.[3,33] Likewise, breast cancer patients with comorbidities tend to visit multiple health care providers and will be more likely to get multiple prescription medications. Multiple prescription medications could have either positive or negative effects on breast cancer patients' medication adherence.[119] However, only one study focused on the impact of physician numbers on medication adherence to breast cancer patients. The study reported that breast cancer patients had better medication adherence when the number of physicians increases.[120] Besides physician numbers, health care provider specialties could impact breast cancer patients' medication adherence as well. Different provider specialties might have different influences on medication adherence. For example, oncologists were found to have a positive effect on medication adherence of adjuvant hormone therapy, but PCPs were found to have a negative effect on the same therapy.[119]

Visiting multiple health care providers might affect patients' treatment outcomes, besides disease factors (e.g., more complex illness) or patient factors (e.g., low satisfaction with previous providers). A study of Medicare beneficiaries found that patients with diabetes who visit more than 3 medication prescribers have poorer glycemic control than those who visit just one medication prescriber.[117] Similarly, patients with hyperlipidemia who visit more than 3 medication prescribers have poorer lipid control than those who visit just one medication

prescriber.[117] Accordingly, visiting multiple health care providers can impact patients' health care service utilization. Previous research found, for cardiometabolic disease patients, the odds ratios of ED visits were 1.16, 1.21, and 1.39 for 2 prescribers, 3 prescribers, and more than 4 prescribers respectively.[53] For the same cohort, the odds ratio of inpatient visits were 1.27, 1.30, and 1.34 for 2 prescribers, 3 prescribers, and more than 4 prescribers respectively.[53] A study focused on older adults reported that the more health care specialists a patient visits, the more hospitalization and ED visits he or she might have.[105] Different connections between health care provider utilization and health care service utilization were observed in the care of cancer survivors. Cancer survivors are more likely to have better health care management when they visit multiple health care providers. One study focused on colorectal cancer survivors found that the odds ratios of underuse of necessary care are 0.37 for patients who visit both PCPs and oncologists, 0.73 for patients who visit PCPs only, and 9.31 for patients who never visit a physician.[50] Another study of cancer survivors with various cancer types (breast, prostate, and colorectal cancer) found that multiple health care providers significantly reduced the odds ratio of hospitalization and ED visits for cancer survivors with multiple comorbidities.[121]

Health care costs of cancer patients with multiple chronic conditions can change with their provider visiting patterns. In 2010, patients with multiple chronic conditions accounted for 71% of health care expenditure in the U.S.[122] Two-thirds of Medicare beneficiaries had multiple chronic conditions, that accounted for 93% of total Medicare spending.[123] Previous research about older adults reported that the average medical expenditure for individual patients increases with the number of involved health care provider specialists.[105] For cancer survivors, the impact of health care providers seems different. A previous study found that the average total medical costs and inpatient costs for cancer survivors decrease as the number of health care providers increases, while outpatient costs do not change.[121]

2.3.3 Continuity of Care

The definition of continuity of care is the "degree to which a series of discrete healthcare events are experienced as coherent and connected and consistent with the patient's medical needs and personal context".[23] Three types of COC exist in every health care setting: information continuity, relational continuity, and management continuity.[23] Information continuity refers to the continuity of knowledge about patients' medication conditions, preferences, values, and context.[23] Relational continuity connects past, current, and future care of patients and is important for primary and mental health care.[23] Management continuity refers to the continuity of health care management by multiple providers to the same patient especially for patients with comorbidities.[23] The three types of COC reflect different aspects of the health care system and could be modified with the adjustment of the health care system. COC could indicate the degree of continuity of discrete health care elements during the health care process.[23]

Another definition of continuity of care is suggested by the American Academy of Family Physicians, which is "the process by which the patient and his/her physician-led care team are cooperatively involved in ongoing health care management toward the shared goal of high quality, cost-effective medical care."[24] This definition focuses on the quality of care and the relationship between patients and their health care provider over time. Shortell et al. also suggested a definition of continuity of care, which is "the extent to which services are received as part of a coordinated and uninterrupted succession of events consistent with the medical care needs of patients".[124] This definition focuses on the care delivery over time and the coordination and consistency among health care settings and providers.

The measurements of COC include objective measurements (standard and non-standard) and subjective measurements.[125] The most popular one is the objective standard measurement, which is conducted by calculating standard indices from medical claims data.[125] The standard index that has been used by researchers includes the Likelihood of Continuity

(LICON), Usual Provider Continuity (UPC), Bice and Boxerman Continuity of Care (COC), and Sequential Nature of Provider Continuity (SECON).[26] The LICON is sensitive to the number of available providers.[26] The SECON is sensitive to changes in the sequential dimension of provider visits.[26] The UPC reflect patients' visit to usual providers and is sensitive to the distribution of visits to individual providers.[26] The Bice and Boxerman COC reflect patients' visit to all providers and are sensitive to the distribution of visits to individual providers.[26] The majority of previous studies used the Bice and Boxerman COC. In this study, we also used the Bice and Boxerman COC as our primary predictor.

Patients with concentrated health care provider visits would have high continuity of care (COC) whereas patients with dispersed health care provider visits would have low COC.[125] Therefore, fragmented health care management could cause poor continuity of care. Previous research suggests that COC is significantly associated with patients' satisfaction, quality of care, and their health outcomes including mortality, medication adherence, health care service utilization, and health care costs.[16-22]

Patients with higher COC were more likely to have a lower risk of mortality.[16,34-36] For example, elderly adults patients who had continuity of care with a primary care physician (PCP) had lower mortality risk (HR=0.84, 95%CI 0.77-0.91) compared with those who didn't.[34] A study focused on elderly diabetes patients found that patients with higher COC with PCPs could lead to a 10% lower mortality risk compared to those with lower COC.[16] After hospital discharge, patients who had long term continuity of care could have a lower mortality risk (HR=0.36, 95%CI 0.20-0.66).[35] A longitudinal study of patients with mental disorder found higher COC was significantly related with lower mortality risk (HR=0.83, 95%CI 0.83-0.83).[126]

COC could affect patients' medication adherence but were only studied by limited research within non-cancer patients.[18,47-49] Within these studies, mixed effects of COC on medication adherence were reported. For example, patients with higher COC were more likely

to adhere to diabetes medication (OR=3.37, 95%CI 3.15-3.60)[18] and statins (OR=6.1, 95%CI: 5.9-6.3) [47]. However, the studies of antihypertensive usage did not find any significant association of COC and medication adherence.[48,49]

COC is closely related to patients' health outcomes.[16,18,19,54] Actually, higher COC would significantly reduce health care cost and service utilization in patients with chronic conditions.[18,19,54,55] For example, a study of senior patients with multiple comorbidities found high COC was associated with less inpatient (Hazard Ratio (HR) 0.97 95%CI 0.96-0.99) and ED visits (HR 0.97 95%CI 0.96-0.98).[54] Another study of patients with diabetes found, for every 0.1-unit increase in COC, patients had significantly lower chances of inpatient (Odds Ratio (OR) 0.95 95%CI 0.95-0.96) and ED visit (OR 0.94 95%CI 0.93-0.94), and lower health care cost ($p<0.05$).[19]

According to the definition, the COC Index could be calculated based on individual health care providers as well as provider specialty groups. Therefore, COC Indices could have different values based on the types of providers involved in the calculations. Previous studies showed that COC Indices defined by different medical disciplines would have different associations with patients' health outcomes.[127,128] For example, Chan et al. found the COC Index based on facility-level and the COC Index based on individual provider level had opposite effects on patients' ED or inpatient visits.[128] Studies are needed to provide more empirical evidence of the association of health outcomes and COC Indices based on multiple medical disciplines.

To our knowledge, only a few studies focused on the association of COC and health outcomes and they were conducted within non-cancer patients. Still, little is known about the association between COC and survival rate within breast cancer patients who have comorbidities. No research has been done for the association of COC and medication adherence within breast cancer patients who had comorbidities. Plus, no previous research

studied the association of COC and health care expenditures and service utilization for breast cancer patients with comorbidities. Thus, to improve health outcome for breast cancer patients with comorbidities, the association of COC on mortality risk, medication adherence, health care service utilization, and health care costs should be studied thoroughly.

2.4 Medication Adherence

2.4.1 Medication adherence

Medication adherence refers to whether patients take their medications continuously and follow the instructions of the prescription.[46] It could be defined as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result."[129] Medication adherence is essential for the treatment of chronic diseases and is closely related to their clinical outcomes.[15,37] Cancer patients with comorbidities often take complex medication regimens and receive care from multiple provider specialties for both cancer and other chronic conditions.[3,33] More than half of the cancer patients aged 65 and older have meaningful comorbidities that require medication therapy.[33] Sixty-seven percent of breast cancer patients have to take long-term hormone therapy.[69,130] Previous research found that adherence to medication significantly reduced the risk of hospitalization by 10-25% for patients with cardiometabolic diseases.[131] Simultaneously, five-year adherence to hormone therapy decreased the mortality rate by 31% and recurrence rate by 4-14% for breast cancer survivors.[41]

Several approaches have been used to measure medication adherence: subjective measurements, objective measurements, and biochemical measurements.[132] Subjective measurements refer to self-reporting, diary, interview, and survey; objective measurements refer to pill count, prescription fill date, MEMS caps; biochemical measurements refer to biomarkers or drug levels in body fluid (blood and urine).[46,132,133] Pharmacy claims data is widely used to measure medication adherence and is the most popular resource for objective measurement.[134,135]

2.4.2 Prevalence of nonadherence

Although medication adherence is very important, nonadherence still commonly exists in both cancer treatment and cardiometabolic disease treatment for cancer patients. Adjuvant

hormone therapy is considered a life-saving treatment for hormone positive breast cancer. At least five years of hormone therapy could greatly reduce the mortality rate and the recurrence rate of breast cancer patients. However, despite the high efficacy of hormone therapy, only 40-70% of breast cancer patients could finish their five-year hormone therapy.[42,136,137] In fact, the risks of discontinuing hormone therapy were 23-41% higher in breast cancer patients with comorbidities than those without comorbidities.[42-45] In breast cancer patients treated by hormone therapy, the risk of mortality for nonadherent patients is 49% higher than for adherent patients.[138]

Even though long-term medication treatments for diabetes, hypertension, and lipid disorder could significantly reduce the risks of cardiovascular diseases, nonadherence to those medications is very common.[132] In fact, the adherence to antidiabetic, antihypertensive, and lipid-lowering therapies is especially poor in breast cancer patients with cardiometabolic diseases. After breast cancer diagnoses, patients with cardiometabolic diseases are less likely to keep up with their long-term medication treatments.[37,139] Research has found that by the end of second-year hormone therapy, 38.6% of patients were nonadherent to antihypertensives, 46% of patients were nonadherent to oral diabetes medications, and 56.3% of patients were nonadherent to statins.[37] Such nonadherence to medication treatments of cardiometabolic diseases could have contributed to the fact that many cancer patients in the study died from non-cancer related causes. Poor adherence to cardiometabolic medications was observed in non-cancer patients. A previous study showed that the percentages of nonadherence to hypertension treatment were 50% for combination medicines and 56% for monotherapy.[140] Eleven percent of patients with coronary heart disease discontinued their statin therapy within 12 months after hospital discharge.[141] When hypertension patients fail to control their blood pressure, their risks of getting a stroke or heart disease may increase. Previous research found that for every 20mm Hg increase in systolic blood pressure or 10mm Hg increase in diastolic blood pressure, the risks of stroke and ischemic heart disease would increase twofold.[142] As the

most popular medication class for lipid disorder, long-term statin treatment was reported to reduce the LDL level by 18-55%.[63] Nonadherence to statins was found to increase the risk of cardiovascular hospitalization and all-cause mortality.[143] For patients with hypertension and lipid disorder, nonadherence to both hypertension and hyperlipidemia treatments was reported to raise stroke death in patients with the odds ratio of 7.43.[144] Similarly, medication nonadherence also happens in diabetes treatments. Previous research found that only 69% of patients with type II diabetes adhere to 18-month antidiabetic medication treatment.[145] For patients treated by oral antihyperglycemics, nonadherent patients had 39% higher all-cause mortality rates and 38% higher hospitalization rates than adherent patients.[146]

Besides poor clinical outcomes, nonadherence is associated with high health care expenditure. A study of cardiometabolic diseases found that between a high adherence group (medication adherence level >80%) and low adherence group (medication adherence level <20%), total health care costs reduced by 50% for diabetes, 40% for hypercholesterolemia, and 14% for hypertension.[131]

2.4.3 Barriers to medication adherence

The World Health Organization (WHO) has identified five potential reasons for medication nonadherence, which include patient-related factors, condition-related factors, therapy-related factors, socioeconomic factors, and health system factors.[46] To improve medication adherence, these barriers to medication adherence need to be understood.

(a) Patient-related factors

Patient-related factors of medication nonadherence include patients' demographics, psychological or behavioral factors, physical impairments, and cognitive impairments.[46,119,147-150] Demographics refer to age, gender, race, and education level. Psychological or behavioral factors refer to forgetfulness, coping behavior, personality traits, and lifestyle. Physical impairments refer to the disability of physical functions like vision problems or impaired

dexterity. Cognitive impairments refer to difficulties in remembering, decision making, and learning. Previous studies showed that younger age, female gender, ethnic minority, and lower education level were associated with medication nonadherence in cardiometabolic disease and breast cancer.[151-155] During antihypertension treatment, a high-stress level was found to be associated with low medication adherence.[156] The odds ratio of low medication adherence was 1.33 for patients with physical impairments compared to those without such conditions.[157] Similarly, the odds ratio of low medication adherence was 2.26 for patients with cognitive impairments compared to patients without it.[157]

(b) Condition-related factors

Condition-related factors include comorbidities and mental health.[46,119,147-150] Patients with comorbidities often take multiple medications and are more likely to have poor medication adherence.[158] A previous study showed that the proportions of hypertension patients with high medication adherence level were 20% for those with no comorbidities, 14% for those have one or two comorbidities, and 11% for those have three to five comorbidities.[159] For breast cancer patients undergoing five years of hormone therapy, nonadherence to antihypertensive was 38.6%, nonadherence to oral diabetes medications was 46%, and nonadherence to statins was 56.3%.[37] Mental health conditions like depression and psychiatric conditions also affect medication adherence.[158] A previous study of cardiometabolic diseases found that nondepressed patients adhered to their medications 69% of the studied days while depressed patients only adhered to their medications 45% of the studied days.[160] For breast cancer patients, depression has significant adverse effects on adherence to hormone therapy.[161,162]

(c) Therapy-related factors

Therapy-related factors include adverse drug events (ADEs), complexity of treatments, choice of drugs, and switching treatment plans.[46,119,147-150] Research has found that ADEs caused 5-10% of medication discontinuation among all other causes.[133] In fact, some patients stop taking their prescriptions when they experience ADEs.[163] For the treatment of breast

cancer, ADEs negatively influence adherence to adjuvant hormone therapy.[119,162] A previous study showed that adherence to estrogen was 20% lower in patients with three ADE reports compared with those with two ADE reports.[164] Complexity of treatment includes the duration of treatments, the numbers of prescriptions, and dosing regimen. Patients with multiple comorbidities are very likely to have complex treatments, which can affect medication adherence.[158,160] For example, medication adherence to hormone therapy was 10% higher for breast cancer patients taking hormone therapy only compared with those taking complex treatments (the combinations of hormone therapy, chemotherapy, radiation therapy and surgery).[165,166] Previous research has suggested that complicated dosing is associated with poor medication adherence.[167,168] Nevertheless, the number of prescriptions has mixed effects on medication adherence.[167] Choice of drugs include the properties of drugs (dose, form, color, taste, smell) and route of administration. Prescriptions of different hormone therapy agents are associated with different medication adherence. One study compared the medication adherence among various hormone therapy agents (tamoxifen, aromatase inhibitors, and the combination of the two) and found that tamoxifen had the highest adherence rate(74%), aromatase inhibitors had the second highest adherence rate(75%), and the combination of the two had lowest adherence rate (69%).[165] Different medication adherence levels were found among different antihypertensive drug classes. A previous non-cancer study showed that the percentages of patients who adhere to angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers were: 51%, 48%, 40%, and 38%.[169] Switching treatment plans refers to adjusting patient's current therapy to another. Previous research found that switching medication had a significant adverse effect on adherence to hormone therapy for breast cancer.[137]

(d) Socioeconomic factors

Socioeconomic factors include health literacy, medication costs, and social supports.[46,119,147-150] Health literacy is defined as the extent to which individuals can acquire, process and

understand information related to health.[170] Based on this information, individuals can make appropriate health decisions regarding prevention and treatment of health conditions.[170] Research shows that health literacy can affect medication adherence and health care service utilization.[133,150,167,168] Patients with low health literacy have higher odds (odds ratio 1.37, 95%CI: 1.08-1.74) of low adherence to their cardiometabolic treatments than those with adequate health literacy.[171] Within breast cancer patients, higher health literacy is linked to better adherence to hormone therapy.[119,165] Social support is another important factor that contributes to medication adherence. Patients with social support (family cohesiveness, married, and living with adults) have higher medication adherence than those without social support.[172] For hormone therapy of breast cancer, long-term adherence was found to be positively related to social support.[162,165,166] Medication costs, especially out-of-pocket costs, can significantly impact medication adherence. Previous research focused on Medicare beneficiaries found that patients with higher out-of-pocket medication costs have higher risks of poor adherence than those with lower out-of-pocket medication costs.[173] For breast cancer treatments, high monthly costs were associated with poor hormone therapy adherence, and reduced medication costs can enhance hormone therapy adherence.[119,174]

(e) Health system-related factors

Health system-related factors include provider-patient relationship, provider-patient communication, access to health care, continuity of health care, and provider-system interaction.[46,119,147-150,175] Poor provider-patient relationship and provider-patient communication were found to be related to poor medication adherence.[150,176] The odds ratio of adherence was 2.41 (95%CI 1.93-3.02) between patients who felt highly confident in their physicians and patients who felt moderately confident in their physicians.[168] Provider-patient communication plays a critical role in enhancing medication adherence.[163] For hormone therapy, patients who experienced better provider-patient communication had a 94% adherence rate while patients who experienced worse provider-patient communication had a 59% adherence rate.[177] Access

to and continuity of health care are also critical to medication adherence.[150,175] The barriers impacting access to health care include poor access to clinical appointments and medication, poor treatment by clinic staff, and the inability to access a pharmacy.[150,175] Continuity of health care is related to switching to a different formulary and changing treatment strategy.[150,175] Previous research found that 9% of hypertension patients singled out transportation to the pharmacy as their barrier to medications adherence.[178] Similarly, 6.5% of patients singled out switching from brand to generic drug as their barrier to antihypertensive adherence.[178] For breast cancer patients, a higher level of access to health care services and easy access to medication is linked to higher level of hormone therapy adherence.[165,174] The interactions of provider and health care system include the interactions within health care providers, providers' knowledge of health care cost, and providers' knowledge of insurance coverage.[150,175] Poor interaction of providers and health care systems can lead to low medication adherence.[179] A previous study suggested that a multidisciplinary disease management team for patients could improve medication adherence to statins and other related therapies.[180]

Very little research regarding the impact of continuity of care on medication adherence has been conducted. Although most research on medication adherence is focused on patient-related barriers, health care providers also contribute to poor medication adherence in patients.[15] Previous research has demonstrated that, even after controlling for the number of comorbidities, medication nonadherence increases with the number of health care provider specialties.[38] This situation is believed to be even more problematic for cancer patients with multiple comorbidities.[9,39] Cancer patients with multiple comorbidities often have to take complex prescription medications and visit multiple health care providers for both cancer and other chronic conditions.[3,33] Multiple prescription medications can have either positive or negative effects on the medication adherence of breast cancer patients.[119] Health care provider specialties influence medication adherence. Previous research reported that oncologists had

positive effects on breast cancer patients' medication adherence while PCPs had negative effects.[119] Moreover, physician numbers can affect medication adherence of breast cancer patients. A previous study found that breast cancer patients had better medication adherence when the number of physicians increased.[120] These complicated health care provider visits are closely related to continuity of care for patients.

Continuity of care could affect patients' medication adherence but has only been studied by limited research within non-cancer patients.[18,47-49] Within these studies, mixed effects of COC on medication adherence were reported. For example, patients with higher COC had higher adherence to diabetes medication (OR=3.37, 95%CI 3.15-3.60)[18] and statins (OR=6.1, 95%CI: 5.9-6.3) [47]. However, the studies of antihypertensive usage did not find any significant association of COC and medication adherence.[48,49]

Breast cancer patients with multiple comorbidities face the challenge of undertaking both cancer treatment and comorbidity treatments. Multiple health care provider specialties involved in care may result in conflicting recommendations, contradictory treatments, and poor continuity of care, which can challenge patients' adherence to prescribed therapies. Therefore, understanding the impact of continuity of care on medication adherence is essential to improving the care of breast cancer patients with comorbidities.

2.5 Health Care Service Utilization and Costs for Breast Cancer Patients with Comorbidities

2.5.1 Health care service utilization for breast cancer patients with comorbidities

Potential measures of health care service utilization for breast cancer patients with comorbidities include inpatient visits, ED visits, outpatient visits, physician office visits, and mortality. When data is available, home health visits and prescription medications can also be measured. These measurements reflect the treatment of cancer and comorbidities. To our knowledge, no previous research has been focused on health care service utilization for breast cancer patients with comorbidities, so we summarized published literature about cancer patients with comorbidities below.

Inpatient visit refers to a hospital stay in which patients are formally admitted to a hospital with a doctor's order.[181] In 2010, 70.4% of total health care services were used by people with multiple chronic conditions for their inpatient stays.[122] The percentages of Medicare beneficiaries who had at least one inpatient admission were 13% of those with 2 to 3 chronic conditions, 30% of those with 4 to 5 chronic conditions, and 63% of those with more than 6 chronic conditions.[51] The frequency of inpatient visits increases as the number of chronic conditions increases for cancer patients with multiple comorbidities.[182]

Outpatient visits refer to hospital services (emergency department services, observation services, outpatient surgery, lab tests, X-rays, or any other hospital services) that patients have within a hospital but without a doctor's order of being admitted to the hospital.[181] The percentages of Medicare beneficiaries who had at least one ED visit were 25% for those with 2 to 3 chronic conditions, 41% for those with 4 to 5 chronic conditions, and 70% for those with more than 6 chronic conditions.[51] Cancer patients with multiple comorbidities were found less likely to have ED visits.[182]

Patients with multiple chronic conditions need to visit multiple health care providers. A previous study showed that patients with multiple comorbidities made 64% of total clinical office visits.[122] In 2010, the percentages of Medicare beneficiaries who had at least one physician office visit were 93% for those with 2 to 3 chronic conditions, 93% for those with 4 to 5 chronic conditions, and 92% for those with more than 6 chronic conditions.[51] For cancer patients with multiple comorbidities, no clear connection was found between physician office visits and the number of comorbidities.[182]

Medicare beneficiaries with multiple comorbidities are more likely to receive home health visits. Research found that more than 87% of home health services were provided to patients with multiple comorbidities in 2010.[122] The percentages of Medicare beneficiaries who had at least one home health visit were 5% for those with 2 to 3 chronic conditions, 14% for those with 4 to 5 chronic conditions, and 36% for those with more than 6 chronic conditions.[51]

Cancer patients with multiple chronic conditions often take multiple medications for disease control. In 2010, 83.1% of total prescription medications were prescribed to patients with multiple comorbidities.[122] Generally, the number of prescription medications would increase as the number of comorbidities increases. However, a study found that for cancer patients, there was no clear connection between the number of prescriptions and the number of comorbidities.[182]

Mortality is an important outcome for cancer patients. In 2012, the five-year, ten-year, and fifteen-year survival rates for female breast cancer patients were 89%, 83%, and 78% respectively.[27,28] Cancer patients with comorbidities had higher mortality rates than those without comorbidities,[30,31,82] since 60% of breast cancer survivors die from causes unrelated to cancer.[32]

2.5.2 The health care cost for breast cancer patients with comorbidities

Health care costs can impact patients' quality of life and create a heavy burden on society and individual patients. According to an analysis of Medical Expenditure Panel Survey data, in the United States, the total direct medical expenditure for breast cancer reached $87.8 billion in 2014.[103] For Medicare beneficiaries, in 2010, the highest national health care cost among all cancer types is breast cancer care ($16.5 billion).[183] In 2020, the estimated health care cost of breast cancer will increase to $20.50 billion.[183] The average health care costs per patient for stage I, II, III, and IV breast cancer in the year of diagnosis are $60,637, $82,121, $129,387, and $134,682 respectively.[184] Cancer patients with more comorbidities have higher health care expenditures and more health care service utilization.[105] The total direct cost for cardiovascular disease in the U.S. was $189.7 billion in 2012.[104] From 2008 to 2013, the increased annual medical expenditure for cancer survivors with heart disease and stroke were $4,595 (95%CI: $3,262-$5,927) and $3,843 (95%CI: $1,983-$5,704) respectively.[182] For Medicaid beneficiaries, the additional medical cost for cancer survivors during the 6-month follow-up were $4,584 for one comorbidity, $13,369 for two comorbidities, and $25,739 for three or four comorbidities.[52]

Health care costs include expenditures on various health care services. In 2014, the proportions of total health care expenditure included 27% for inpatient, 1% for ED visits, 58% for outpatient or physician office visits, and 2% for home health visits.[185] For cancer survivors who were Medicaid beneficiaries, the additional inpatient costs for 6-month follow-up were $2,727 for one comorbidity, $9,891 for two comorbidities, $18,211 for three or four comorbidities.[52] The additional outpatient costs for 6-month follow-up were $1,006 for one comorbidity, $1,319 for two comorbidities, $2,396 for three or four comorbidities.[52] The additional prescription medication costs for 6-month follow-up were $435 for one comorbidity, $1,033 for two comorbidities, $2,199 for three or four comorbidities.[52] For breast cancer, an estimation from

national survey data indicated that the total direct medical expenditure was $87.8 billion in 2014, where 58% was for hospital outpatient visits or doctor visits, and 28% was for hospitalization.[103]

2.5.3 The impact of continuity of care on health care service utilization and costs

Several factors including patient's health behaviors, medication adherence, health care providers, and continuity of care could impact patients' health care service utilization and costs. Our research will focus on the impact of continuity of care on health outcomes. Patients with concentrated health care provider visits would have high COC whereas patients with dispersed health care provider visits would have low COC.[125] COC is closely related to patients' satisfaction and their health outcomes.[16,18,19,54]

Health care providers can influence health care service utilization and costs for breast cancer survivors with comorbidities. Previous research indicates that cancer patients with multiple comorbidities are often under-treated for their comorbidities following cancer diagnoses, which might be caused by poor coordination between oncologists and PCPs.[4,8,9] The under-treatment of comorbidities following cancer diagnoses can cause high mortality and increased costs.[10-14] For patients with cardiometabolic conditions, the frequency of health care service utilization can increase with the number of health care provider specialties after controlling for the number of comorbidities.[53] However, visiting multiple health care providers might have slightly different influences for cancer patients compared to others. One study found that multiple health care providers significantly enhanced the use of necessary care for cancer patients with multiple comorbidities.[50] Another study found that multiple health care providers significantly reduced the odds ratio of hospitalization and ED visits for cancer survivors with multiple comorbidities.[121] While previous research suggests that the average medical costs for older patients increase with the number of health care specialists patients visit,[105] for cancer survivors with comorbidities, the average total medical and inpatient costs decrease as the number of health care providers increases.[121] The underlying rationale for this relationship is

believed to be related to the prioritization of comorbidities by non-cancer providers. According to the definition of COC, patients with dispersed health care provider visits would have low COC.[125]

COC is closely related to patients' health outcomes.[16,18,19,54] Actually, research found higher COC would significantly reduce health care cost and service utilization in patients with chronic conditions.[18,19,54,55] For example, a study of senior patients with multiple comorbidities found high COC was associated with less inpatient and ED visits (OR<1, 95%CI<1).[54] Another study of patients with diabetes found, for every 0.1-unit increase in COC, patients had significantly lower chances of inpatient and ED visit (OR<1, 95%CI<1), and lower health care cost ($p<0.05$).[19]

To our knowledge, there is no systematic quantitative analysis regarding health care service utilization and costs focused on breast cancer patients with comorbidities along with their continuity of care. It is important to conduct such study for identifying ideal management strategies or the combination of providers.

CHAPTER 3 METHODS

3.1 Data source and Aims

In this study, we used the linkage of two large population-based sources of data, which includes cancer registry data from the Surveillance, Epidemiology and End Results (SEER) Program and Medicare claims data from 2006 to 2014.[186] The information from SEER data includes clinical records, demographics, and cause of death for cancer patients. The Medicare claims data provides records of patients' covered health care services from the start of Medicare enrollment until death. The data were first linked in 1991 and have been updated through 2014. The linkage of these two data sources identifies the records of a population subgroup which can be used for epidemiological and health care-related research. The National Cancer Institute (NCI), the SEER registry, and the Center for Medicare and Medicaid Services (CMS) collaboratively contribute to the linkage of SEER-Medicare data.

The data set is used to address the following aims:

Specific Aim 1: To examine patterns of continuity of care and the risk of mortality for breast cancer patients with comorbidities for up to five years of cancer survival.

A retrospective cohort study of newly diagnosed female breast cancer patients with cardiometabolic comorbidities was conducted. The primary outcome was all-cause mortality. COC index, a validated measure accounting for both the frequency and dispersion of healthcare provider visits, was measured yearly in two ways (Specialty and Individual COC). Kaplan-Meier Curves were plotted for patients' crude mortality rates. Cox proportional hazards models estimated the hazard ratio (HR) of all-cause mortality that was associated with the COC Index.

Specific Aim 2: To determine hormone therapy adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care among breast cancer patients with cardiometabolic diseases.

A retrospective cohort study with a new user design was conducted to identify female breast cancer patients who had hormone therapy (HT) prescriptions within 12-month of cancer diagnoses. Patients were followed for up to four years after HT initiation. Yearly COC indices (Specialty and Individual COC) were measured. The primary outcome was medication adherence per year, defined as the proportion of days covered (PDC)$\geqslant$80% and PDC<80%. Mixed-effects logistic regression models analyzed the associations of COC indices and medication adherence to hormone therapy, antihypertensives, hyperlipidemia medications, and diabetes medications.

<u>Specific Aim 3</u>: To examine the associations between continuity of care with patients' outcomes including health care service utilization and costs.

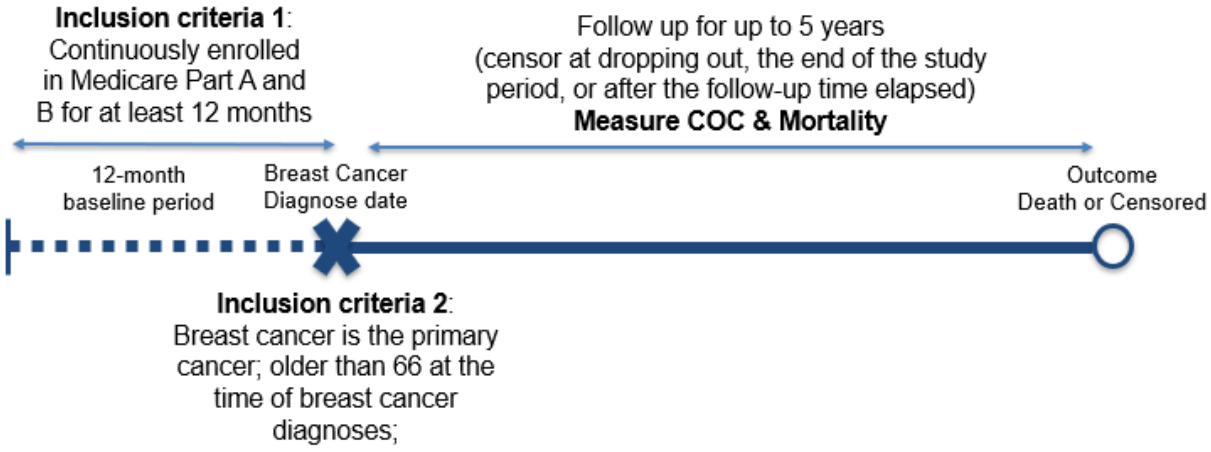
A retrospective cohort study identified newly diagnosed breast cancer patients with hormone therapy (HT). Health care service utilization and costs were examined yearly for up to four years after HT initiation. COC Indices were calculated based on provider specialty groups (Specialty COC) and individual providers (Individual COC). Two-stage models including a mixed-effects logistic regression model and a mixed-effects linear regression model (with a log linked and a gamma distribution) were used to determine the association between COC indices and health care service (emergency department (ED), inpatient) utilization and costs after HT initiation.

3.2 Study Sample and Study Design

For Aim 1

A retrospective new user cohort study was conducted to identify female patients who were 1) newly diagnosed with breast cancer as their primary cancer; 2) 66 years or older at the time of breast cancer diagnoses; 3) continuously enrolled in Medicare Part A and B for at least 12 months before breast cancer diagnoses; and 4) continuously enrolled in Medicare Part A, B, and D until censoring. Patients' breast cancer diagnoses (ICD-O-3 C500-509) were identified in SEER registry data.[187] Patients were excluded from the study if they were enrolled in Managed Care (n=75,840) or if their information about cancer diagnoses was missing (n=4262). A 12-month baseline period before breast cancer diagnosis was used to identify a patient's comorbidities (hypertension, hyperlipidemia, and diabetes) and calculate the Charlson Comorbidity Index (CCI). Finally, a total of 59,472 female breast cancer patients were included in the study (Figure 3.1). A patient's first breast cancer diagnosis date was the index date of the study. After the index date, the patient was followed up for up to 5 years of survival. Reasons for censoring included death, dropping out, reaching the end of the study period, or elapsing of the follow-up time (Figure 3.1).

Figure 3.1 Study Design for Aim 1



For Aim 2 and 3

A longitudinal study was conducted within a group of SEER-Medicare patients who had estrogen receptor-positive breast cancer and cardiometabolic diseases from 2006 to 2014. This study used a new user design to identify patients who initiated hormone therapy (HT) within one year after their first breast cancer diagnoses (Figure 3.2). A 12-month baseline period before breast cancer diagnosis was used to identify patients' cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes) and sociodemographic information. Patients' estrogen receptor status and tumor stage were identified from the SEER registries. The prescription date of first oral HT was defined as the index date. Based on the clinical guideline for breast cancer treatment, HT starts without or after surgery to eliminate disease progression and prevent cancer reoccurrence.[74] To get a longer follow-up period for a larger sample size, this study only included patients who initiated HT within 12 months after breast cancer diagnoses as suggested by previous studies.[138] Selected patients were followed from the index date until the end of the observation period. A patient was marked as censoring if her record showed death, dropping out, reaching the end of the study period, or after the follow-up time elapsed. To allow a homogenized time interval for measuring the predictor and outcome variables, only patients with a full year enrollment (year 1, 2, 3, or 4) of each survival year were included. Within this longitudinal study, the predictor and outcome variables were Continuity of Care (COC) Index and Proportion of Days Covered (PDC), which were measured cross-sectionally within each time interval (yearly after the index date).

We limited the study population to female breast cancer patients who (1) were older than 66; (2) were diagnosed with positive estrogen receptor; (3) continuously enrolled in Medicare Part A, B and D for a 12-month baseline period before their initial breast cancer diagnoses; (4) received at least one prescription of oral HT within one year after breast cancer diagnosis; (5) continuously enrolled in Medicare Part A, B, and D until the end of the observation period

(Figure 3.3). Patients were excluded if they did not have breast cancer as their primary cancer (n=4,262) and were eligible for managed care program (n=75,840). The eligible patients were followed for up to 1, 2, 3, or 4 years after HT initiation. Thus, a total of 8,414 patients with 18,203 person-years of observation were included in the aim 3 study. The aim 2 studied medication adherence. A requirement of more than 2 prescriptions of HT within each observation year was applied. The observation would be considered missing for that observation year if the patient had less than 2 prescriptions of HT during that time interval. Finally, the aim 2 study included a total of 8,081 patients with 16,080 person-years of observation. The diagnosis of breast cancer (ICD-O-3 C500-509) and status of estrogen receptor (ER) were identified in SEER registry data.[187] Cardiometabolic diseases were identified as the patient had at least one inpatient visit or two outpatient visits during the baseline period of cardiometabolic diseases in her Medicare claims (hypertension ICD-9 401-405, hyperlipidemia ICD-9 272, and diabetes ICD-9 250).[106,188-190]

The aim 2 study focused on medication utilization. According to patients' HT and cardiometabolic medication treatments, the therapeutic groups in this study were: HT, antihypertensives, hyperlipidemia medications, and diabetes medications. Since this study used prevalent cohort for cardiometabolic treatment groups, the measurement of all selected medication usage started from the HT initiation date. Oral HT included tamoxifen, aromatase inhibitors (AI) (anastrozole, letrozole, and exemestane).[119,138,191] For antihypertensives, this study selected the most frequently prescribed drugs, which included diuretics, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.[106] Hyperlipidemia medications included statins.[101,106] For diabetes medications, this study focused on all oral medication treatment of type II diabetes (metformin, sulfonylureas, thiazolidinediones, and all others).[106] The selected medications were identified by the National Drug Code (NDC) codes from the Medicare Part D data.

Figure 3.2 Study Design for Aim 2&3

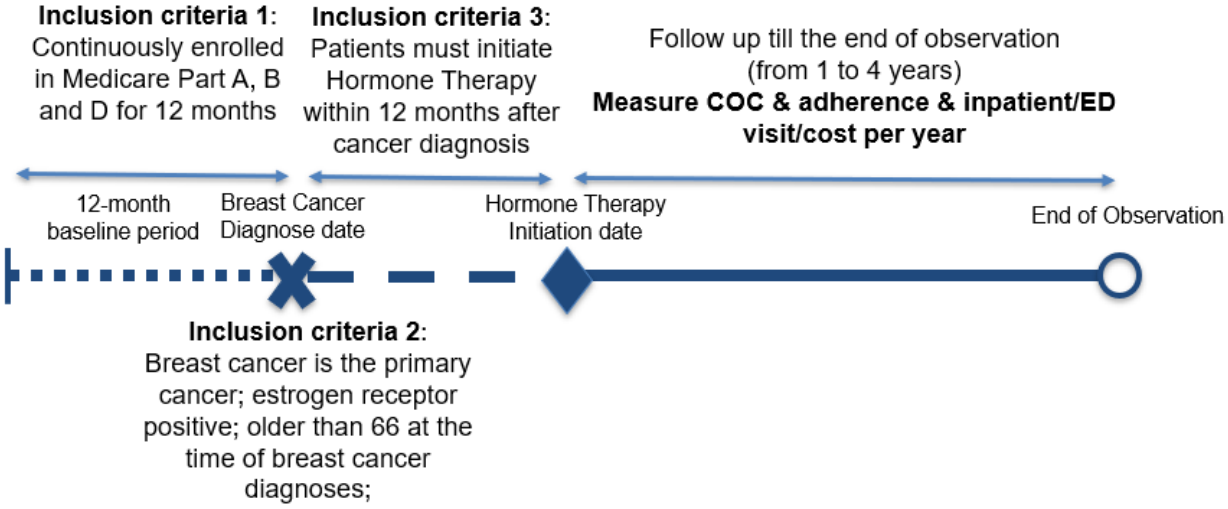
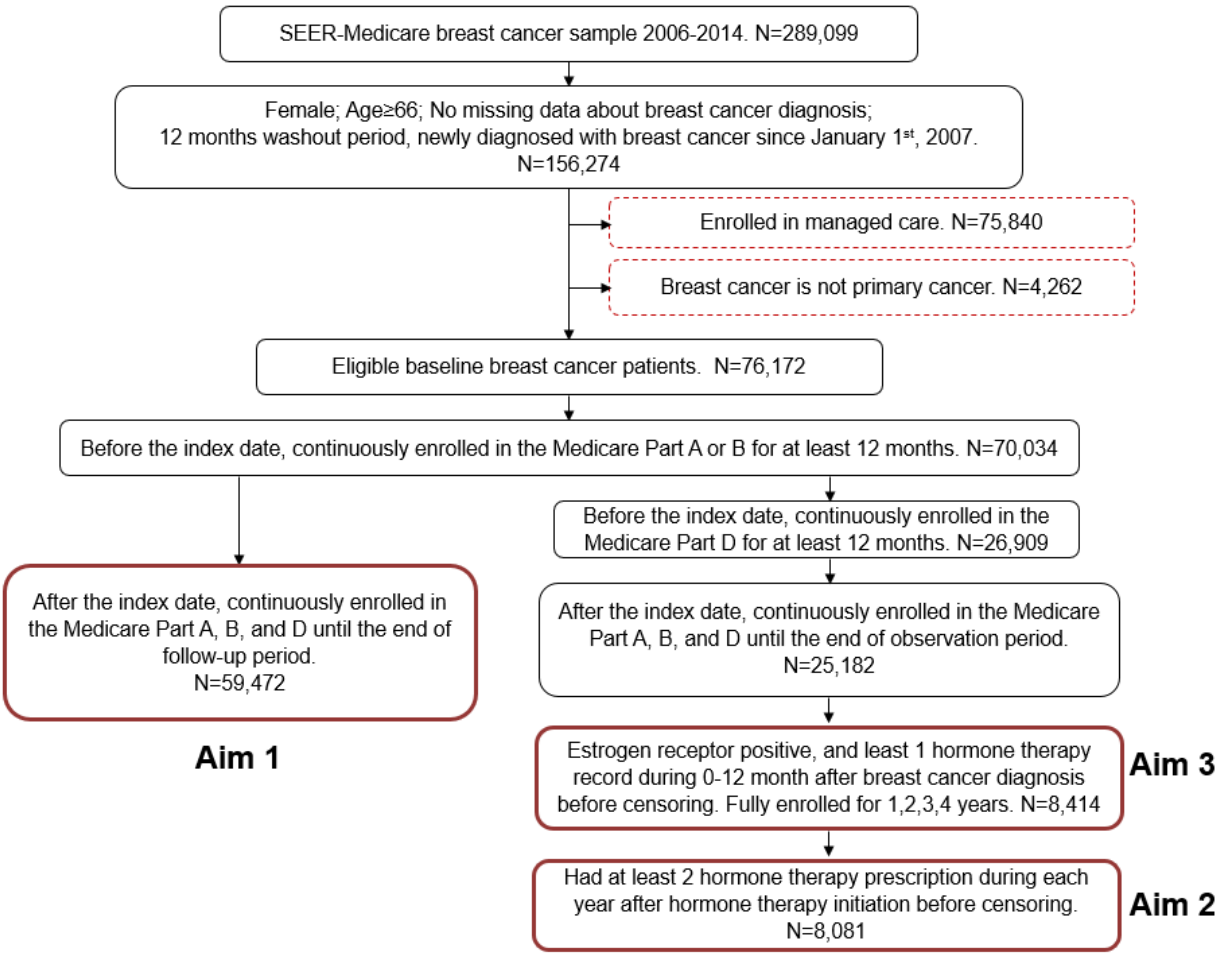


Figure 3.3 Study Sample Flow Chart



3.3 Measurements

We have three specific aims in this study. Aim 1 examined patterns of continuity of care and the risk of mortality for breast cancer patients with comorbidities for up to five years of cancer survival. Aim 2 determined HT adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care among breast cancer patients with cardiometabolic diseases. Aim 3 examined the associations between continuity of care with patients' outcomes including health care service utilization and costs. We identified the information for data analyses of our three aims from the SEER-Medicare-linked database. The study variables were classified into three groups: predictors, covariables, and outcome variables.

3.3.1 Predictor

Continuity of Care

Continuity of care indicates the degree of continuity of discrete health care elements during the health care process, which includes information continuity, relational continuity, and management continuity.[23] Several indices were developed to estimate continuity of care quantitatively.[26,125,192] This study chose the Bice-Boxerman COC Index,[25] because it was a commonly used empirical measurement for continuity of care, which could enable researchers to obtain timely estimations.[18,54,55,125,193] The COC Index measures continuity of care based on individuals' utilization of different providers, which includes an individual's total number of visits for one episode of disease or a certain period to a single provider or a group of specific providers.[25] Thus, the COC Index counts for both the frequency of visits to each provider and the dispersion of visits between providers. In this study, the COC Index was measured based on every single provider (Individual, PCP, Oncologist, Other COC Indices) and each provider specialty group (Specialty COC Index). The Individual COC Index reflects the extent of

continuity of care to which a patient visits a single provider. Similarly, the Specialty COC Index indicates the degree of continuity of care to which a patient visits one type of physician specialist.

The general equation (equation 3.1) to calculate the COC Index is[25]:

$$COC = \frac{\sum_{j=1}^{S} n_j^2 - N}{N(N-1)} \qquad \text{(equation 3.1)}$$

To estimate the Specialty COC Index: $N =$ the total number of visits; $n =$ the number of visits to provider specialty j; $s =$ the number of provider specialties. To estimate the Individual COC Index: $N =$ the total number of visits; $n =$ the number of visits to provider j; $s =$ the number of providers. To get a stable COC Index, this study required $N \geq 4$.[194]

In this study, the COC was measured for each patient within each observation year in two different ways including the Specialty COC Index and Individual COC Index. The Specialty COC Index was calculated based on three health care specialty groups: PCP, Oncologist, and Other (ex. Cardiology, Endocrinology), which indicated the degree of continuity of care to which a patient visits one group of physician specialists. The Individual COC Index was calculated based on each health care provider who involved in patients' care after breast cancer diagnoses. The Individual COC Index reflected the extent of continuity of care to which a patient visits a single health care provider. The COC Index has a scale of 0 (maximum dispersion) to 1 (maximum concentration). For example, if a patient visited a different health care provider (a single provider for the Individual COC and one provider specialty type for the Specialty COC) for each of her visit, the COC Index of this patient was 0. If a patient visited the same health care provider (a single provider for the Individual COC; one provider specialty type for the Specialty COC) for all her visits, the COC Index of this patient was 1. Another example, if a patient had a total of 12 visits to health care providers, within which she had 4 visits to 4 different PCPs, 4 visits to 4 different Oncologists, and 4 visits to 4 different Other specialists, then her Specialty

COC and Individual COC Indices were 0.27 and 0 respectively. Table 3.1 demonstrates a few examples of different COC Indices.

The COC Indices of this study only counted for health care providers visits from outpatient records, which were further limited to all outpatient visits with the diagnoses of breast cancer and cardiometabolic diseases (hypertension, hyperlipidemia, or diabetes). Provider specialties included in this study were: primary care provider (PCP), Oncologist, and other specialties (Other). Health care provider specialties were identified from outpatient records by variable HCFASPEC. PCP included family practice, general practice, internal medicine, obstetrics and gynecology, and geriatrics (HCFASPEC= 01, 08, 11, 16, and 38).[121,195] Oncologist included radiation oncologist, medical oncologist, surgeon, and surgical oncologist (HCFASPEC= 02, 24, 36, 83, 90, 91, 92, and 98).[121,195] Other specialist included all other physician specialists Variable RFR_UPIN from the outpatient records was used to identify single health care providers. Since breast cancer patients with cardiometabolic diseases have several disease conditions than others, these patients have more frequent visits to physicians than non-physicians. Thus, we only included physicians in our study. Records without valid HCFASPEC values or RFR_UPIN values were excluded from the calculations of the COC Indices. In the aim 1 study, COC Indices were measured for each survival year after the primary breast cancer diagnosis. In the aim 2 and 3 study, COC Indices were measured for each observation year after HT initiation.

Table 3.1 Continuity of Care Index Calculation

Variables	P1*	P2*	P3*	Total Visit	COC Index
	1	1	1	3	0.000
	0	1	2	3	0.333
	0	0	3	3	1.000
	6	1	1	8	0.536
	5	2	1	8	0.393

4	3	1	8	0.321
4	2	2	8	0.286
3	3	2	8	0.250
4	4	0	8	0.429
3	5	0	8	0.464
2	6	0	8	0.571
1	7	0	8	0.750

*P1/P2/P3 could be provider specialty groups or each provider. For the Specialty COC, P1/P2/P3 would be PCP/Oncologist/Other group. For the Individual COC, P1/P2/P3 would be three different providers.

3.3.2 Covariables

In this study, the measurements of covariables and predictors were based on the patient's baseline information during the 12-month washout period before the index date.

(a) Patient demographic information

Age of diagnosis: The age of diagnosis in years for each patient was included in the study as a continuous variable. To better describe the cohort, patients were categorized into age groups: 66-70, 71-75, 76-80, and >80 years.[196] Variable 'age_dx' indicates age and can be retrieved from the SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF) data.

Race: In the aim 1 study, patients were classified into five groups according to race: White, Black, Hispanic, Asian, and Other. In the aim 2&3 study, patients were classified into three groups according to race: White, Black, and Other. The variable 'napiia' indicates race and could be retrieved from the SEER-Medicare PEDSF data.

Poverty level: Patients' poverty levels were categorized into five levels: 0-5%, 5-10%, 10-20%, 20-100%, and unknown.[42] The variable 'census_pov_ind' indicates poverty level and can be retrieved from the SEER-Medicare PEDSF data.

Marital status: Patients' marital status (variable 'mar_stat') can be found in the SEER-Medicare PEDSF data. In this study, the marital status of patients can be classified into married and unmarried.[42]

Region: The state-level geographic information of patients (variable 'REG') can be retrieved from the SEER-Medicare PEDSF data. The regions of practice (Northeast, Midwest, South, and West) were defined based on the state-level geographic information.

(b) Patient breast cancer status

Tumor stage: Patient's tumor stage (variable 'adjajccstg') can be categorized into I, II, III and IV. The SEER-Medicare PEDSF data includes variable 'adjajccstg'.

Survival time: Survival time in years after breast cancer diagnosis for each patient was included in the study as a continuous variable. A patient's survival time was calculated by subtracting the time of first breast cancer diagnosis from the time of claim. The variable 'ddxflag' in the SEER-Medicare PEDSF data can be retrieved to estimate survival time.

(c) Patient comorbidities status

The Charlson Comorbidity Index (CCI): We used a modified CCI (the National Cancer Institute (NCI) Comorbidity Index) in this study. The comorbidity score for each patient was calculated by the NCI comorbidity index, which is a modified Charlson Comorbidity Index (CCI) and suggested for use by the NCI.[84,190,197,198] The NCI index was developed by Klabunde in 2000 and was specifically used for measurement of comorbidities in cancer patients.[84,190,198] The information can be extracted from the hospital (Medicare Part A) and the physician (Medicare Part B) claims data a year before the date of cancer diagnosis excluding the month of diagnosis.[190] To avoid false positives, for physician claims, the same condition needed to appear twice in a patient's diagnoses more than 30 days apart.[190] The NCI index is constructed by two steps.[84] First, the estimated

coefficient for each condition was multiplied with the corresponding condition indicators identified from hospital or physician claims. Second, the products of these multiplications of all conditions were summarized to create a single score. The NCI index includes 16 comorbidities, which are identified by specific ICD-9 codes (listed in Table 3.3).[190] However, our research focused on breast cancer patients with cardiometabolic diseases. Therefore, we excluded conditions that are related to hypertension, hyperlipidemia, and diabetes (listed in Table 3.3) when we calculated the NCI Comorbidity index.

Hypertension (0/1): The diagnosis of hypertension can be identified by ICD-9 codes (401.x, 402.x, 403.x, 404.x, and 405.x; details are listed in Table 3.2) in hospital (Medicare Part A, variable 'dgn_cd1-25'') or physician (Medicare Part B, variable 'dgn_cd1-25'') claims data. The patient was be marked as having hypertension when she had one hospital claim or two separate physician claims in a period greater than 30 days.[190]

Hyperlipidemia (0/1): The diagnosis of hyperlipidemia can be identified by ICD-9 codes (272.x; details are listed in Table 3.2) in hospital (Medicare Part A, variable 'dgn_cd1-25') or physician (Medicare Part B, variable 'dgn_cd1-25') claims data. The patient was marked as having hyperlipidemia when she had one hospital claim or two separate physician claims in a period greater than 30 days.[190]

Diabetes (0/1): The diagnosis of type 2 diabetes can be identified by ICD-9 codes (250.x; details are listed in Table 3.2) in hospital (Medicare Part A, variable 'dgn_cd1-25') or physician (Medicare Part B, variable 'dgn_cd1-25'') claims data. The patient was marked as having diabetes mellitus when she had one hospital claim or two separate physician claims in a period greater than 30 days.[190]

Number of comorbidities (0, 1, 2, and 3): The definition of the number of comorbidities is the summary of the number of comorbidities that a patient had (hypertension, hyperlipidemia, or diabetes) during the baseline period.

(d) Breast cancer treatment

Hormone therapy (HT) (0/1): The exposure of HT was defined by whether a patient received at least one prescription of oral HT within 12 months of first breast cancer diagnosis before recurrence.[42] The patient also had a clinical record of positive estrogen or progesterone receptors.[42] In the aim 1 study, the binary variable 'HT' was identified yearly after breast cancer diagnosis by the NDC codes from the Medicare Part D data (Table 3.4), including oral tamoxifen and aromatase inhibitors (AI) (anastrozole, letrozole, and exemestane).[119,138,191] In the aim 2&3 study, the binary variable 'HT' was identified yearly after HT initiation.

Chemotherapy (0/1): Chemotherapy was defined by the Current Procedural Terminology (CPT) billing codes (ICD-9 codes: V58.1, V66.2, V67.2) from the Medicare claims data Part A and B (listed in Table 3.5).[42,199] In the aim 1 study, the binary variable 'Chemotherapy' was identified yearly after breast cancer diagnosis. In the aim 2&3 study, the binary variable 'Chemotherapy' was identified yearly after HT initiation.

Surgery (0/1): Surgery was defined by the ICD-9 codes: 85.2-85.4 from the Medicare claims data after a patient's first breast cancer diagnosis before recurrence (listed in Table 3.5).[42,199] In the aim 1 study, the binary variable 'Surgery' was identified yearly after breast cancer diagnosis. In the aim 2&3 study, the binary variable 'Surgery' was identified yearly after HT initiation.

Radiation therapy (0/1): Patients were assigned to exposed or non-exposed groups. Radiation therapy was defined by the ICD-9 codes: V58.0; V66.1; V67.1 from the Medicare claims data after a patient's first breast cancer diagnosis before recurrence (listed in Table 3.5).[42,199] In the aim 1 study, the binary variable 'Radiation therapy' was identified yearly after breast cancer diagnosis. In the aim 2&3 study, the binary variable 'Radiation therapy' was identified yearly after HT initiation.

3.3.3 Outcome variables

Aim 1: To examine patterns of continuity of care and the risk of mortality for breast cancer patients with comorbidities for up to five years of cancer survival.

Time to mortality: A patient's date of death was identified from the SEER's registry and observed for up to 5 years after her initial breast cancer diagnosis. The patient's survival time was the time interval between the date of initial breast cancer diagnosis and date of death. An observation was censored at the date of dropping out, by the end of the study period, or after the follow-up time elapsed.

Aim 2: To determine hormone therapy adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care among breast cancer patients with cardiometabolic diseases.

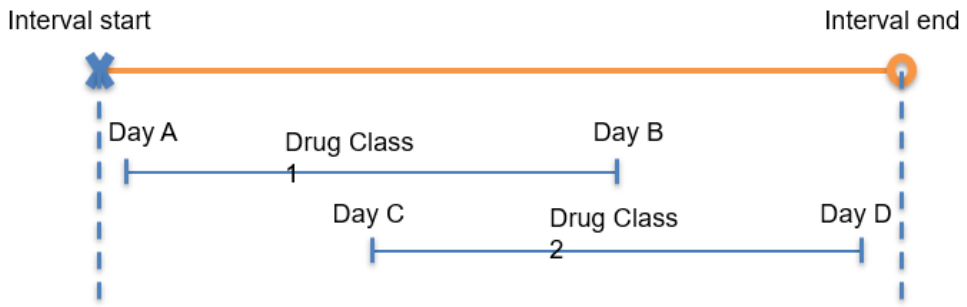
Proportion of Days Covered (PDC): Patients' adherence to oral HT, antihypertensives, hyperlipidemia medications, and diabetes medications were measured separately by Proportion of Days Covered (PDC) using the Medicare claims part D data. PDC was widely used by previous studies to measure medication adherence of a class of drugs which were used for concomitant therapy or had switches of medications within the class.[106,200] To reduce the underestimation of medication adherence caused by patients' inpatient visits, this study used an adjusted PDC excluding the days of inpatient stays from the observation period.[201] The PDCs for each therapeutic groups were measured yearly after patients' HT initiation.

The PDC was measured based on the Medicare claims part D data of each patient annually within each therapeutic group (HT, antihypertensives, hyperlipidemia medications, and diabetes medications) after the index date (HT initiation) (Figure 3.4,

equation 3.2). Since this study used a prevalent cohort for cardiometabolic treatments, the measurement of all selected medication usage started from the HT initiation date. First, a supply-matrix was built for each patient. The matrix recorded the supply of each medication class for each day of the whole study period within therapeutic groups. Next, the days of supply for each prescription were added to the prescription filling date. If the days covered by the prescriptions were overlapped, the next prescription filling date would be adjusted to the next date of the previous prescription running out. Then, the supply-matrix was partitioned into submatrices for each observation year. Fourth, within each observation year, the days covered were estimated by adding the days of supply which had at least one medication within the therapeutic group from the first prescription observed date until the end of that year. Then, PDC was calculated by dividing the days covered by the days evaluated adjusted for hospital stays within that year(equation 3.2).[118,202] To get a reliable measurement of medication adherence, only patients who filled more than two prescriptions within the same therapeutic group were included in the study. This medication class based PDC calculation might cause potential overestimation of medication adherence. Still, it could accommodate the complications of measuring adherence to concomitant therapy or switching of medications within the class.[118,202]

Medication adherence: Patients were classified as adherent when PDC ≥ 80% or non-adherent when PDC < 80%.[106,135,201,203,204]

Figure 3.4 Measuring Medication Adherence to Different Medication Classes within the Same Therapeutic Group



$$PDC = \frac{Days\ between\ A\ and\ D, with \geq 1\ drug\ available}{Days\ between\ A\ and\ Interval\ end - hospital\ stay} \qquad \text{(equation 3.2)}$$

Aim 3: To examine the associations between continuity of care with patients' outcomes including health care service utilization and costs.

Since the continuity of care was estimated using COC Indices based on patients' provider office visits in outpatient record, this study excludes the measurements of outpatient visits and outpatient costs to avoid collinear effects.

Health care service utilization was determined by whether a patient had an ED visit or an inpatient visit during each follow-up year of the study period. In this study, a patient's ED visits and inpatient visits were measured per observation year based on each related condition (breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) as well as all conditions (all-cause) using the Medicare part A and B data. ED visits and inpatient visits were measured from the Medicare inpatient and outpatient files. ED visits included the emergency department visits during inpatient and outpatient visits. Inpatient visits only included the inpatient stays excluding emergency department visits.

Health care costs were estimated by the Medicare costs per patient per year and were adjusted to reflect 2014 dollars using the consumer price index.[205] In this study, a patient's ED costs, and inpatient costs were measured per observation year based on each related condition (breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) as well as all conditions (all-cause) using the Medicare part A and B data.

All files from the SEER-Medicare data were linked by a unique patient identification number (patient_id).

3.4 Data analysis by aims

Aim 1: To examine patterns of continuity of care and the risk of mortality for breast cancer patients with comorbidities for up to five years of cancer survival.

Descriptive analyses summarized patients' characteristics for each comorbidity group (0, 1, 2, and 3 comorbidities). Chi-Square tests were used to compare categorical variables. The average COC Indices (Specialty COC Index and Individual COC Index) were calculated annually through 1 to 5 survival years after breast cancer diagnoses. ANCOVA tests were used to compare average COC Indices among different tumor stages or numbers of comorbidities for different years. The Kaplan-Meier curves for the survival rates of breast cancer patients with different numbers of comorbidities and tumor stages were also plotted.

Cox Proportional-Hazard Models were used to estimate the association of COC Indices with patients' survival. This study selected the most representative patients' characteristics as the covariates for statistic models to avoid over-adjustment. Specifically, the models controlled for demographic information (age, race, marriage, poverty level, and region), comorbidity (hypertension, hyperlipidemia, diabetes, and CCI), breast cancer stage, and breast cancer treatment. The effects of the Specialty COC Index and Individual COC Index on patients'

survival were modeled separately. This study divided COC Indices into four levels (1st quartile: 0-25%, 2nd quartile: 26-50%, 3rd quartile:51-75%, and 4th quartile: 76-100%) based on the quartiles of their distributions to present a more intuitive Hazard Ratio (HR). The Specialty COC Index range for each quartile is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.41, 3rd quartile:0.41-0.52, and 4th quartile: 0.52-1. The Individual COC Index range for each quartile is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.33, 3rd quartile:0.33-0.52, and 4th quartile: 0.52-1. Since cancer patient might use highly intensive or dispersed care during the end-of-life, there might be concerns of ambiguous causal ordering.[125,126] This study used lagged effects models to avoid the uncontrollable changes in COC Indices due to the end-of-life. [125,126] Within the lagged effects models, the COC Index from the previous observation year was added as a control variable for the COC Index from the current observation year. The lagged effects models were adjusted for patients' characteristics as well as the COC Index from the previous survival year.

The Cox Proportional Hazard Model looks like:

$$(start(t), stop(t)) * censor = COC\ (t) + age + race + marriage + region + poverty\ level + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + surgery + chemotherapy + radiationtherapy$$

(equation 3.3)

The lagged effects Cox Proportional Hazard Model looks like:

$$(start(t), stop(t)) * censor = COC\ (t) + COC(t-1) + age + race + marriage + region + poverty\ level + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + surgery + chemotherapy + radiationtherapy$$

(equation 3.4)

Since patients' characteristics may contribute to their mortality, we conducted sensitivity analyses to test the robustness of this study. Three types of models were conducted for the sensitivity analyses: unadjusted models, partially adjusted models, and models using the first year COC Indices as predictors. Patients with different demographic backgrounds, comorbidities, and cancer treatments may have different risks of mortality. We used unadjusted models which only controlled for survival year to test the models' sensitivity to these covariates. Also, different cancer treatment strategies might contribute to patients' risks of mortality. We used partially adjusted models to determine if the types of cancer treatment undertook by patients contributed to patients' survival. In the partially adjusted models, all covariates from the fully adjusted models in the main analyses were controlled except variables of cancer treatments. Besides these analyses, we also conducted analyses using the first year COC Indices to predict patients' probabilities of survival. These models were used to test the association of COC and mortality's sensitivity to different analysis methods.

Aim 2: To determine hormone therapy adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care among breast cancer patients with cardiometabolic diseases.

Descriptive statistics summarized patients' characteristics for each medication theraputic group. The average COC Index scores (Specialty COC Index and Individual COC Index) of each year after HT initiation were also calculated. Patients' adherence to HT, antihypertensives, hyperlipidemia medications and diabetes medications were estimated yearly by patients' medication records through the study period.

Mixed-effects logistic regression models controlled for the random effect of individuals were used to estimate the association of the COC Index and the likelihood of adherence, where the Specialty COC Index and the Individual COC Index were modeled separately. The analyses were adjusted for demographic characteristics (age group, race, marriage, poverty level, and

region), tumor stages, existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes), CCI, and other cancer treatments. To avoid unbalanced covariates caused by a very small proportion of observations in surgery, chemotherapy, and radiation therapy (Table 4.2.1), we grouped these treatments as one variable called other cancer treatment in the regression models. To better interpret the clinical meaning of COC Indices and their associations with medication adherence, we divided COC Indices into quartiles (0-25% 1st quarter, 26-50% 2nd quarter, 51-75% 3rd quarter, and 76-100% 4th quarter) for logistic regression analyses. The Specialty COC Index range for each quartile is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.40, 3rd quartile:0.40-0.49, and 4th quartile: 0.49-1. The Individual COC Index range for each quartile is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.32, 3rd quartile:0.32-0.50, and 4th quartile: 0.50-1. Since the continuity of care has more influence on patients' medication adherence of the current year, this study did not control for the lagged effects of the COC Index in regression models. The fully adjusted logistic regression model looks like:

$$
\begin{aligned}
&logit(adherence) \\
&\quad = COC + age + race + marriage + poverty\ level + region + \ tumor\ stage \\
&\quad + other\ cancer\ treatment + hypertension + hyperlipidimia + diabetes + CCI \\
&\quad + year
\end{aligned}
$$

(equation 3.5)

Sensitivity analyses were performed to test the robustness of the models. We used models with fewer covariates to check the models' covariates sensitivity. First, patients' demographic backgrounds, comorbidities, and cancer treatments might be associated with their medication adherence. Thus, the unadjusted logistic regression was conducted, within which the analysis was only adjusted for years after HT initiation. Second, patients might discontinue their concurrent medications when a new cancer treatment was started. Therefore, to test the model's sensitivity of patients' cancer treatment other than HT, the partially adjusted logistic

regression model was built, controlling for all covariates in the fully adjusted models except for the other cancer treatment. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary NC).

Aim 3: To examine the associations between continuity of care with patients' outcomes including health care service utilization and costs.

Descriptive analyses were conducted to summarize patients' characteristics, health care service utilization, and COC Indices. Patient characteristics included: age groups, race groups, marriage status, poverty levels, regions, tumor stages, other cancer treatments, existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes), and CCI. Health care service utilization included ED visit and inpatient visit.

This study used mixed-effects logistic regression models to estimate the associations of COC Indices and the likelihood of ED visit or inpatient visit separately for each related condition (all-cause, breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related). Each COC Index (Specialty COC and Individual COC) was independently served as the primary predictor of the logistic regression models. Mixed-effects models were used to control the randomized effects caused by repeated measurement of each patient in the analyses.

Based on previous studies, two-stage models were recommended to estimate the health care cost with a gamma distribution.[206,207] In this study, the distribution of ED cost and inpatient cost both followed gamma distribution (data not shown). Thus, we used two-stage models to estimate the association of COC Indices (Specialty COC and Individual COC) and health care costs for each service type (ED or inpatient) under each related condition (all-cause, breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) separately.[206,207] Random effects caused by individual patients was controlled in the mixed

effects models. The first part of the models was a mixed-effects logistic regression model estimating the probability of positive health care cost. The second part of the models was a mixed-effects linear regression model with a gamma distribution and log link function estimating the distribution of positive health care cost.[206,207] Then the predicted health care cost of each observation was generated by multiplying the probability from the first part of the models and the predicted positive costs from the second part of the models. The 1000 bootstrap samples were used to estimate the effect of the COC Index on the mean and 95% Confident Interval (CI) of health care cost for each health care service type at each condition. The 2-stage models look like:

Logistic regression

$$logit(visit(0/1)) = COC + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + Charlson\ Index + year + other\ cancer\ treatment$$

(equation 3.6)

Linear regression with gamma distribution and log link function:

$$log(cost) = COC + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + Charlson\ Index + year + other\ cancer\ treatment$$

(equation 3.7)

To better interpret COC Indices with clinical meanings, we divided these COC Indices into quartile levels (0-25% 1st quarter, 26-50% 2nd quarter, 51-75% 3rd quarter, and 76-100% 4th quarter) in regression analyses. The range for each quartile for Specialty COC Index is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.40, 3rd quartile:0.40-0.49, and 4th quartile: 0.49-1. The

range for each quartile for Individual COC Index is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.32, 3rd quartile:0.32-0.50, and 4th quartile: 0.50-1. Since only a very small percentage of patients had surgery, chemotherapy, and radiation therapy in the cohort, we grouped these variables as one (other cancer treatment) in the regression models. All models were adjusted for patients' demographic information (age, race, marriage status, poverty level, region), tumor stage, existing diseases (hypertension, hyperlipidemia, and diabetes), CCI, other cancer treatment, and years after HT initiation.

Sensitivity analyses were used to test the robustness of this study. To estimate whether our findings were sensitive to our choice of covariates, we conducted sensitivity analyses using models with reduced numbers of variables as well as lagged effect models. First, patients' characteristics, comorbidities, and cancer treatments might influence their health care service utilization and costs. Thus, we used unadjusted models, which only adjusted for the years after HT initiation. Second, out of all covariates, cancer treatments could greatly contribute to patients' health care service utilization and costs. Therefore, we used partially adjusted models, which controlled for all covariates from the fully adjusted models except for the variable 'other cancer treatment'. Third, there might be uncontrollable changes in COC Indices due to spillover.[125,126] Thus, lagged effects models were used to test models' sensitivity to COC Indices spillover. In the lagged effects models, we added COC Indices from the previous observation year as an additional control variable to baseline characteristics as covariates to the COC Indices from the current observation year. The lagged effect 2-stage models look like:

Logistic regression

$$logit(visit(0/1)) = COC(t) + COC(t-1) + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment \quad \text{(equation 3.8)}$$

Linear regression with gamma distribution and log link function:

$$log(cost) = COC(t) + COC(t-1) + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment$$ (equation 3.9)

All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary NC).

Table 3.2 The ICD-9 codes for breast cancer, hypertension, hyperlipidemia, and diabetes diagnoses

Diseases	ICD-9 codes	Reference
Breast Cancer	174 Malignant neoplasm of female breast	189,208
	174.0 Malignant neoplasm of nipple and areola of female breast	
	174.1 Malignant neoplasm of central portion of female breast	
	174.2 Malignant neoplasm of upper-inner quadrant of female breast	
	174.3 Malignant neoplasm of lower-inner quadrant of female breast	
	174.4 Malignant neoplasm of upper-outer quadrant of female breast	
	174.5 Malignant neoplasm of lower-outer quadrant of female breast	
	174.6 Malignant neoplasm of axillary tail of female breast	
	174.8 Malignant neoplasm of other specified sites of female breast	
	174.9 Malignant neoplasm of breast (female)	
	175 Malignant neoplasm of male breast	
	175.0 Malignant neoplasm of nipple and areola of male breast	
	175.9 Malignant neoplasm of other and unspecified sites of male breast	
	233.0 Carcinoma in situ of breast	
Hypertension	401 Essential hypertension	106,188,189
	401.0 Malignant essential hypertension	
	401.1 Benign essential hypertension	
	401.9 Unspecified essential hypertension	
	402 Hypertensive heart disease	
	402.0 Malignant hypertensive heart disease	
	402.00 Malignant hypertensive heart disease without heart failure	
	402.01 Malignant hypertensive heart disease with heart failure	
	402.1 Benign hypertensive heart disease	
	402.10 Benign hypertensive heart disease without heart failure	
	402.11 Benign hypertensive heart disease with heart failure	
	402.9 Unspecified hypertensive heart disease	
	402.90 Unspecified hypertensive heart disease without heart failure	
	402.91 Unspecified hypertensive heart disease with heart failure	
	403 Hypertensive chronic kidney disease	
	403.0 Malignant hypertensive renal disease	
	403.00 Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified	

403.01 Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end-stage renal disease

403.1 Benign hypertensive renal disease

403.10 Hypertensive chronic kidney disease, benign, with chronic kidney disease stage I through stage IV, or unspecified

403.11 Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end-stage renal disease

403.9 Unspecified hypertensive renal disease

403.90 Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified

403.91 Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end-stage renal disease

404 Hypertensive heart and chronic kidney disease

404.0 Malignant hypertensive heart and renal disease

404.00 Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified

404.01 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified

404.02 Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end-stage renal disease

404.03 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end-stage renal disease

404.1 Benign hypertensive heart and renal disease

404.10 Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified

404.11 Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified

404.12 Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end-stage renal disease

404.13 Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end-stage renal disease

404.9 Unspecified hypertensive heart and renal disease

490.90 Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified

	404.91 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	
	404.92 Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end-stage renal disease	
	404.93 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end-stage renal disease	
	405 Secondary hypertension	
	405.0 Malignant secondary hypertension	
	405.01 Malignant renovascular hypertension	
	405.09 Other malignant secondary hypertension	
	405.1 Benign secondary hypertension	
	405.11 Benign renovascular hypertension	
	405.19 Other benign secondary hypertension	
	405.9 Unspecified secondary hypertension	
	405.91 Unspecified renovascular hypertension	
	405.99 Other unspecified secondary hypertension	
Hyperlipidemia	272 Disorders of lipid metabolism	106,188,189
	272.0 Pure hypercholesterolemia	
	272.1 Pure hyperglyceridemia	
	272.2 Mixed hyperlipidemia	
	272.3 Hyperchylomicronemia	
	272.4 Other and unspecified hyperlipidemia	
	272.5 Lipoprotein deficiencies	
	272.6 Lipodystrophy	
	272.7 Lipidoses	
	272.8 Other disorders of lipid metabolism	
	272.9 Unspecified disorder of lipid metabolism	
Diabetes mellitus	250 Diabetes mellitus	106,188,189
	250.0 Diabetes mellitus without mention of complication	
	250.00 Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	
	250.01 Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled	
	250.02 Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled	
	250.03 Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled	
	250.1 Diabetes with ketoacidosis	
	250.10 Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled	

250.11 Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled

250.12 Diabetes with ketoacidosis, type II or unspecified type, uncontrolled

250.13 Diabetes with ketoacidosis, type I [juvenile type], uncontrolled

250.2 Diabetes with hyperosmolarity

250.20 Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled

250.21 Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled

250.22 Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled

250.23 Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled

250.3 Diabetes with other coma

250.30 Diabetes with other coma, type II or unspecified type, not stated as uncontrolled

250.31 Diabetes with other coma, type I [juvenile type], not stated as uncontrolled

250.32 Diabetes with other coma, type II or unspecified type, uncontrolled

250.33 Diabetes with other coma, type I [juvenile type], uncontrolled

250.4 Diabetes with renal manifestations

250.40 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled

250.41 Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled

250.42 Diabetes with renal manifestations, type II or unspecified type, uncontrolled

250.43 Diabetes with renal manifestations, type I [juvenile type], uncontrolled

250.5 Diabetes with ophthalmic manifestations

250.50 Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled

250.51 Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled

250.52 Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled

250.53 Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled

250.6 Diabetes with neurological manifestations

250.60 Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled

250.61 Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled

250.62 Diabetes with neurological manifestations, type II or unspecified type, uncontrolled

250.63 Diabetes with neurological manifestations, type I [juvenile type], uncontrolled

250.7 Diabetes with peripheral circulatory disorders

250.70 Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled

250.71 Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled

250.72 Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled

250.73 Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled

250.8 Diabetes with other specified manifestations

250.80 Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled

250.81 Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled

250.82 Diabetes with other specified manifestations, type II or unspecified type, uncontrolled

250.83 Diabetes with other specified manifestations, type I [juvenile type], uncontrolled

250.9 Diabetes with unspecified complication

250.90 Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled

250.91 Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled

250.92 Diabetes with unspecified complication, type II or unspecified type, uncontrolled

250.93 Diabetes with unspecified complication, type I [juvenile type], uncontrolled

Table 3.3 The ICD-9 codes for the NCI index definition[190]

Condition	Definition by ICD-9 Code
Acute Myocardial Infarction	ICD-9 Diagnosis: 410.xx with inpatient length of stay >2 days
History of Myocardial Infarction	ICD-9 Diagnosis: 412.bb
Congestive Heart Failure	ICD-9 Diagnosis: 398.91, 425.4x-425.5x, 425.7x-425.9x, 428.xx
Peripheral Vascular Disease	ICD-9 Diagnosis: 093.0x, 440.xx-441.xx, 442.0x-442.8x, 443.1x-443.9x, 447.70-447.73, 785.4x, V43.4x; ICD-9 Procedure: 00.60, 38.13, 38.14, 38.15, 38.16, 38.18, 38.33, 38.34, 38.36, 38.38, 38.43, 38.44, 38.46, 38.48, 38.68, 39.25, 39.29
Cerebrovascular Disease (CVD)	ICD-9 Diagnosis: 430.xx- 438.xx; ICD-9 Procedure: 00.61, 00.62, 00.63, 00.65, 38.12, 38.32, 38.42, 39.22, 39.28, 39.74
Chronic Obstructive Pulmonary Disease (COPD)	ICD-9 Diagnosis: 416.8x-416.9x, 490.xx-496.xx, 500.xx-505.xx, 506.4x, 519.1x
Dementia	ICD-9 Diagnosis: 290.xx, 291.0x-291.2x, 292.82, 294.1x, 331.0x-331.2x, 331.82
Paralysis (Hemiplegia or Paraplegia)	ICD-9 Diagnosis: 342.xx, 344.0x-344.6x, 344.9x
Diabetes	ICD-9 Diagnosis: 250.bb, 250.0x-250.3x
Diabetes with Complications	ICD-9 Diagnosis: 250.4x-250.9x, 362.0x
Renal Disease	ICD-9 Diagnosis: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.xx-583.xx, 585.xx-586.xx, 588.xx, V42.0x, V45.1x, V56.xx; ICD-9 Procedure: 39.27, 39.42, 39.95, 54.98, 55.69
Mild Liver Disease	ICD-9 Diagnosis: 070.32-070.33, 070.54, 571.2x, 571.4x-571.6x
Moderate/Severe Liver Disease	ICD-9 Diagnosis: 070.22-070.23, 070.44, 456.0x-456.2x, 572.2x-572.8x, V42.7x; ICD-9 Procedure: 39.1b, 42.91, 50.5x
Peptic Ulcer Disease	ICD-9 Diagnosis: 531.xx-534.xx
Rheumatologic Disease	ICD-9 Diagnosis: 710.0x, 710.1x, 710.4x, 714.0x-714.2x, 714.81, 725.bb
AIDS	ICD-9 Diagnosis: 042.xx-044.x, V08.bb, 795.71

b: denotes blank; x: denotes any character including blank.

Table 3.4 The NDC codes for hormone therapy medications[209]

Class	Drug	NDC
Anti-estrogen therapy		
	Tamoxifen*	N021807; A070929; A090878; A075797; A074732; A206694; A070929; A090878; A075797; A074732; A206694; N017970; N017970; A076179; A076398; A075740; A074539; A076027; A074504; A076179; A076398; A075740; A076027; A074504
	Toremifene	N020497
	Fulvestrant	N021344
Aromatase inhibitors (AI)		
	Anastrozole*	A090568; A200654; A091164; A090732; A090088; A091051; A079220; A078944; A078058; A078485; A078921; N020541; A091242; A091331; A079007; A091177; A078322; A078984
	Letrozole*	N020726; A090934; A091303; A091191; A090491; A203796; A201804; A202716; A078190; A200161; A090289; A090789; A090838; N209935; A090292; A091638; A091098; A202048; A091466; A090196
	Exemestane*	N020753; A200898; A203315; A209208; A077431
	Aminoglutethimide	N018202
Anti-androgen therapy		
	Goserelin Acetate	N019726; N020578
	Leuprolide	A074728; A078885; A075471; N020011; N019732; N020708; N020517; N020517; N020517; N020263; N020263; N020263; N020263; N020263; N021343; N021379; N021488; N021731; N203696; N203696; N021088; A075721; N019010; N020011; N020263; N020263
Other	Megestrol	N021778; A203960; A075671; A075681; A075997; A076721; A204688; A203139; A074621; A072422; A074458; A074621; A072423; A074458; N020264; A077404; N016979; N016979; A070646; A074745; A070647

* hormone therapy was used for aim 2 and aim 3.

Table 3.5 The ICD-9 codes and CPT codes for breast cancer treatments identification[199]

Breast cancer treatment	ICD-9 codes	CPT codes	Revenue center codes	SEER radiation delivery variables and codes
Surgery	85.2; 85.20-22; 85.33-36; 85.23; 85.4; 85.41-48;	19160; 19162; 19120; 19125; 19126; 19180; 19182; 19200; 19220; 19240; 19260; 19271; 19272; 19301-19307		
Radiation	92.21-29; V580; V661; V671	77261-77263; 77280; 77285; 77290; 77295; 77299; 77300; 77301; 77305; 77310; 77315; 77321; 77331-77334; 77336; 77338; 77370-77373; 77399; 77300-77419; 77421-77423; 77427; 77435; 77465; 77470; 77499; 77600; 77605; 77610; 77615; 77260; 77750; 77761-77762; 77776-77778; 77789; 77790; G0173; G0174; G0178; G0242; G0243; G0251; G0338-G0340; 61770; 61793; S8049; G8378; G8379; C9726; C9728; D5984-D5985; A4650;	radiation oncology indicator switch (0280; 0289); therapeutic radiology indicator switch (0330; 0333)	rad1-rad10 (1-6: yes; 0,7-9: no); radsurg1-radsurg10 (2-6,9: yes; 0: no)
Chemotherapy		C1167; C9115; C9120; C9127; C9214; C9399; C9411; C9415; C9420; C9421; C9430-C9432; C9440; G0356; G8371; G8373; G8374; J0270; J0640; J1950; J7150; J8520; J8521; J8530; J8610; J8700; J8999-J9001; J9035; J9045; J9070; J9080; J9090; J9093-J9097; J9170; J9175; J9178; J9180; J9190; J9200; J9202; J9217-J9219; J9250; J9260; J9264; J9265; J9280; J9291; J9293; J9295; J9355; J9357; J9390; J9395; J9999; C8953-C8955; G0355; G0359; G0359; G0359; G0361; G8371; G8374; Q0081; Q0083-Q0085		

CHAPTER 4 RESULTS

4.1 Aim 1 Results

4.1.1 Abstract

Background: Breast cancer patients with comorbidities have high mortality risk and need to see multiple healthcare providers.

Objective: To examine the association of continuity of care (COC) and the risk of mortality for breast cancer patients with comorbidities.

Methods: A retrospective cohort study of newly diagnosed female breast cancer patients (n=57,578) with comorbidities (hypertension, hyperlipidemia, and diabetes) was conducted using the 2006-2014 SEER-Medicare data. The primary outcome was all-cause mortality (assessed annually for up to 5 years). The COC index, a validated measure accounting for both the frequency and dispersion of healthcare provider visits, was measured yearly with a scale of 0 (dispersed) to 1 (concentrated) and in two ways: Specialty (unique specialist groups: Primary Care Physicians (PCP), Oncologists, and Other specialists (Other)), Individual (all individual providers regardless of specialty) COC Indices. Descriptive analysis and Chi-Square test were used for patients' characteristics. ANCOVA analysis was used for COC Indices comparison. Kaplan-Meier Curves were plotted for patients' crude mortality rate. Cox proportional hazards models estimated the hazard ratio (HR) of all-cause mortality associated with the quartile of the COC Index.

Results: The average scores increased slightly across the entire study period for both COC Indices ($p<0.05$). Patients with stage IV breast cancer had the highest Specialty COC and Individual COC Indices than others ($p<0.05$). Patients' crude mortality rate decreased with survival time and positively associated with advanced tumor stages and more comorbidities ($p<0.05$). Patients who received high continuity of care based on the Specialty COC Index (4th

vs. 1st quartile, HR 1.34, 95%CI 1.29-1.40) had higher risks of mortality compared with those who received low continuity of care. However, patients who received high continuity of care based on the Individual COC Index (4th vs. 1st quartile, HR 0.53, 95%CI 0.51-0.54) had lower risks of mortality compared to those who received low continuity of care.

Conclusion: This study examined the association between COC and mortality risk for breast cancer patients. Higher levels of Individual COC were related to lower mortality risk. Higher levels of Specialty COC were related to higher mortality risk, which might be confounded by uncontrolled factors. It is necessary to better understand the relationship between continuity and the risk of mortality in different study settings when developing interventions to improve cancer survivorship care.

4.1.2 Introduction

The United States has a high prevalence of Breast cancer with an estimated 12% of women developing breast cancer during their lifetime.[58] In 2016, 246,660 women were diagnosed with breast cancer.[27] Although the survival rate for breast cancer patients has increased from 75% in 1978 to 89% in 2012, breast cancer is still the second most deadly cancer in women.[27,28,63] Previous research found that 32.2% of breast cancer patients have comorbidities, and 10% of breast cancer patients have two or more comorbidities.[82] Cancer patients with comorbidities have higher risks of mortality than those without comorbidities.[30,31,82] In fact, a randomized clinical trial showed that 60% of breast cancer survivors died from comorbidities unrelated to cancer.[32] Several studies found that patients with comorbidities were under-treated for their comorbidities following cancer diagnoses, which can cause high mortality.[10-14]

Cancer patients with multiple comorbidities are often faced with the need to see multiple health care specialists.[1] The distribution of patients' visits to different specialists was reported as 32% to primary care physicians (PCPs), 18% to oncologists, 13% to surgeons, and 36% to other specialists.[1] However, these specialists might not communicate adequately during the follow-up care of cancer patients with comorbidities.[1] Thus, health care providers are challenged with the need for communication and coordination of patients treatments across different providers.[1,6] Surgeons and oncologists are less likely to recommend curative cancer treatment for cancer patients with comorbidities than for cancer patients without comorbidities regardless of clinical guidelines.[1,6,7] These complications were often associated with poor continuity and coordination of care.[4,8,9] Although strategies were developed to promote communication and coordination among health providers for cancer survivorship,[115] only limited effects of these strategies were found on cancer survivorship care.[57]

Continuity of care (COC) is essential to the health care system since it indicates physicians' continuity of knowledge about patients' medical conditions, service provision for

patients, and the health care management by multiple providers to the same patient.[23,107] Likewise, COC could reflect the cooperation of one patient and his/her physician or care team during the process of health care management aiming at delivering high quality and cost-effective medical care to the patient.[24,25] The definition of COC is the "degree to which a series of discrete healthcare events are experienced as coherent and connected and consistent with the patient 's medical needs and personal context".[23] COC is significantly associated with patients' satisfaction, quality of care, and their health care outcomes including medication adherence, health care service utilization, health care costs, and mortality.[16-22]

Previous studies found patients with higher COC were more likely to have a lower risk of mortality.[16,34-36] For example, elderly adults who had continuity of care based on percent of follow up days with a primary care physician (PCP) had lower mortality risk (HR=0.84, 95%CI 0.77-0.91) compared with those who didn't.[34] A study focused on elderly diabetes patients found that patients with higher COC with PCPs resulted in a 10% reduction in mortality risk compared to those with lower COC.[16] Besides, one study showed different associations of COC and the risk of mortality when different medical disciplines were taken into account for COC measurements.[127] However, these studies only focused on non-cancer patients. Still, less is known about the association between COC and the risk of mortality within cancer patients who have comorbidities.

This study focused on the association of COC and the risk of mortality within breast cancer patients with cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes). It was reported that about 28% of breast cancer patients have cardiometabolic diseases who have a prevalence of hypertension, hyperlipidemia, and diabetes estimated at 44%,73%, and 30% respectively.[87] Breast cancer patients with cardiometabolic diseases have a higher risk of mortality than those without cardiometabolic diseases.[32] These patients were more likely to visit multiple health care providers with more diverse specialties but receive poor continuity of care during their follow-up care after cancer diagnoses.[1,57] In the U.S. health care system, specialists

and PCPs have different roles and responsibilities for the follow-up care of cancer patients with comorbidities.[1] Specialists most often focus on providing patients with guidance and treatments in their areas of expertise.[1] PCPs provide general as well as cancer-related health care services to patients, often covering all aspects of patient care.[1] However, limited research has been done for the continuity of care during breast cancer survivorship. We are not clear about the continuity of care for breast patients under the scopes of health care provider specialties and individual providers. Therefore, the objectives of this research are to 1) measure the continuity of care based on health care provider specialties and individual providers and 2) examine the association of continuity of care and the risk of mortality for breast cancer patients with cardiometabolic comorbidities for up to five years of cancer survival. The finding of this study could provide strong evidence to policymakers and others helping them guide future changes in the healthcare delivery system and promoting the survivorship care for breast cancer patients.

4.1.3 Methodology

Data Source and Participants

This study used the linkage of the Surveillance, Epidemiology and End Results (SEER) and Medicare claims (SEER-Medicare) data from 2006 to 2014. The SEER data provided high-quality information about patients' electronic health records including tumor diagnosis, tumor pathology, tumor histology, tumor stage, mortality, and demographic characteristic. The Medicare claims data includes the Medicare Part A (hospital visit), Part B (outpatient, physician office visit, clinic visit, and other health facility utilization), and Part D (prescription drug usage).[186]

A retrospective cohort study was conducted to identify eligible breast cancer patients who were 1) newly diagnosed with breast cancer as their primary cancer; 2) 66 years or older at the time of breast cancer diagnoses; 3) continuously enrolled in Medicare Part A and B for at least 12 months before breast cancer diagnoses; and 4) continuously enrolled in Medicare Part A, B, and D after diagnoses until the end of following up period. Patients' breast cancer diagnoses (ICD-O-3 C500-509) were identified in the SEER registry data.[187] Patients were excluded from the study if they were enrolled in Managed Care (n=75,840) or if their information about cancer diagnoses was missing (n=4262). A 12-month baseline period before breast cancer diagnosis was used to identify a patient's comorbidities (hypertension, hyperlipidemia, and diabetes) and calculate the Charlson Comorbidity Index (CCI). Finally, a total of 59,742 female breast cancer patients were included in the study (Figure 4.1.1). A patient's first breast cancer diagnosis date was the index date of the study. After the index date, the patient was followed for up to 5 years of survival. Censoring included death, dropping out, reaching the end of the study period, or elapsing of the follow-up time (Figure 4.1.2).

Figure 4.1.1 Sample Flow Chart

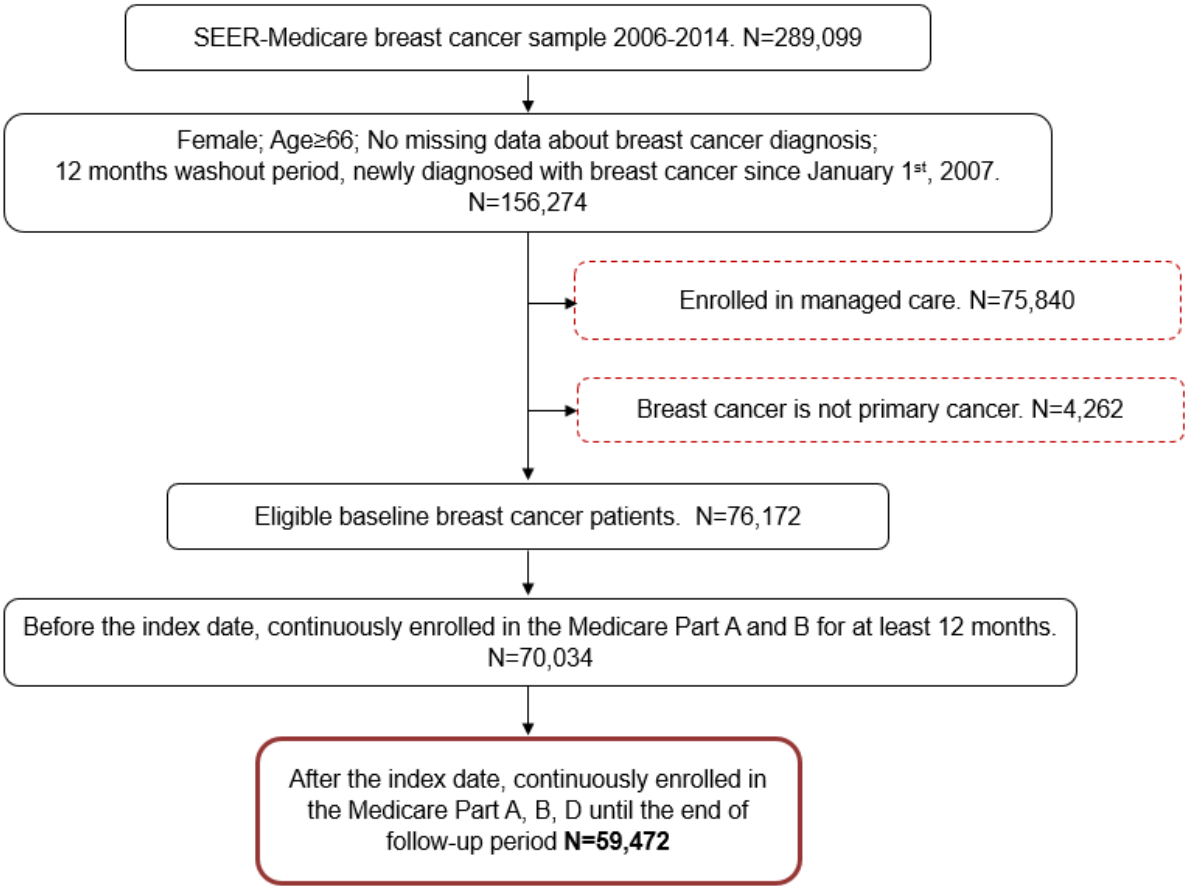
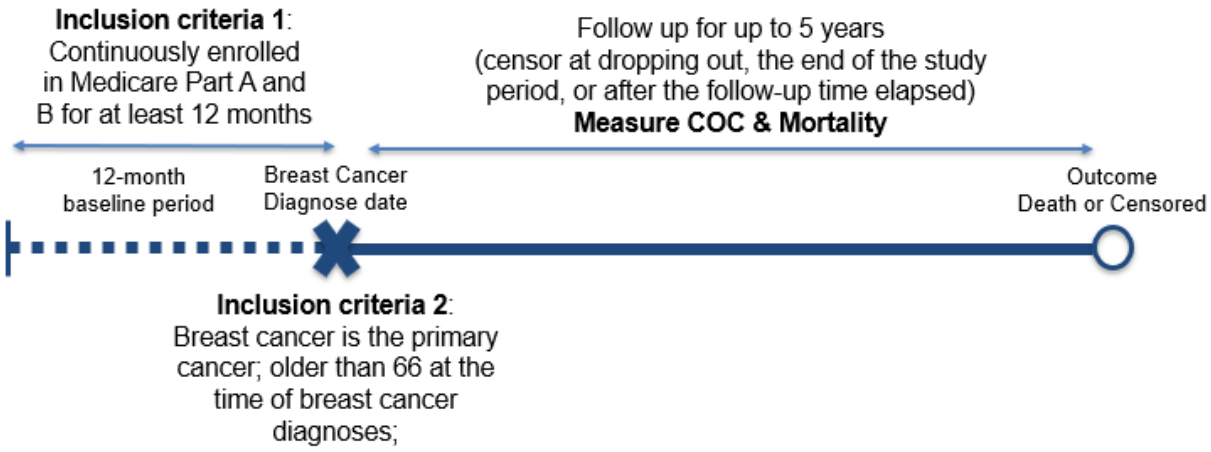


Figure 4.1.2 Study Design



Measurement of Continuity of Care

Several indices have been developed to estimate continuity of care quantitatively.[26,125,192] This study utilized the Bice-Boxerman COC Index,[25] because it was a commonly used empirical measurement for continuity of care, which could enable researchers to obtain timely estimations.[18,54,55,125,193] COC Index measures continuity of care based on individuals' utilization of different providers, which includes an individual's total number of visits for one episode of disease or a certain time period to a single provider or a group of specific providers.[25] Thus, the COC Index counts for both the frequency of visits to each provider and the dispersion of visits between providers.

The general equation to calculate the COC Index is[25]:

$$COC = \frac{\sum_{j=1}^{s} n_j^2 - N}{N(N-1)}$$

To estimate Specialty COC Index: $N =$ the total number of visits; $n =$ the number of visits to provider specialty j; $s =$ the number of provider specialties. To estimate Individual COC Index: $N =$ the total number of visits; $n =$ the number of visits to provider j; $s =$ the number of providers. To get a stable COC Index, this study required $N \geq 4$.[194]

In this study, the COC was measured for each patient within each observation year in two different ways including a Specialty COC Index and an Individual COC Index. Specialty COC Index was calculated based on three health care specialty groups: PCP, Oncologist, and Other (e.g. Cardiology, Endocrinology), which indicated the degree of continuity of care to which a patient visits one group of physician specialists. Individual COC Index was calculated based on each health care provider who involved in patients' care after breast cancer diagnoses. The Individual COC Index reflected the extent of continuity of care to which a patient visits a single health care provider. The COC Index has a scale of 0 (maximum dispersion) to 1 (maximum

concentration). For example, if a patient visited a different health care provider (a single provider for Individual COC, and one provider specialty type for Specialty COC) for each of her visit, the COC Index of this patient was 0. If a patient visited the same health care provider (a single provider for Individual COC, and one provider specialty type for Specialty COC) for all her visits, the COC Index of this patient was 1. Table 4.1.1 demonstrates a few examples of different COC Indices.

In this study, the calculations of COC Indices were only based on outpatient health care providers visits, which were further limited to all outpatient visits with the diagnoses of breast cancer and cardiometabolic diseases (hypertension, hyperlipidemia, or diabetes).[19] Provider specialties included in this study were: primary care provider (PCP), Oncologist, and other specialist (Other). Health care provider specialties were identified from outpatient claims using variable HCFASPEC in outpatient files. PCP included family practice, general practice, internal medicine, obstetrics and gynecology, and geriatrics (HCFASPEC= 01, 08, 11, 16, and 38).[121,195] Oncologist included radiation oncologist, medical oncologist, surgeon, and surgical oncologist (HCFASPEC= 02, 24, 36, 83, 90, 91, 92, and 98).[121,195] Other specialist included all other physician specialists. Variable RFR_UPIN from the outpatient records was used to identify single health care providers. Since cancer patients with cardiometabolic diseases had more frequently visits to physicians than non-physicians, this study only included patients visits to physicians.

Outcome Variables and Covariates

The primary outcome variable was all-cause mortality. A patient's date of death was identified from the SEER's registry and observed for up to 5 years after her initial breast cancer diagnosis. A patient's survival time was the time interval between the date of her initial breast cancer diagnosis and her date of death. An observation was censored at the date of dropping out, reaching the end of the study period, or elapsing of the follow-up time.

A patient's baseline characteristics were obtained from the SEER's registry, and the Medicare claims data. Age groups (66-70, 71-75, 76-80, and >80), race groups (Asian, Black, White, and Other), marriage status (yes and no), poverty levels (0-5%, 5-10%, 10-20%, and 20-100%), regions (Midwest, Northeast, South, and West), and tumor stages (0, I, II, III, and IV) were obtained at the time of the patient's cancer diagnosis. Hypertension (0/1, ICD-9 codes: 401-405), hyperlipidemia (0/1, ICD-9 codes: 272), diabetes (0/1, ICD-9 codes: 250), number of comorbidities (0, 1, 2, and 3), and the Charlson Comorbidity Index (CCI) were identified during the 12-month baseline period. A modified CCI suggested by the NCI was calculated in this study.[84,190,197,198] To avoid the collinear effect, the CCI was adjusted to exclude hypertension, hyperlipidemia, and diabetes.[210] This study also measured breast cancer treatments (surgery, chemotherapy, radiation therapy, and hormone therapy) as individual binary variables which were received by a patient during the entire follow up period. ICD-9 codes from a patient's Medicare claims data were used to identify types of cancer treatment (surgery, ICD-9 codes: 85.2-85.4; chemotherapy, ICD-9 codes: V58.1, V66.2, V67.2; radiation therapy, ICD-9 codes: V58.0; V66.1; V67.1).[42,199] Hormone therapy was identified by NDC codes from the Medicare Part D prescription claims data, including tamoxifen and aromatase inhibitors (AI) (anastrozole, letrozole, and exemestane).[119,138,191]

Statistical Analysis

Descriptive analyses summarized patients' baseline characteristics of each comorbidity groups (0, 1, 2, and 3 comorbidities). Chi-Square tests were used to compare categorical variables. The average COC Indices (Specialty COC Index and Individual COC Index) were calculated annually through 1 to 5 survival years after breast cancer diagnoses. ANCOVA tests were used to compare average COC Indices among different tumor stages or numbers of comorbidities for different years. The Kaplan-Meier curves for the Survival rates of breast cancer patients with different numbers of comorbidities and tumor stages were also plotted.

Cox Proportional-Hazard Models were used to estimate the association of COC Indices with patients' survival. This study selected the most representative baseline characteristics as the covariates for statistical models to avoid over-adjustment. Specifically, the models controlled for demographic information (age, race, marriage, poverty level, and region), comorbidity (hypertension, hyperlipidemia, diabetes, and CCI), breast cancer stage, and breast cancer treatment. The effects of the Specialty COC Index and Individual COC Index on patients' survival were modeled separately. This study divided COC Indices into four levels (1st quartile: 0-25%, 2nd quartile: 26-50%, 3rd quartile:51-75%, and 4th quartile: 76-100%) based on the quartiles of their distributions to present a more intuitive Hazard Ratio (HR). The Specialty COC Index range for each quartile is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.41, 3rd quartile:0.41-0.52, and 4th quartile: 0.52-1. The Individual COC Index range for each quartile is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.33, 3rd quartile:0.33-0.52, and 4th quartile: 0.52-1. Since cancer patient might use highly intensive or dispersed care during the end-of-life, there might be concerns of ambiguous causal ordering.[125,126] This study used lagged effects models to avoid the uncontrollable changes in COC Indices due to the end-of-life.[125,126] Within the lagged effects models, the COC Index from the previous observation year was added as a control variable for the COC Index from the current observation year. The lagged effects models were adjusted for baseline characteristics as well as the COC Index from the previous survival year.

The Cox Proportional-Hazard Model looks like:

$$(start(t), stop(t)) * censor = COC\ (t) + age + race + marriage + region + poverty\ level + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + surgery + chemotherapy + radiationtherapy$$

The lagged effects Cox Proportional-Hazard Model looks like:

$$(start(t), stop(t)) * censor = COC\ (t) + COC(t-1) + age + race + marriage + region + poverty\ level + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + surgery + chemotherapy + radiationtherapy$$

Since patients' characteristics may contribute to their mortality, we conducted sensitivity analyses to test the robustness of this study. Three types of models were conducted for the sensitivity analyses: unadjusted models, partially adjusted models, and models using the first year COC Indices as predictors. Patients with different demographic backgrounds, comorbidities, and cancer treatments may have different risks of mortality. We used unadjusted models which only controlled for survival year to test the models' sensitivity to these covariates. Also, different cancer treatment strategies might contribute to patients' risks of mortality. We used partially adjusted models to determine if the types of cancer treatment undertook by patients contributed to patients' survival. In the partially adjusted models, all covariates from the fully adjusted models in the main analyses were controlled except variables of cancer treatments. Besides these analyses, we also conducted analyses using the first year COC Indices to predict patients' probabilities of survival. These models were used to test the association of COC and mortality's sensitivity to different analysis methods.

4.1.4 Result

Patients' baseline characteristics by the numbers of comorbidities at baseline are presented in Table 4.1.2. The numbers of patients diagnosed with 0, 1, 2, and 3 comorbidities were 15,768 (26%), 16,448 (28%), 19,088 (32%), and 8,168 (13%). The number of patients with each cardiometabolic disease was: Hypertension, 36,603 (62%); Hyperlipidemia, 30,409 (51%); and Diabetes, 12,116 (20%). The percentages of patients diagnosed with stages 0, I, II, III, and IV breast cancer were 17%, 44%, 24%, 7%, and 5%.

To verify whether the COC Index could represent the frequency of visits to each provider and the dispersion of visits between providers within this study cohort, we plotted the changes of total number of visits to each provider type and number of visits to different providers in each type over time (Appendix Figure Aim1.1) as well as the changes of COC Indices over time (Figure 4.1.3). From these plots, COC Indices decreased as the numbers of visits to each provider type increased. However, COC Indices only slightly decreased as the number of visits to different providers increased. Total number of visits to each provider type (PCP, Oncologist, and Other) decreased as survival years increased. Total number of visits to each provider type (PCP, Oncologist, and Other) also decreased as survival years increased. Within these plots, patients' visits to Oncologist decreased the most from year 1 to year 2 after breast cancer diagnoses compared to their visits to PCP or Other.

To explain the details of patients' specialty group visits, we listed out the percentage of visits to each provider specialty group by different Specialty COC Index levels across survival years in Appendix Table Aim 1.8. Patients with the first quartile of Specialty COC Index had equal proportions of visits to PCP, Oncologist, and Other. Patients with the fourth quartile of Specialty COC Index had more concentrated visits to one specific specialty group than others. For example, in the first year, patients with high levels of Specialty COC Index had high

percentages of Oncologist visits. From the second year, patients with high levels of Specialty COC Index had high percentages of Other specialist visits.

Figure 4.1.3 shows the changes of COC Indices over time. All COC Indices increased slightly over time ($p<0.05$). For example, the Specialty COC Index increased from 0.44±0.14 in year 1 to 0.47±0.18 in year 5. The Individual COC Index increased from 0.37±0.21 in year 1 to 0.40±0.25 in year 5. Patients with stage IV breast cancer had the highest average Specialty COC and Individual COC during the entire study period compared to others ($p<0.05$) (Appendix Table Aim1.1).

The Kaplan-Meier curves for survival rates are shown in Figure 4.1.4. The probability of survival decreased with advanced breast cancer stages. Patients with stages I, II, III, and IV breast cancer had significantly lower probabilities of survival compared to patients with stage 0 breast cancer ($p<0.001$). For example, patients with stage IV breast cancer had the lowest survival probability during the whole study period compared to others. The survival probability for these patients declined from 95% to 46% during the entire study period. However, the probability of survival for patients with stage 0 breast cancer remained above 90% during the whole study period. Similarly, the overall survival probability decreased with the numbers of comorbidities($p<0.001$). Patients with 3 comorbidities had the lowest survival probability while patients with 0 comorbidity had the highest survival probability during the entire study period.

The adjusted Hazard Ratios (HRs) of mortality with and without lagged effects control are presented in Figure 4.1.5 and Figure 4.1.6 respectively. Given the temporal precedence established with the lagged model, we have more confidence in the results of this model than the contemporaneous model(Figure 4.1.5). Patients with high levels of Specialty COC Index (4th vs 1st quartile, HR:1.34, 95%CI 1.29-1.40; 3rd vs 1st quartile, HR:1.59, 95%CI 1.52-1.65; 2nd vs 1st quartile, HR:1.34, 95%CI 1.28-1.39) had higher risks of mortality than those with the lowest level of Specialty COC Index. However, patients with high levels of Individual COC Index

(4th vs 1st quartile, HR:0.53, 95%CI 0.51-0.54; 3rd vs 1st quartile, HR:0.57, 95%CI 0.55-0.59; 2nd vs 1st quartile, HR:0.67, 95%CI 0.64-0.69) had lower risks of mortality than those with the lowest level of Individual COC Index. Sensitivity analyses by unadjusted models and partially adjusted models found similar results with the fully adjusted models (Figure 4.1.5 and 4.1.6). Models using the first year COC Indices to predict patients' probabilities of survival also got similar results (Appendix Table Aim1.6-7).

4.1.5 Discussion

To our knowledge, this is the first longitudinal study that analyzed the association between continuity of care and the risk of mortality within breast cancer patients who had cardiometabolic comorbidities. After controlling for a number of potential confounding characteristics, we found significant associations between continuity of care and the risk of mortality based on two types of COC Indices. These associations were consistent in all sensitivity analyses with or without lagged effects. The lagged effects models avoid the ambiguous causal ordering caused by the increased need for specialist care at the end-of-life.[125,126]. However, the results were contradictory among different types of COC Indices. Even though higher continuity of care to an individual provider was significantly associated with reduced mortality risks, higher continuity of care to a specialty group was significantly associated with increased mortality risks.

Our findings of Individual COC inversely associated with the risks of mortality were consistent with most previous studies. For example, one study found that patients with mental disorders had a lower mortality risk (HR=0.83, 95%CI: 0.83-0.83) when they had a higher psychiatrists continuity of care.[126] Another study found that patients had a lower mortality risk (HR=0.96, 95%CI: 0.95–0.96) when they had a higher PCP continuity of care.[36] Similarly, studies that did not use the COC Index also found that continuity visits to an individual provider was associated with a lower mortality risk.[16,34] The protective effect of high continuity of care to an individual provider on patients' mortality risk could be explained by their effects of reducing incomplete information, preventing overlapping or contradictory care, and improving the quality of care during health care management. Cancer patients with multiple comorbidities need to see various health care specialists. However, these specialists might not communicate adequately during the follow-up care of cancer patients with comorbidities.[1] Consequently, health care providers often faced challenges from incomplete information, overlapping or contradictory care

when making treatment decisions for cancer patients with comorbidities.[1,6] Also, continuity of care is an important prerequisite for the quality of care during health care management.[21,22] Patients with high continuity of care to an individual provider were more focused on visiting one health care provider and had continuity of care from the provider. Therefore, the treatment barriers caused by poor coordination between multiple health care providers could be reduced. Thus, patients could receive better quality of care and result in a lower risk of mortality.

However, our findings of Specialty COC proportionally associated with the risks of mortality were different from our findings of Individual COC models. Unfortunately, only limited studies reported similar results. For example, two previous studies both found increased COC linked with increased risks of mortality based on all physician visits.[127,211]

The first explanation of the associations of high continuity of care (Specialty COC) and high risks of mortality might be the types of medical disciplines involved in the analysis. Due to the definition, the Specialty COC Index was calculated based on specialty groups (PCP, Oncologist, or Other) and measured the continuity of care based on a patient's utilization of different specialty groups. Whereas, the Individual COC Index were calculated based on individual health care providers and measured the continuity of care based on a patient's utilization of individual providers. Thus, even though a patient visited providers within the same specialty group, she might still visit multiple individual providers. For example, if a patient only visited different PCPs, she would have a high Specialty COC Index and a low Individual COC Index. Thus, patients with high mortality risk could have high continuity of care to a specialty group while still have low continuity of care to an individual provider.

The second explanation of these associations may be the uncontrolled confounding factors due to the unmeasured disease severity of breast cancer and comorbidities. For instance, patients who had severe side effects from cancer treatments or patients with slow recovery processes from their breast cancer might need to have frequent visits to oncologists.

Then, these patients would have high continuity of care to a specialty group. A previous study found that breast cancer patients with undetected comorbidities had a higher mortality rate than others.[196] Therefore, although these patients had high continuity of care based on specialty groups, their heavy disease burdens would still cause a high risk of mortality.

The third explanation of these associations could be patients' behavior which includes patients' care-seeking behavior and lifestyle modification. For example, patients who followed medical instructions and paid regular visits to their health care providers might have low continuity of care to a specialty group if they were suggested to visit multiple specialty groups. These patients would benefit from visiting multiple specialty groups and might have a low risk of mortality. However, the referral to multiple providers might cause less continuous care. Since these providers are more likely to be temporary providers that step in when there is a high risk to the patient. Plus, lifestyle modification is very important for patients with cardiometabolic diseases. However, it is hard to control for lifestyle modification in claims data analyses. Patients with poor lifestyle modifications might have a higher risk of mortality although they might have better continuity of care to a specialty group.

Our research is subject to several limitations. First, we included female breast cancer patients older than 66 who did not enroll in managed care. Thus, our results might not be generalizable to breast cancer patients who are male, younger than 66 or have other health insurance. Second, we were not able to control for all confounding factors related to disease severity. For instance, cancer treatment could get different responses and cause varieties of serious adverse events. Plus, patients' disease severities of their cardiometabolic diseases are hard to control. Previous research found undetected comorbidities could cause higher mortality risk.[36,196] In this study, we did our best to control for cancer stage, cancer treatment, comorbidities, and the CCI. Third, we could not detect patients' behavior by using claims data. Patients' care seeking behavior is closely related to their health care outcomes. Also, lifestyle

modification is an important treatment strategy for patients with cardiometabolic diseases.[63,93] Unfortunately, the SEER-Medicare data does not include information about patients' behavior. The limitation of the data set prevented us from controlling for patients' care-seeking behavior and lifestyle modification in our study. Fourth, patients' visits to other health care providers (e.g., nurse practitioners or physician assistants) were not included in the study. Therefore, the findings of our study only reflect the continuity of care based on patients' visits to physicians. Future studies including non-physician providers are needed. Fifth, our study only used the records of patients' visits to outpatient physician offices for the calculations of COC Indices. Thus, we could not detect the influence of continuity of care on the risk of mortality during inpatient stays, which might cause biased results. Sixth, the calculation of the COC Index has limitations. To get a stable COC Index, we followed the suggestion by previous research, which only includes patients who had the records of more than 4 visits to a specific provider or a specialty group per time interval.[194] Therefore, patients with less than 4 visits were excluded from the study. These patients might have less disease burden compared with patients with more than 4 visits. Plus, we excluded the records without valid HCFASPEC values or RFR_UPIN values during the calculations of the COC Indices. Thus, the health care services provided by these physicians were missed in our study.

In addition, the Bice-Boxerman COC Index measures the continuity of care that a patient had with her health care provider during the process of health care management.[24] Therefore, the COC Index reflects the continuity of care but not the coordination of health care providers.[23] Previous studies proved that the COC Index is sensitive to the concentration of unique provider visits but not sensitive to patients' total health care provider visits.[24,194] Unfortunately, the COC Index could only show patients' overall provider visits without the details regarding the interactions between patients and providers. These details of interactions could be studied through patient and provider surveys.[125] However, the COC Index is a convenient assessment

for continuity of care, which could be obtained from medical claims data. Thus, studying the association of the COC Index and health outcome could get a timely estimation of the effect of continuity of care on health outcome. Also, we could ensure the robustness of our study with the help of multiple sensitivity analyses.

This study provided empirical evidence of the associations of continuity of care with mortality risk within breast cancer patients who had cardiometabolic comorbidities. We found mixed associations of COC Indices and mortality risks. Better continuity of care to an individual provider was significantly related to lower risks of mortality. However, better continuity of care to a specialty group was significantly related to higher risks of mortality. The mixed associations might be caused by types of medical disciplines, patient subgroups, uncontrolled disease severities, patients' behavior, and treatment processes. These results indicated that concentrated individual provider visits could protect patients from all-cause mortality. Whereas, concentrated specialties visits could cause a high risk of mortality in patients. The contradictory results of different COC models provoked the needs for further studies. In the future, better understandings of the continuity of care based on different medical disciplines are needed. These future studies should be conducted in different care settings for different cancer types within wide varieties of patient populations. Also, the evidence provided by this study should be considered carefully by policymakers and others when guiding future changes in the health care delivery system. Notably, it is essential to building the models of continuous and coordinated care and helping improve the quality of care for cancer survivorship.

Table 4.1.1 Continuity of Care Index Calculation

Variables	P1*	P2*	P3*	Total Visit	COC Index
	1	1	1	3	0.000
	0	1	2	3	0.333
	0	0	3	3	1.000
	6	1	1	8	0.536
	5	2	1	8	0.393
	4	3	1	8	0.321
	4	2	2	8	0.286
	3	3	2	8	0.250
	4	4	0	8	0.429
	3	5	0	8	0.464
	2	6	0	8	0.571
	1	7	0	8	0.750

*P1/P2/P3 could be provider specialty groups or each provider. For the Specialty COC Index, P1/P2/P3 would be PCP/Oncologist/Other group. For the Individual COC Index, P1/P2/P3 would be three different providers.

Table 4.1.2 Baseline Characteristics of Breast Cancer Patients with Different Numbers of Comorbidities

		Number of Comorbidities				
Characteristics	Level	0	1	2	3	All
N(%)						
All		15768	16448	19088	8168	59472
Age*	66-70	4937(31.31%)	3745(22.77%)	3620(18.96%)	1664(20.37%)	13966(23.48%)
	71-75	4417(28.01%)	4037(24.54%)	4695(24.60%)	2194(26.86%)	15343(25.80%)
	76-80	2910(18.46%)	3374(20.51%)	4363(22.86%)	1923(23.54%)	12570(21.14%)
	>80	3504(22.22%)	5292(32.17%)	6410(33.58%)	2387(29.22%)	17593(29.58%)
Race*	Asian	170(1.08%)	185(1.12%)	292(1.53%)	158(1.93%)	805(1.35%)
	Black	514(3.26%)	734(4.46%)	1033(5.41%)	858(10.50%)	3139(5.28%)
	Other	390(2.47%)	391(2.38%)	515(2.70%)	302(3.70%)	1598(2.69%)
	White	14694(93.19%)	15138(92.04%)	17248(90.36%)	6850(83.86%)	53930(90.68%)
Marriage*	Yes	8188(51.93%)	7952(48.35%)	9028(47.30%)	3750(45.91%)	28918(48.62%)
	No	7580(48.07%)	8496(51.65%)	10060(52.70%)	4418(54.09%)	30554(51.38%)
Region*	Midwest	2605(16.52%)	2672(16.25%)	2777(14.55%)	1124(13.76%)	9178(15.43%)
	Northeast	6741(42.75%)	7063(42.94%)	7708(40.38%)	3134(38.37%)	24646(41.44%)
	South	5088(32.27%)	5368(32.64%)	6953(36.43%)	3289(40.27%)	20698(34.80%)
	West	1334(8.46%)	1345(8.18%)	1650(8.64%)	621(7.60%)	4950(8.32%)
Poverty*	0-5%	4585(29.08%)	4648(28.26%)	5376(28.16%)	1996(24.44%)	16605(27.92%)
	5-10%	4831(30.64%)	4815(29.27%)	5598(29.33%)	2334(28.57%)	17578(29.56%)
	10-20%	4164(26.41%)	4399(26.74%)	5066(26.54%)	2279(27.90%)	15908(26.75%)
	20-100%	2022(12.82%)	2379(14.46%)	2798(14.66%)	1422(17.41%)	8621(14.50%)
	Unknown	166(1.05%)	207(1.26%)	250(1.31%)	137(1.68%)	760(1.28%)
Hypertension	0	15768(100.00%)	6112(37.16%)	989(5.18%)	-	22870(38.45%)

	1	-	10336(62.84%)	18099(94.82%)	8168(100.00%)	36603(61.55%)
Hyperlipidemia	0	15768(100.00%)	11202(68.11%)	2093(10.97%)	-	29064(48.87%)
	1	-	5246(31.89%)	16995(89.03%)	8168(100.00%)	30409(51.13%)
Diabetes	0	15768(100.00%)	15582(94.73%)	16006(83.85%)	-	47357(79.63%)
	1	-	866(5.27%)	3082(16.15%)	8168(100.00%)	12116(20.37%)
Tumor Stage*	0	2357(14.95%)	2803(17.04%)	3352(17.56%)	1352(16.55%)	9864(16.59%)
	I	6572(41.68%)	7235(43.99%)	8656(45.35%)	3415(41.81%)	25878(43.51%)
	II	3724(23.62%)	3868(23.52%)	4357(22.83%)	2049(25.09%)	13998(23.54%)
	III	1189(7.54%)	1087(6.61%)	1215(6.37%)	621(7.60%)	4112(6.91%)
	IV	1148(7.28%)	651(3.96%)	743(3.89%)	369(4.52%)	2911(4.89%)
	Unknown	778(4.93%)	804(4.89%)	765(4.01%)	362(4.43%)	2709(4.56%)
Surgery*	0	12907(80.43%)	13200(79.74%)	15245(79.62%)	6277(76.72%)	47629(79.47%)
	1	3140(19.57%)	3354(20.26%)	3903(20.38%)	1905(23.28%)	12302(20.53%)
Chemotherapy*	0	14027(87.41%)	14788(89.33%)	17197(89.81%)	7248(88.58%)	53260(88.87%)
	1	2020(12.59%)	1766(10.67%)	1951(10.19%)	934(11.42%)	6671(11.13%)
Radiation Therapy	0	12190(75.96%)	12505(75.54%)	14527(75.87%)	6293(76.91%)	45515(75.95%)
	1	3857(24.04%)	4049(24.46%)	4621(24.13%)	1889(23.09%)	14416(24.05%)
Hormone Therapy*	0	13758(85.74%)	13965(84.36%)	15919(83.14%)	6758(82.60%)	50400(84.10%)
	1	2289(14.26%)	2589(15.64%)	3229(16.86%)	1424(17.40%)	9531(15.90%)
CCI (mean ± std)		0.16±0.48	0.41±0.80	0.60±1.01	0.87±1.29	0.47±0.92

* Chi Square test, P-value<0.05.

Table 4.1.2 showed patients' characteristics of the study population for patients with different numbers of comorbidities. Number and percentage of patients in each level of covariates were counted and compared by Chi-square distribution.

Figure 4.1.3 Average Continuity of Care Index among Breast Cancer Patients during the whole study period.

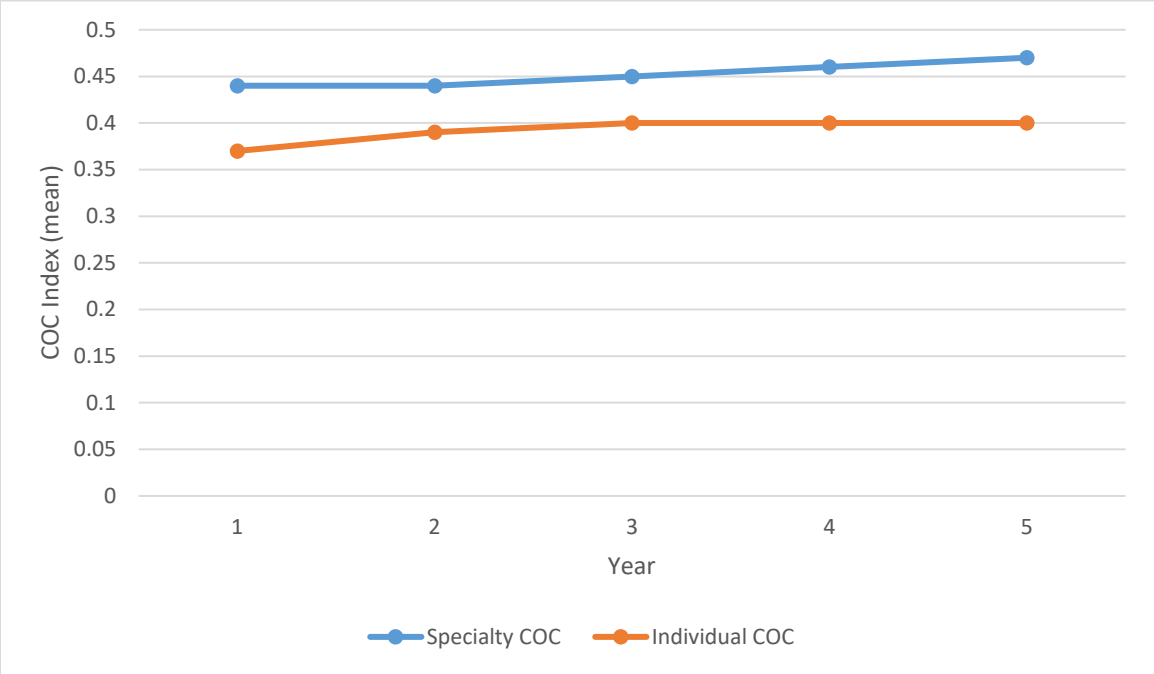
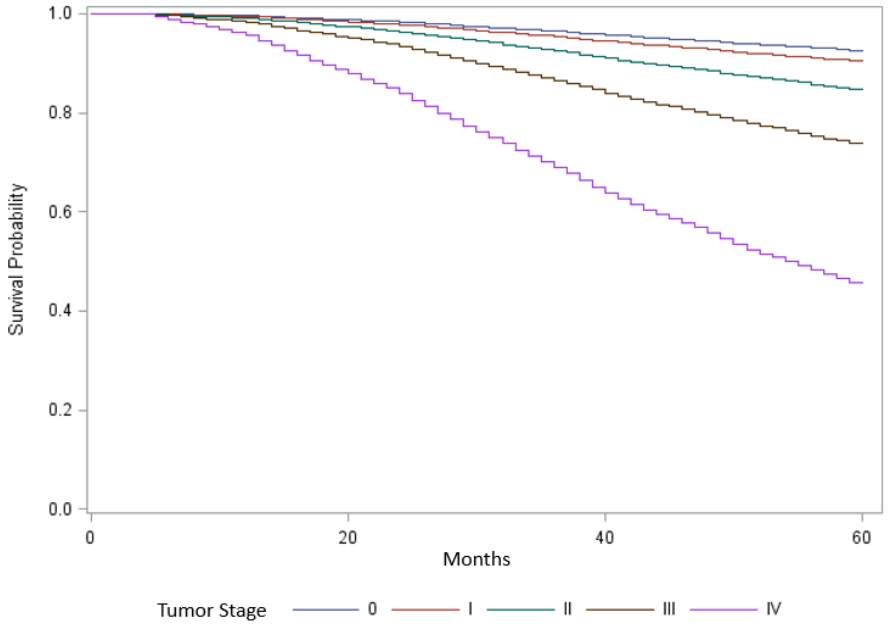


Figure 4.1.3 illustrated the COC Index change during the whole study period for each type of COC Index (Specialty, Individual). ANCOVA analyses were applied to compare the average COC among different years.

Figure 4.1.4 Kaplan-Meier Curve for the Survival Rate of Breast Cancer Patients

A. Tumor Stage (tumor stage I vs. 0, HR=1.32; tumor stage II vs. 0, HR=2.18; tumor stage III vs. 0, HR=4.11; tumor stage IV vs. 0, HR=12.52; p<0.001)



B. Numbers of Comorbidities (comorbidities 1 vs. 0, HR=1.25; comorbidities 2 vs. 0, HR=1.25; comorbidities 3 vs. 0, HR=1.52; p<0.001)

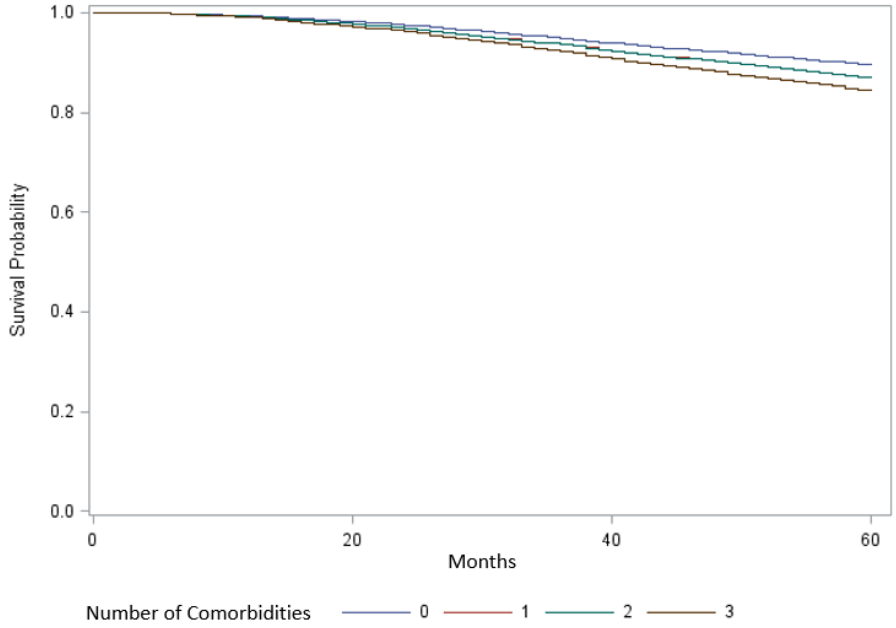
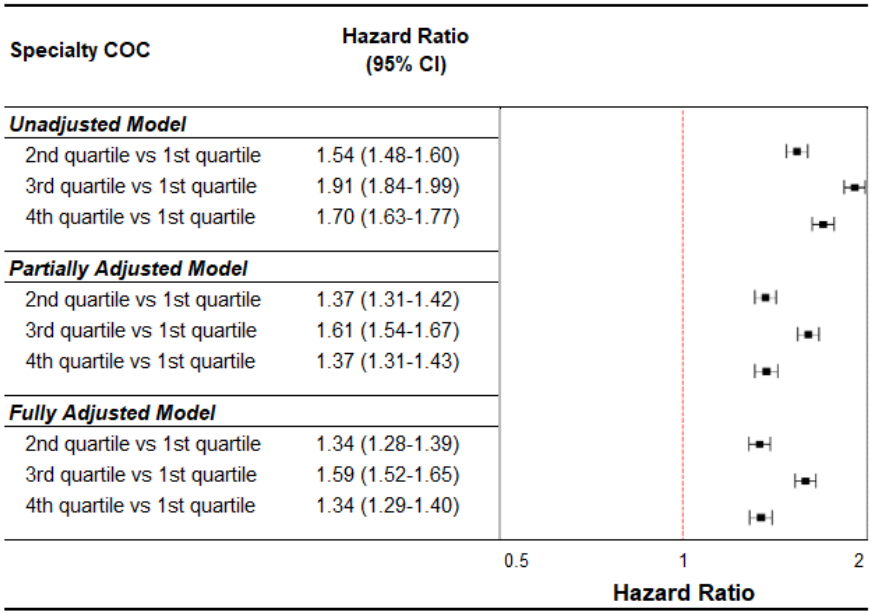


Figure 4.1.4 illustrated the Kaplan-Meier curves for the survival rates of breast cancer patients with different numbers of comorbidities and tumor stages

Figure 4.1.5 Effect of Continuity of Care on the Hazard Ratio of Mortality, with lagged effects.

A. Specialty COC



B. Individual COC

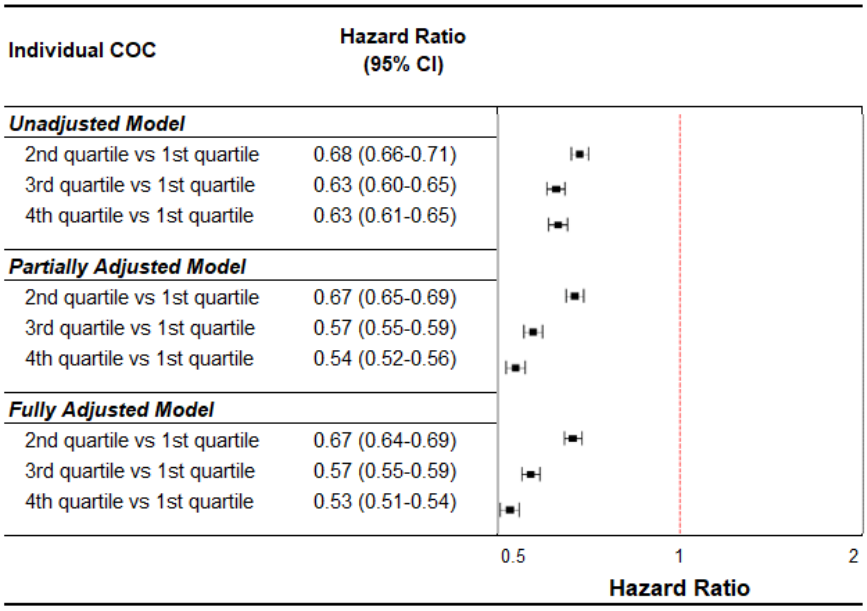
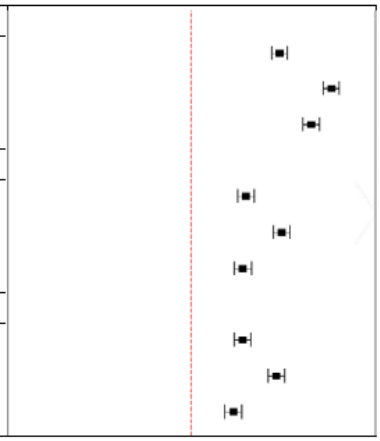


Figure 4.1.5 showed the forest plots for the effect of continuity of care on the Hazard Ratio of mortality, with lagged effects. Cox Hazard models generated the results adjusting for the lagged COC Indices from the previous year. The unadjusted models used the COC indices as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Figure 4.1.6 Effect of Continuity of Care on the Hazard Ratio of Mortality.

A. Specialty COC

Specialty COC	Hazard Ratio (95% CI)
Unadjusted Model	
2nd quartile vs 1st quartile	1.40 (1.35-1.44)
3rd quartile vs 1st quartile	1.70 (1.65-1.75)
4th quartile vs 1st quartile	1.57 (1.52-1.62)
Partially Adjusted Model	
2nd quartile vs 1st quartile	1.23 (1.19-1.27)
3rd quartile vs 1st quartile	1.41 (1.36-1.45)
4th quartile vs 1st quartile	1.22 (1.18-1.25)
Fully Adjusted Model	
2nd quartile vs 1st quartile	1.22 (1.18-1.25)
3rd quartile vs 1st quartile	1.38 (1.34-1.42)
4th quartile vs 1st quartile	1.17 (1.14-1.21)



B. Individual COC

Individual COC	Hazard Ratio (95% CI)
Unadjusted Model	
2nd quartile vs 1st quartile	0.67 (0.65-0.69)
3rd quartile vs 1st quartile	0.63 (0.61-0.65)
4th quartile vs 1st quartile	0.68 (0.66-0.70)
Partially Adjusted Model	
2nd quartile vs 1st quartile	0.65 (0.63-0.67)
3rd quartile vs 1st quartile	0.58 (0.56-0.59)
4th quartile vs 1st quartile	0.56 (0.54-0.58)
Fully Adjusted Model	
2nd quartile vs 1st quartile	0.65 (0.63-0.67)
3rd quartile vs 1st quartile	0.57 (0.55-0.59)
4th quartile vs 1st quartile	0.55 (0.53-0.56)

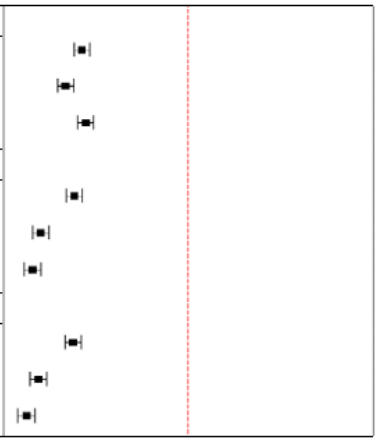


Figure 4.1.6 showed the forest plots for the effect of continuity of care on the Hazard Ratio of mortality. Cox Hazard models generated the results. The unadjusted models used the COC indices as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were adjusted for age group, race, marriage, poverty

level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

4.2 Aim 2 Results

4.2.1 Abstract

Background: Breast cancer patients with comorbidities need to take multiple medications and see multiple healthcare providers. Continuity of care across these providers may influence patients' medication taking behavior.

Objective: To determine hormone therapy adherence, cardiometabolic medication adherence, and the association of medication adherence and continuity of care (COC) among breast cancer patients with cardiometabolic diseases.

Methods: Female breast cancer patients who had hormone therapy prescriptions within 12-month of cancer diagnoses were identified from the SEER-Medicare data (2006-2014). Patients were followed for up to four years after hormone therapy initiation. The Yearly COC Index was measured with a scale of 0 (dispersed) to 1 (concentrated) reflecting the frequency and dispersion of healthcare provider visits. The Specialty COC Index was measured based on unique specialist groups (Primary Care Physicians (PCP), Oncologists, and Other specialists (Other)). The Individual COC Index was measured based on each healthcare provider. The primary outcome was medication adherence, defined as the proportion of days coverage (PDC)≥80% and PDC<80%. Mixed-effect logistic regression models analyzed the associations of the COC Index and medication adherence to hormone therapy, antihypertensives, hyperlipidemia medications, and diabetes medications.

Results: A total of 8,081 breast cancer patients who took hormone therapy and cardiometabolic medications (antihypertensives: 5,817; hyperlipidemia medications: 3,767; diabetes medications: 1,082) were eligible for the study. The adherence rates for Hormone Therapy from year 1 to year 4 decreased from 74.48% to 64.40%. Patients with higher levels of Specialty COC Index were less likely to adhere to antihypertensives (4^{th} vs. 1^{st} quartile, Odd Ratio (OR)

0.86, 95%CI 0.76-0.96) and hyperlipidemia medications (4th vs. 1st quartile, OR 0.81, 95%CI 0.70-0.94). Patients with higher levels of Individual COC Index were more likely to adhere to hyperlipidemia (4th vs. 1st quartile, OR 1.17, 95%CI 1.01-1.36) and diabetes medications (4th vs. 1st quartile, OR 1.51, 95%CI 1.12-2.00).

Conclusion: A high percentage of breast cancer patients didn't adhere to their long-term Hormone Therapy. The increased Individual COC Index and the decreased Specialty COC Index were associated with better medication adherence to cardiometabolic medications. The associations found in our study should be considered carefully by policymakers when developing the interventions of improving medication therapy for cancer patients with cardiometabolic diseases. These interventions could be adjusting the current health care service to a more individual provider concentrated and specialties coordinated format, such as locking into a practice or promoting cancer related medical home model.

4.2.2 Introduction

Close to 70% of breast cancer patients are estrogen receptor-positive (ER+).[64,71] Plus, about 28% of breast cancer patients have cardiometabolic diseases including hypertension, hyperlipidemia, and diabetes.[87,88] According to clinical practice guidelines, a minimum of five years of hormone therapy has been recommended for ER+ breast cancer patients.[40] Thus, most breast cancer patients with cardiometabolic comorbidities may need long term treatments for breast cancer as well as comorbidities.[69,130] Previous research found that five years of adjuvant tamoxifen treatment significantly reduced patients' mortality rate by 31%.[41] Besides, medication treatment of cardiometabolic diseases could significantly reduce cardiovascular morbidity and mortality rates ($p<0.05$).[96-98] However, many breast cancer patients with comorbidities failed to adhere to their medications.[37,42,136,137] For example, only 40-70% of breast cancer patients could finish their five-year hormone therapy (HT).[42,136,137] By the end of their second-year hormone therapy, patients' adherence rates for antihypertensives, statins, and oral diabetes medications were 62%, 61%, and 24% respectively.[37] Multiple factors contribute to nonadherence, one of them is the fragmented health care system in the United States.[46]

Within the fragmented health care system, cancer patients with comorbidities often need to visit different health care providers for their cancer and comorbidities.[3,33] A previous study found, for cancer patients, the proportion of physician office visits to primary care providers (PCP), oncologists, and other specialists were 32%, 18%, and 50% respectively.[1] Patients with multiple health care provider visits were more likely to have poor medication adherence.[15] In fact, the risks of discontinuing hormone therapy were 23-41% higher in breast cancer patients with comorbidities than in those without comorbidities.[42-45] Although strategies were developed to promote communication and coordination among health providers for cancer survivorship,[115] previous studies did not report significant effects of these strategies on medication adherence.[57] The highly dispersed health care provider visits could lead to poor continuity of care.[23]

Therefore, concerns regarding the association of medication adherence and continuity of care were raised by researchers.[4,8,9,150]

Continuity of care (COC) is the degree to which one patient and his/her health care provider cooperated and connected during the process of health care management, which includes information continuity, relational continuity, and management continuity.[23-25] Continuity of care could be measured by Bice-Boxerman COC Index, which measures management continuity and counts for patients' discrete and concentrated provider visits.[26]. COC could affect patients' medication adherence.[18,47-49] Limited studies have been done for the association of COC and cardiometabolic medications adherence. Mixed effects of COC on medication adherence were reported. For example, patients with higher COC had higher adherence to diabetes medication (OR=3.37, 95%CI 3.15-3.60)[18] and statins (OR=6.10, 95%CI: 5.90-6.30)[47]. However, no significant association of COC and medication adherence were found in the usage of antihypertensives.[48,49] In the U.S. health care system, specialists and PCPs have different roles and responsibilities for the follow-up care of cancer patients with comorbidities.[1] Therefore, cancer patients with comorbidities were more likely to receive poor continuity of care after their cancer diagnoses.[1] The situation is even worse for ER+ breast cancer patients who have cardiometabolic comorbidities. Previous studies found breast cancer patients with cardiometabolic diseases had poor medication adherence to their HT and cardiometabolic medications.[37,42,136,137] To the best of our knowledge, no research has been done for the association of COC and medication adherence within breast cancer patients who had cardiometabolic comorbidities. Plus, it is not clear about the different roles of continuity of care in medication adherence based on health care provider specialties and individual providers respectively. Thus, studies are needed to help to understand the association of COC and medication adherence within these patients.

The purpose of this study was to determine the association of COC and medication adherence to hormone therapy and cardiometabolic medications in breast cancer patients with cardiometabolic comorbidities. The medications in this study included oral hormone therapy medications, antihypertensives, hyperlipidemia medications, and oral diabetes medications.

4.2.3 Method

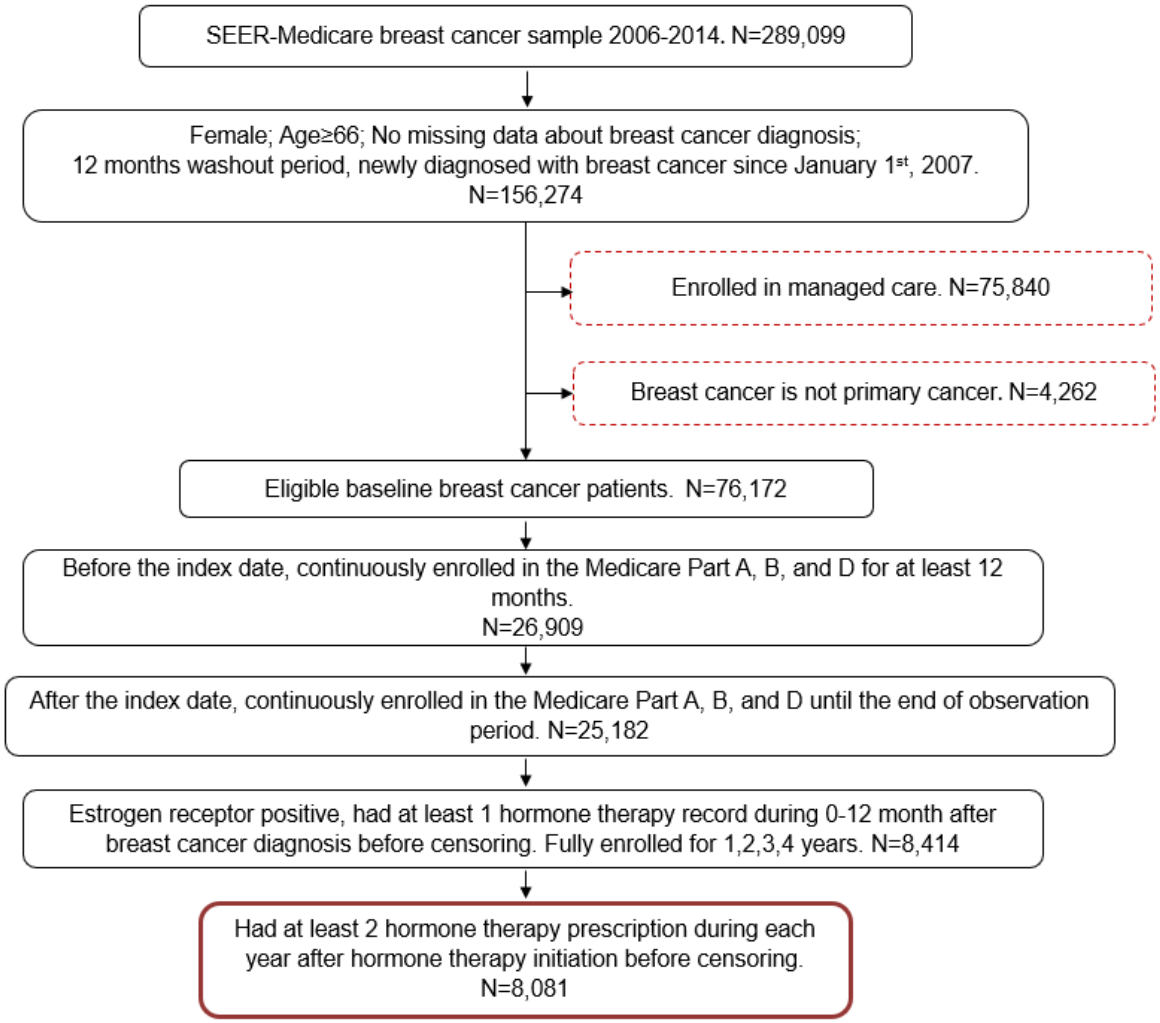
Study Design and Sample

This study used the Surveillance, Epidemiology and End Results (SEER) linked Medicare Claims data from 2006 to 2014. The linkage of SEER-Medicare data is supported by the SEER registry, the National Cancer Institution (NCI), and the Centers for Medicare and Medicaid Services (CMS). The SEER registry data contained clinical records, demographic information, and mortality information for cancer patients. Medicare claims data included medication records, health care service utilizations, and costs.

A longitudinal study was conducted within a group of SEER-Medicare patients who had estrogen receptor-positive breast cancer and cardiometabolic diseases from 2006 to 2014. This study used a new user design to identify patients who initiated hormone therapy (HT) within one year after their first breast cancer diagnoses. A prevalent cohort was used for cardiometabolic medication treatments. The follow up of this cohort started from the date of HT initiation. We limited the study population to female breast cancer patients who (1) were older than 66; (2) were diagnosed with positive estrogen receptor forms of breast cancer; (3) continuously enrolled in Medicare Part A, B, and D for a 12-month baseline period before their initial breast cancer diagnoses; (4) received at least one prescription of oral HT within one year after breast cancer diagnosis; (5) continuously enrolled in Medicare Part A, B, and D until the end of the observation period; and (6) received at least two prescriptions of HT during each observation year. The date of first HT prescription was defined as the Index date of the study. Patients were excluded if they did not have breast cancer as their primary cancer (n=4,262). Patients were also excluded if they were enrolled in a managed care program (n=75,840), since managed care program contained medical claims which were undetectable in Medicare data. The selected patients were followed for up to 1, 2, 3, or 4 full years after HT initiation. Within each observation year, eligible patients should have at least 2 prescriptions of HT. The observation

would be considered missing for that observation year if a patient had less than 2 prescriptions of HT during that time interval. The resulting cohort included a total of 8,081 patients with 16,080 person-years of observation (Figure 4.2.1). The diagnosis of breast cancer (ICD-O-3 C500-509) and status of estrogen receptor (ER) were identified in SEER registry data.[187] Cardiometabolic diseases were identified as a patient with at least one inpatient visit or two outpatient visits during the baseline period of cardiometabolic diseases in her Medicare claims (hypertension ICD-9 401-405, hyperlipidemia ICD-9 272, and diabetes ICD-9 250).[106,188-190] The predictor (Continuity of Care (COC)) and outcome variable (medication adherence) of this study were measured cross-sectionally within each observation year after HT initiation.

Figure 4.2.1 Study Sample Flow Chart



Measurement of Continuity of Care

The Bice-Boxerman Continuity of Care (COC) Index was calculated to measure continuity of care, which could be applied based on individual providers or provider specialty groups [25] The COC Index reflects a patient's concentration of visiting one provider or one specialty group during a specific period.[25] This Index has been commonly used in previous studies to measure the continuity of care for patients who had multiple comorbidities.[125]

In this study, two types of COC Indices were calculated separately based on patients' visits to groups of health care provider specialties (Specialty COC Index) and a single health care provider of all specialties (Individual COC Index). The health care provider specialties included in this study were: PCP, Oncologist, and Other specialties. When constructing the COC Indices, only conditions (breast cancer, hypertension, hyperlipidemia, and diabetes[19]) related provider visits in outpatient claims were included in the study and the COC Indices were measured yearly after patients' HT initiation. According to the suggestion from previous research, this study required at least 4 total provider visits to calculate a stable COC Index.[194] The COC Index has a range of 0 to 1. A high COC Index score stands for concentrated continuity of care, while a low COC Index score stands for dispersed continuity of care.

Measurement of Medication Adherence

According to patients' HT and cardiometabolic medication treatments, the therapeutic groups in this study were: HT, antihypertensives, hyperlipidemia medications, and diabetes medications. Since this study used a prevalent cohort for cardiometabolic medication treatments, the measurement of all selected medication usages started from the date of HT initiation. Oral HT included tamoxifen and aromatase inhibitors (AI) (anastrozole, letrozole, and exemestane).[119,138,191] For antihypertensives, this study selected the most frequently prescribed drugs included diuretics, β-blockers, calcium-channel blockers, angiotensin-converting enzyme

inhibitors, and angiotensin receptor blockers.[106] Hyperlipidemia medications included statins.[101,106] For diabetes medications, this study focused on all oral medication treatment of type II diabetes (metformin, sulfonylureas, thiazolidinediones, and all others).[106] The selected medications were identified by the National Drug Code (NDC) codes from the Medicare Part D data.

Patients' adherence to oral HT, antihypertensives, hyperlipidemia medications, and diabetes medications were measured separately by using Proportion of Days Coverage (PDC) based on the Medicare Part D claims data. PDC was widely used by previous studies to measure medication adherence of a class of drugs which were used for concomitant therapy or had switches of medications within the class.[106,200] To reduce the underestimation of medication adherence caused by patients' inpatient visits, this study used an adjusted PDC excluding the days of inpatient stays from the observation period.[201]

The PDC was measured for each patient annually within each therapeutic group (HT, antihypertensives, hyperlipidemia medications, and diabetes medications) after the index date (HT initiation) (equation 1). First, a supply-matrix was built for each patient. The matrix recorded the supply of each medication class for each day of the whole study period within therapeutic groups. Next, the days of supply for each prescription were added to the prescription filling date. If the days covered by the prescriptions were overlapped, the next prescription filling date would be adjusted to the next date of the previous prescription running out. Then, the supply-matrix was partitioned into submatrices for each observation year. Fourth, within each observation year, the days covered were estimated by adding the days of supply which had at least one medication within the therapeutic group from the first prescription observed date until the end of that year. Then, PDC was calculated by dividing the days covered by the days evaluated adjusted for hospital stays within that year(equation 1).[118,202] To get a reliable measurement of medication adherence, only patients who filled more than two prescriptions within the same

therapeutic group were included in the study. This medication class based PDC calculation might cause potential overestimation of medication adherence. Still, it could accommodate the complications of measuring adherence for concomitant therapy or switching of medications within the class.[118,202] Patients were classified as adherent when PDC ≥ 80% and non-adherent when PDC < 80%.[106,135,201,203,204]

$$PDC = \frac{Days\ between\ A\ and\ D, with \geq 1\ drug\ available}{Days\ between\ A\ and\ Interval\ end - hospital\ stay} \quad \text{(equation 1)}$$

Covariates

Covariates of this study were identified from the SEER registry data and the Medicare claims data. Patients' characteristics were identified from SEER registry data during the baseline period, which included age group (66-70, 71-75, 76-80, and >80), race (Black, White, and Other), marriage status (Yes and No), poverty level (0-5%, 5-10%, 10-20%, 20-100%), region (Midwest, Northeast, South, West), and tumor stage (0, I, II, III, and IV). Patients' existing cardiometabolic diseases (hypertension (Yes/No), hyperlipidemia (Yes/No), and diabetes (Yes/No)) were identified from the Medicare claims data during the baseline period. Comorbidities were measured by the NCI Charlson Comorbidity Index (CCI) using patients' Medical claims during the baseline period.[84,190,197,198] To avoid collinear effects, this study excluded conditions that are related to hypertension, hyperlipidemia, and diabetes from the calculation of the CCI.[210] Breast cancer treatments (including surgery, chemotherapy, radiation therapy, and hormone therapy) were identified for each patient yearly after HT initiation. Due to the small proportions of patients using surgery (2%), chemotherapy (6%), and radiation therapy (19%), this study combined these cancer treatments together as one binary covariate. ICD-9 codes from patients' Medicare claims identified surgery, chemotherapy, and radiation therapy (surgery, ICD-9 codes: 85.2-85.4; chemotherapy, ICD-9 codes: V58.1, V66.2, V67.2; radiation

therapy, ICD-9 codes: V58.0; V66.1; V67.1).[42,199] Hormone therapy (tamoxifen and AI) was identified by the NDC codes from the Medicare Part D data.[119,138,191]

Statistical Analysis

Descriptive statistics summarized patients' baseline characteristics for each medication theraputic group. The average COC Index scores (Specialty COC Index and Individual COC Index) of each year after HT initiation were also calculated. Patients' adherence to HT, antihypertensives, hyperlipidemia medications and diabetes medications were estimated yearly by patients' medication records through the study period.

Mixed effects logistic regression models controlling for the random effect of individuals were used to estimate the association of the COC Index and the likelihood of adherence, where the Specialty COC Index and the Individual COC Index were modeled separately. The analyses were adjusted for demographic characteristics (age group, race, marriage, poverty level, and region), tumor stages, existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes), CCI, and other cancer treatments. To avoid unbalanced covariates caused by a very small proportion of observations in surgery, chemotherapy, and radiation therapy (Table 4.2.1), we grouped these treatments as one variable called other cancer treatment in the regression models. To better interpret the clinical meaning of COC Indices and their associations with medication adherence, we divided COC Indices into quartiles (0-25% as 1st quarter, 26-50% as 2nd quarter, 51-75% as 3rd quarter, and 76-100% as 4th quarter) based on the COC Index distributions for mixed-effect logistic regression analyses. The Specialty COC Index range for each quartile is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.40, 3rd quartile:0.40-0.49, and 4th quartile: 0.49-1. The Individual COC Index range for each quartile is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.32, 3rd quartile:0.32-0.50, and 4th quartile: 0.50-1. Since the continuity of care has more influence on patients' medication adherence during the current year, this study did not

control for the lagged effect of the COC Index in regression models. The fully adjusted mixed-effect logistic regression model looks like (equation 2):

$$logit(adherence) = COC + age + race + marriage + poverty\ level + region + \ tumor\ stage + other\ cancer\ treatment + hypertension + hyperlipidimia + diabetes + CCI + year$$

(equation 2)

Sensitivity analyses were performed to test the robustness of the models. We used models with fewer covariates to check the models' covariates sensitivity. First, patients' demographic backgrounds, comorbidities, and cancer treatments might associate with their medication adherence. Thus, the unadjusted logistic regression was conducted, within which the analysis was only adjusted for years after HT initiation. Second, patients might discontinue their concurrent medications when a new cancer treatment was started. Therefore, to test the model's sensitivity of patients' cancer treatment other than HT, the partially adjusted logistic regression model was built, controlling for all covariates in the fully adjusted models except for the other cancer treatment. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary NC)

4.2.4 Result

This study identified 8,081 female hormone-receptor-positive breast cancer patients in the SEER-Medicare data between January 2006 and December 2014. These patients started hormone therapy within 12 months after breast cancer diagnoses. The baseline characteristics of patients in therapeutic groups of hormone therapy (HT) (n=8,081), HT plus antihypertensives (n=5,817), HT plus hyperlipidemia medications (n=3,767), and HT plus diabetes medications (n=1,082) are presented in Table 4.2.1. The population contained 3% Black, 4% Other, and 93% White. For different age groups, the population distributions were 26% (age 66-70), 29% (age 71-75), 21% (age 76-80), and 24% (age >80). The percentage of patients had stage 0, I, II, III, and IV breast cancer at diagnoses were 1.79%, 55.96%, 29.74%, 6.66%, and 3.38%. The percentage of patients from Midwest, Northeast, South, and West were 14.18%, 41.65%, 35.97%, and 8.19%.

Figure 4.2.2 shows the average COC Index scores for each therapeutic group during the whole study period. The average scores of the Specialty COC Index were slightly lower in patients who adhered to antihypertensives and hyperlipidemia medication than in those who did not. For example, the average scores of the Specialty COC Index of patients taking antihypertensives ranged from 0.43 (year 1) to 0.43 (year 4) for the adherence group but ranged from 0.43 (year 1) to 0.45 (year 4) for the non-adherence group. The average scores of the Individual COC Index were slightly higher in patients who adhered to their medications than in those who did not adhere to their medications. For example, the average scores of the Individual COC Index ranged from 0.41 (year 1) to 0.49 (year 4) for the adherence group of diabetes medications but ranged from 0.39 (year 1) to 0.39 (year 4) for the non-adherence group.

Figure 4.2.3 illustrates the proportions of patients who adhered and did not adhere to their medications (HT, antihypertensives, hyperlipidemia medications, and diabetes

medications) at each year after HT initiation. The numbers of patients who had HT were 8,081 (year 1), 4,555 (year 2), 2,444 (year 3), and 1,000 (year 4). During the four years follow-up period after HT initiation, the percentage of patients who adhered to HT decreased by 10% (74.48% to 64.40%, year 1 to year 4). Similarly, the proportions of patients who adhered to antihypertensives, hyperlipidemia medications, and diabetes medications decreased by 6% (75.43% to 69.82%, year 1 to year 4), 3% (64.40% to 61.72%, year 1 to year 4), and 12% (66.08% to 53.97%, year 1 to year 4) respectively.

Patients' likelihood of adherence to medication therapy was estimated by mixed-effect logistic regression models and illustrated in forest plots (Figure 4.2.4 and 4.2.5, full models in appendix table Aim 2.2-5). In the fully adjusted models, patients were less likely to adhere to all medications when their levels of Specialty COC Index were higher. The associations were not significant in HT adherence with ORs of 0.92 (2^{nd} vs. 1^{st} quartile, 95%CI 0.83-1.01), 0.91 (3^{rd} vs. 1^{st} quartile, 95%CI 0.82-1.01), and 0.97 (4^{th} vs. 1^{st} quartile, 95%CI 0.87-1.08). However, the associations were significant in antihypertensives adherence (3^{rd} vs. 1^{st} quartile, OR: 0.86, 95%CI 0.76-0.97; 4^{th} vs. 1^{st} quartile, OR: 0.86, 95%CI 0.76-0.98) and hyperlipidemia medications adherence (4^{th} vs. 1^{st} quartile, OR: 0.81, 95%CI 0.70-0.94). Patients were more likely to adhere to cardiometabolic medications when their levels of Individual COC Index were higher. The associations were not significant in HT adherence with OR of 1.03 (4^{th} vs. 1^{st} quartile, 95%CI 0.92-1.15). However, the associations were significant in the adherence of hyperlipidemia medications (3^{rd} vs. 1^{st} quartile, OR=1.16, 95%CI 1.01-1.34; 4^{th} vs. 1^{st} quartile, OR=1.17, 95%CI 1.01-1.36) and the adherence of diabetes medications (2^{nd} vs. 1^{st} quartile, OR=1.40, 95%CI 1.04-1.87; 4^{th} vs. 1^{st} quartile, OR=1.50, 95%CI 1.12-2.00).

Similar results were obtained in the sensitivity analyses using the unadjusted and partially adjusted models. The results of the unadjusted and partially adjusted models are

presented in Figure 4.2.4 and 4.2.5. The results of the full models of fully adjusted and partially adjusted models are presented in Appendix Table Aim 2.2 to Appendix Table Aim 2.5.

4.2.5 Discussion

This study estimated the association of continuity of care and medication adherence in 8,081 breast cancer patients who had cardiometabolic comorbidities. We compare the effect of two types of COC Indices (Specialty COC Index and Individual COC Index) on four therapeutic groups separately (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). After controlling for patients' characteristics, our fully adjusted models found significant associations among COC and medication adherence (Figure 4.2.3, Appendix Table Aim 2.2-11). High continuity of care to a specialty group was associated with low medication adherence however high continuity of care to an individual provider was associated with high medication adherence. Similar results were obtained in the sensitivity analyses using unadjusted models and partially adjusted models. To our knowledge, the present study is among the first that focused on the association of continuity of care and medication adherence in breast cancer patients with cardiometabolic comorbidities.

Our study showed high individual continuity of care was associated with high medication adherence to medications for hyperlipidemia and diabetes. The positive associations agreed with the findings of previous studies. These studies suggested continuity of care and access to care are very critical to medication adherence.[150,175] Poor coordination and continuity of care can lead to low medication adherence.[179] Warren et al. found patients with a high COC Index level had more likelihood of adherence to statins (RR=1.05, 95%CI 1.04-1.07).[17] Chen et al. reported patients with a high COC Index level had more likelihood of adherence to diabetes medications (RR=3.37, 95%CI 3.15-3.60).[18] Our findings suggested that the concentrated visits to individual health care providers could have positive effects on medication adherence. Future studies in different study settings are needed to provide more evidence in the research area.

However, our study also showed, high continuity of care to a specialty group resulted in lower adherence to medications for hypertension and hyperlipidemia. Since very little research

has been done for the association of COC and Medication adherence, no published results showed the inverse associations between high COC and low medication adherence. Still, studies did acknowledge that they could not find clear evidence of the association between COC and medication adherence.[48,212] For example, Uijen et al. found, for heart failure patients, the continuity of care based on Specialty groups had no significant impact on patients' medication adherence.[48] Robles et al. acknowledged that there was no significant association between continuity of care based on all provider visits and antihypertensive adherence.[212] The results of the Specialty COC models suggested that the dispersed visiting of multiple health care specialties could have a positive influence on medication adherence. The different results between the Individual COC and the Specialty COC models provoked the needs of future studies. The future studies should estimate the impact of continuity of care to a specialty group as well as to an individual provider of various medical disciplines in patients within different settings.

The mixed findings in our study could be interpreted in several alternative ways. First, we included different medical disciplines in this study for different COC Indices. Since the COC Index could be applied based on an individual provider or provider specialty groups,[25] the Specialty COC Index in this study was calculated based on provider specialty groups (PCP, Oncologist, and Other) and measured patients' continuity visiting of health care specialty groups. In contrast, the Individual COC Index was calculated based on a patient's visits to individual providers and measured patients' continuity visiting of individual providers. Therefore, the patient might have different continuity of care according to the definitions of different COC Indices. For example, if a patient had a total of four visits to four individual PCP during a time interval, her Individual and Specialty COC Indices could be 0 (low continuity of care based on each individual providers) and 1 (high continuity of care based on specialty groups) respectively. Plus, a previous study showed that COC Indices calculated based on different medical

disciplines could have different effects on patients' mortality.[127] Thus, the mixed associations between COC Indices and medication adherence found in our study are understandable.

Second, there might be uncontrollable confounding factors that could affect our results. Medication adherence can be influenced by patient-related factors, condition-related factors, therapy-related factors, socioeconomic factors, and health system factors.[46] Patients' characteristics like younger age, ethnic minority, and lower education level were found to be significantly associated with medication non-adherence in patients with cardiometabolic diseases or breast cancer.[151-155] Actually, we found similar results in our study (Appendix Table 2-6). The findings of our study showed patients who were older, or Black were less likely to adhere to their HT. Patients who were married or had higher CCIs were less likely to adhere to their antihypertensives. Patients who were younger or minorities (Black or Other) were less likely to adhere to their hyperlipidemia medication. Patients who were minorities (Black or Other) or had higher CCIs were less likely to adhere to their diabetes medication. Condition-related and therapy-related factors could also influence medication adherence. Previous studies suggested that depression and adverse drug events could significantly reduce patients' HT adherence despite the recommendations of cancer treatment.[161,162,164] Therefore, these uncontrollable confounding factors could affect patients' medication adherence regardless of their continuity of care.

Third, patients' behavior is essential to their medication adherence. Patients who follow the instructions from their health care providers are more likely to adhere to their medication treatments. Also, these patients might be more likely to pay regular visits focused on specific health care providers and have high continuity of care to an individual provider. However, cancer patients with comorbidities might have to visit multiple health care specialties.[3,33] Therefore, these patients could also have low continuity of care to a specialty group. Thus,

patients with high continuity of care to an individual provider and low continuity of care to a specialty group are more likely to adhere to their medications.

We observed decreased medication adherence rates in all four therapeutic groups over the follow-up period (Figure 4.2.2), which is consistent with some previous studies. For example, Hershman studied HT adherence in breast cancer patients and found the adherence rate decreased from 63% to 59% from year 1 to year 4.[42] Similarly, the HT adherence rate change in our study was 74% to 64% from year 1 to year 4. Vrijens et al. found the probability of adherence to antihypertensives decreased 50% during a one-year observation period within hypertension patients.[213] Our study found a 6% decrease in antihypertensive adherence during the 4-year observation period within breast cancer patients who had hypertension. However, our observations of patients' adherence to hyperlipidemia and diabetes medications overtime were different from previous studies. We found decreased medication adherence to hyperlipidemia and diabetes medications over the follow-up period. Previous studies found increased medication adherence to statins and diabetes medications within their longitudinal analyses.[18,214] These differences might be caused by different settings between their studies and our study. Their studies focused on the adherence to cardiometabolic medications within non-cancer patients. However, our study focused on medication adherence within breast cancer patients with cardiometabolic comorbidities. The barriers of medication adherence within cancer patients are even more complicated than others.[164] For example, breast cancer patients might experience serious adverse drug events or severe drug-drug interactions during their treatment processes which might affect their medication adherence.[164] As a previous study showed, after two-year HT, patients' adherence rates for antihypertensives, statins, and oral diabetes medications were 62%, 61%, and 24% respectively.[37]

This study has several limitations. First, we only included breast cancer patients older than 66, since SEER-Medicare data only included the records of elderly cancer patients.

Previous research showed breast cancer patients within younger age groups might have different HT adherence.[42] Therefore, in future research, it could be helpful to study the association of continuity of care and medication adherence within breast cancer patients who had younger ages. Second, we were unable to address all potential confounding factors, which included undetected comorbidities, care-seeking behavior, lifestyle, drug-drug interaction, and adverse drug event. Previous studies found these confounding factors had significant effects on patients' medication adherence and health outcomes. [46,161,162,164,196] We did not control for the number of medications in our study. However, since the number of medications correlated with the number of comorbidities and disease severity, we controlled for patients' comorbidities and CCI Index in our study. Previous research also found low-income subsidy for Medicare part D might affect patients' medication adherence.[215] However, we did not directly control for patients' eligibility of low-income subsidy. Instead, we controlled for patients' poverty levels, since patients' poverty levels could decide their eligibility for the low-income subsidy.[216] Third, our study only included patients who had more than 4 provider visits per year to get stable COC Indices.[194] Thus, medication adherence in patients who had less than 4 provider visits remains unknown. Fourth, the measurement we used for medication adherence might cause overestimation. To get a reliable measurement, we only included patients with more than 2 prescriptions within the same therapeutic group of that time interval when calculated medication adherence. These patients could have higher PDC than patients with less than 2 prescriptions of that year. Also, the medication adherence in our study was estimated based on medication class to accommodate the complication of switching and concomitant therapy within the same class.[118,202]. Thus, we overestimate medication adherence by considering switching and concomitant therapy within the same class as continued treatment. Plus, we used adjusted PDC excluding patients' hospital stays for each time interval.[201] Therefore, patients' PDC estimation would be higher than their actual PDC. Fifth, there was missing data due to the prerequisites of PDC and the COC Index calculations in our longitudinal study. A patient with less than 2

prescriptions did not have a valid PDC of that year. A patient with less than 4 provider visits did not have a valid COC Index of that year. However, a reliable imputation method was applied for the missing data during our statistical analysis.[217]. Sixth, the application of the COC Index might not be able to reflect the details of patient-provider interaction and provider-provider cooperation. However, the COC Index could allow us to get timely estimations of continuity of care and patients' health outcomes. Seventh, the calculation of COC Indices did not include patients' all health care provider visits. For example, patients' visits to non-physicians (e.g., nurse practitioners or physician assistants) were not included. Patients' visits to providers without valid HCFASPEC or RFR_UPIN values were also excluded from the calculations of COC Indices. Thus, the continuity of care based on these provider visits was not included in our study and needed further investigation.

The present study examined the association of COC and medication adherence. Our findings contributed to the growing research interest of cancer survivorship care by providing empirical evidence of the association of continuity of care and medication adherence. The result of this study showed that high percentages of breast cancer patients didn't adhere to their long-term HT. Increased continuity of care to an individual provider was associated with patients' better medication adherence to cardiometabolic medications, which indicated the protective effect of the concentrated visiting to individual providers on medication adherence. However, increased continuity of care to a specialty group was associated with patients' lower medication adherence to medications, which indicated the negative effect of concentrated visiting to provider specialties on medication adherence. Thus, the findings in our study should be considered carefully by policymakers when developing the interventions of improving medication therapy for cancer patients with cardiometabolic diseases. These interventions could be adjusting the current health care service to a more individual provider concentrated and

specialties coordinated format, such as locking into a practice, or promoting cancer related medical home model.

Table 4.2.1 Baseline Characteristics of Breast Cancer Patients, who Receive Hormone Therapy, Antihypertensives, Hyperlipidemia Medications, and Diabetes Medications

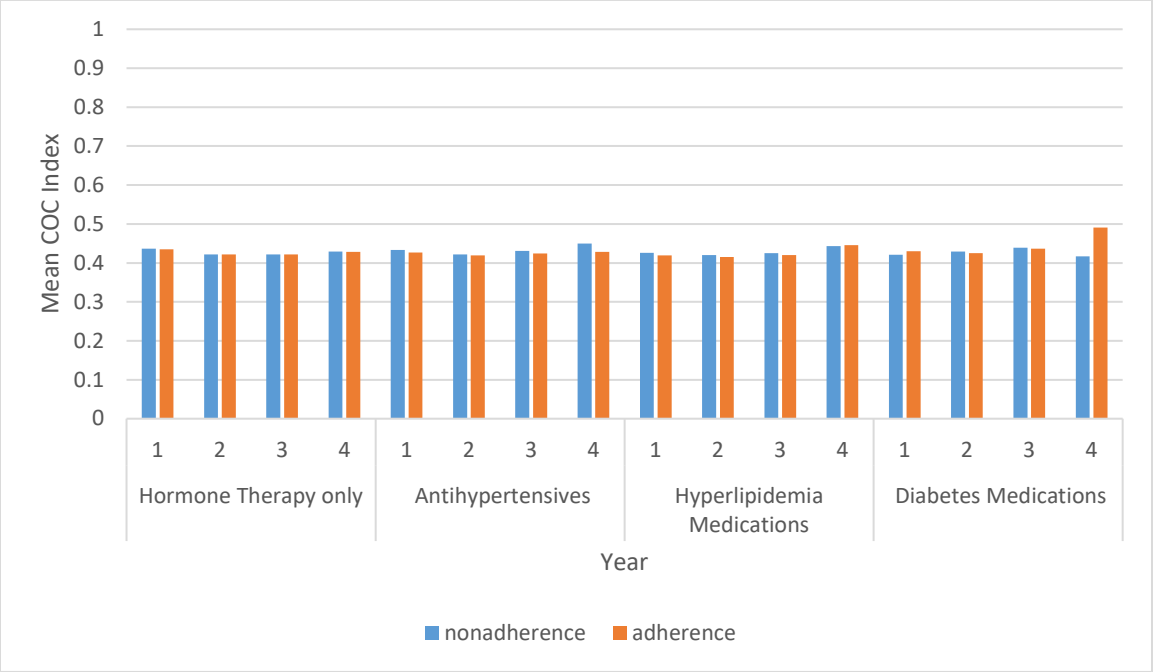
Characteristics	Level	Hormone Therapy	Hormone Therapy & Antihypertensives	Hormone Therapy & Hyperlipidemia Medications	Hormone Therapy & Diabetes Medications
N(%)					
All		8081	5817	3767	1082
Age	66-70	2063 (25.53%)	1298 (22.31%)	893 (23.71%)	297 (27.45%)
	71-75	2321 (28.72%)	1623 (27.90%)	1093 (29.02%)	333 (30.78%)
	76-80	1717 (21.25%)	1298 (22.31%)	850 (22.56%)	228 (21.07%)
	>80	1980 (24.50%)	1598 (27.47%)	931 (24.71%)	224 (20.70%)
Race	Black	218 (2.70%)	194 (3.34%)	108 (2.87%)	50 (4.62%)
	Other	317 (3.92%)	218 (3.75%)	141 (3.74%)	52 (4.81%)
	White	7546 (93.38%)	5405 (92.92%)	3518 (93.39%)	980 (90.57%)
Marriage	marriage	4032 (49.89%)	2767 (47.57%)	1879 (49.88%)	525 (48.52%)
	other	4049 (50.11%)	3050 (52.43%)	1888 (50.12%)	557 (51.48%)
Poverty	0-5%	2297 (28.42%)	1595 (27.42%)	1054 (27.98%)	257 (23.75%)
	5-10%	2417 (29.91%)	1727 (29.69%)	1139 (30.24%)	280 (25.88%)
	10-20%	2096 (25.94%)	1514 (26.03%)	980 (26.02%)	320 (29.57%)
	20-100%	1086 (13.44%)	837 (14.39%)	504 (13.38%)	188 (17.38%)
	unknown	185 (2.29%)	144 (2.48%)	90 (2.39%)	37 (3.42%)
Region	Midwest	1146 (14.18%)	829 (14.25%)	550 (14.60%)	149 (13.77%)
	Northeast	3366 (41.65%)	2366 (40.67%)	1530 (40.62%)	456 (42.14%)
	South	2907 (35.97%)	2131 (36.63%)	1373 (36.45%)	406 (37.52%)
	West	662 (8.19%)	491 (8.44%)	314 (8.34%)	71 (6.56%)
Tumor Stage	0	145 (1.79%)	102 (1.75%)	89 (2.36%)	580 (53.60%)

	I	4522 (55.96%)	3222 (55.39%)	2187 (58.06%)	329 (30.41%)
	II	2403 (29.74%)	1738 (29.88%)	1080 (28.67%)	84 (7.76%)
	III	538 (6.66%)	412 (7.08%)	225 (5.97%)	41 (3.79%)
	IV	273 (3.38%)	199 (3.42%)	97 (2.57%)	21 (1.94%)
	unknown	200 (2.47%)	144 (2.48%)	89 (2.36%)	14 (2.23%)
Hypertension					
	0	2924 (36.42%)	1251 (21.61%)	997 (26.53%)	194 (17.98%)
	1	5104 (63.58%)	4538 (78.39%)	2761 (73.47%)	885 (82.02%)
Hyperlipidemia					
	0	3498 (43.57%)	2238 (38.66%)	842 (22.41%)	284 (26.32%)
	1	4530 (56.43%)	3551 (61.34%)	2916 (77.59%)	795 (73.68%)
Diabetes					
	0	6300 (78.48%)	4304 (74.35%)	2667 (70.97%)	972 (90.08%)
	1	1728 (21.52%)	1485 (25.65%)	1091 (29.03%)	104 (16.67%)
Surgery					
	0	8008 (98.35%)	6045 (98.36%)	4083 (98.55%)	1213 (98.46%)
	1	134 (1.65%)	101 (1.64%)	60 (1.45%)	19 (1.54%)
Chemotherapy					
	0	7634 (93.76%)	5770 (93.88%)	3923 (94.69%)	1149 (93.26%)
	1	508 (6.24%)	376 (6.12%)	220 (5.31%)	83 (6.74%)
Radiation Therapy					
	0	6597 (81.02%)	5012 (81.55%)	3392 (81.87%)	1009 (81.90%)
	1	1545 (18.98%)	1134 (18.45%)	751 (18.13%)	223 (18.10%)
CCI (mean(std))					
		0.45 (0.87)	0.52 (0.94)	0.53 (0.96)	0.54 (0.98)

Table 4.2.1 showed patients' characteristics of the study of each therapeutic group. Number and percentage of patients in each level of covariates were counted.

Figure 4.2.2 The COC Index of Breast Cancer Patients, who Receive Hormone Therapy, Antihypertensives, Hyperlipidemia Medications, and Diabetes Medications

A. Specialty COC



B. Individual COC

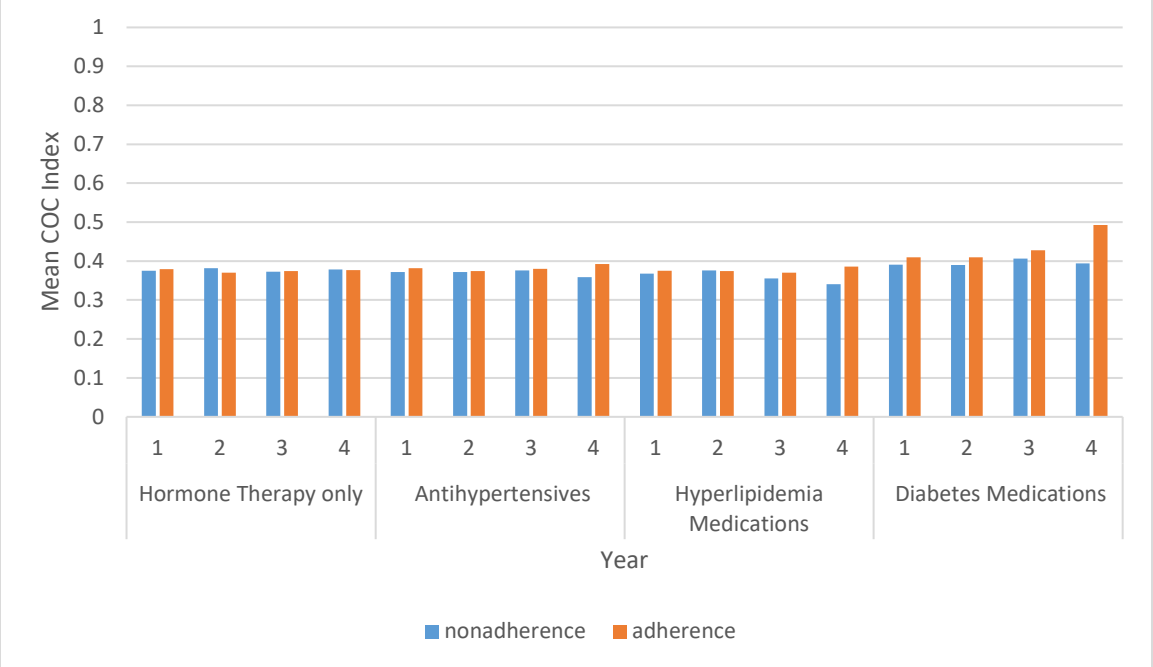
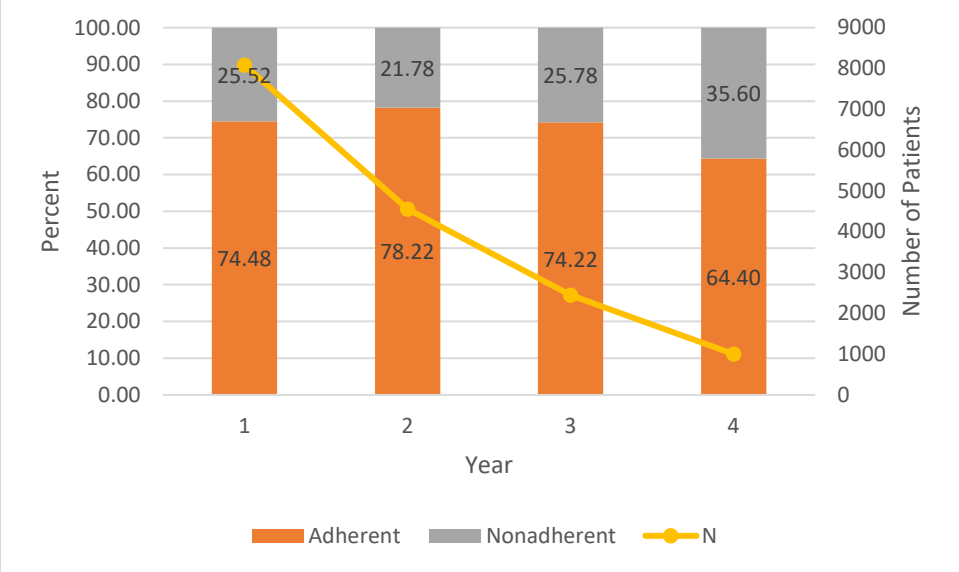


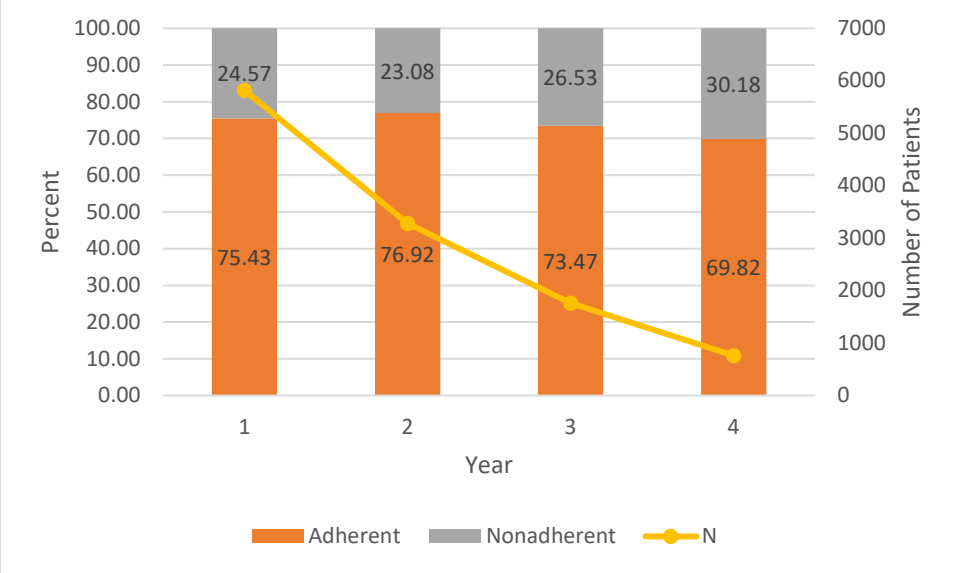
Figure 4.2.2 showed the mean (std) COC Index (Specialty and Individual) change during the whole study period for each therapeutic group (HT, antihypertensives, hyperlipidemia medications, and diabetes medications).

Figure 4.2.3 Proportion of Adherent and Non-adherent Breast Cancer Patients on Medication Therapy by Therapeutic Class, with time intervals of 1 year during the whole study period

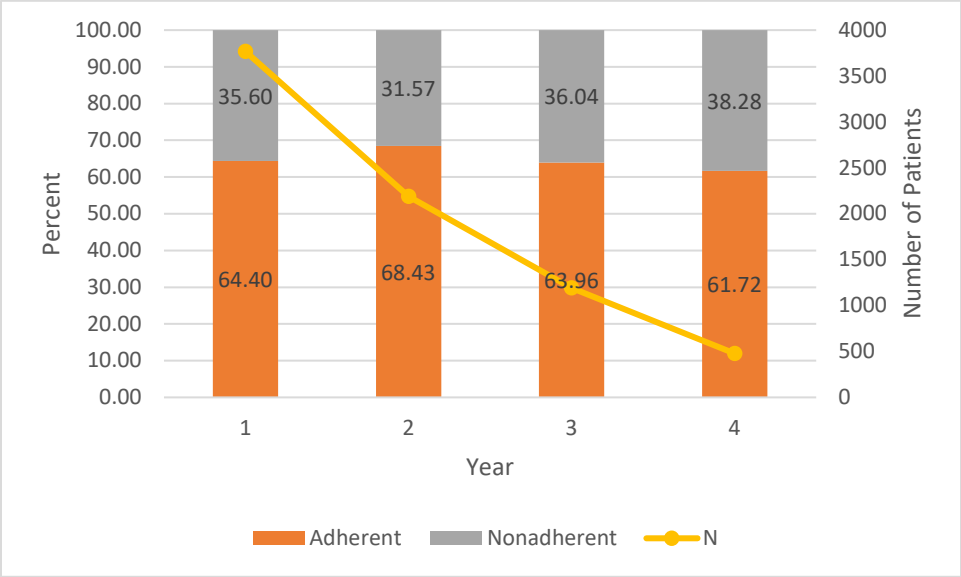
A. Hormone Therapy



B. Antihypertensives



C. Hyperlipidemia Medications



D. Diabetes Medications

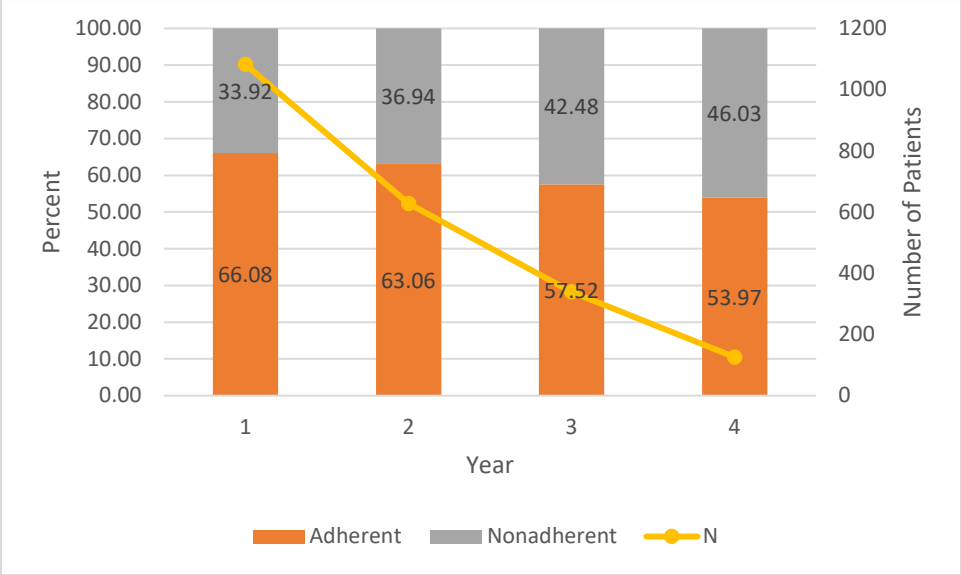
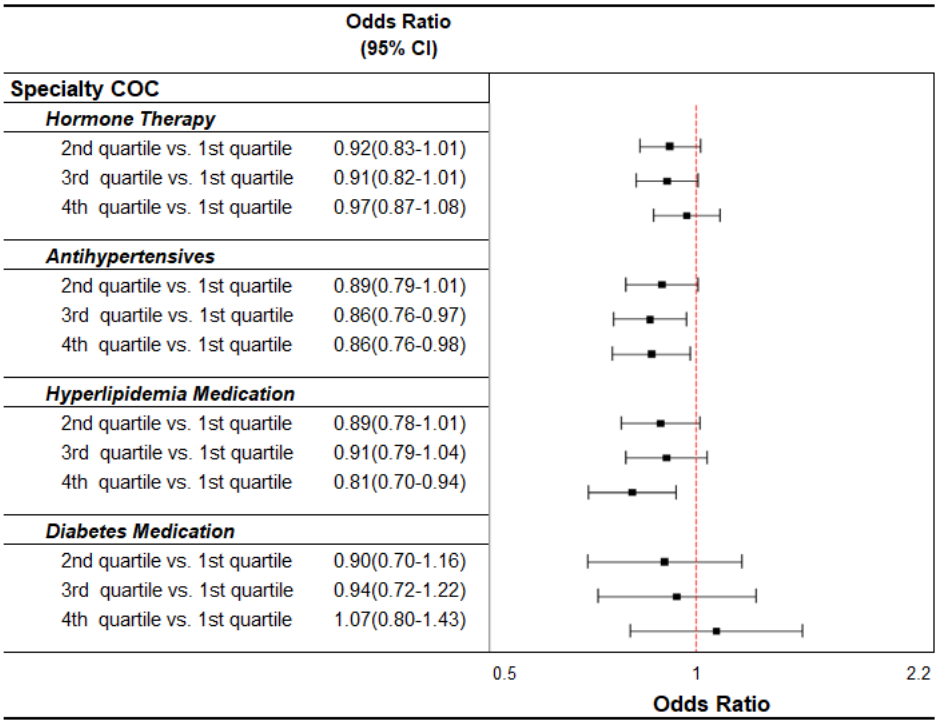


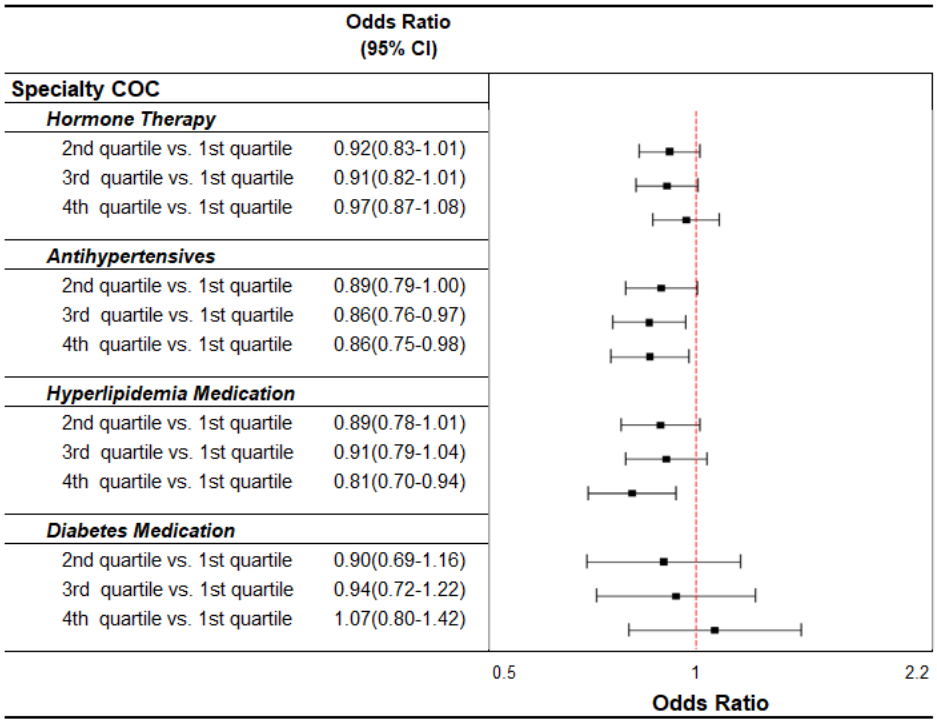
Figure 4.2.3 showed the raw medication adherence and non-adherence rates change during the whole study period for each therapeutic group (HT, antihypertensives, hyperlipidemia medications, and diabetes medications).

Figure 4.2.4 Forest Plot Showing the Association Between Medication Adherence and the Specialty COC Index for Breast Cancer Patients after hormone therapy initiation

A. Fully Adjusted Models



B. Partially Adjusted Models



C. Unadjusted Models

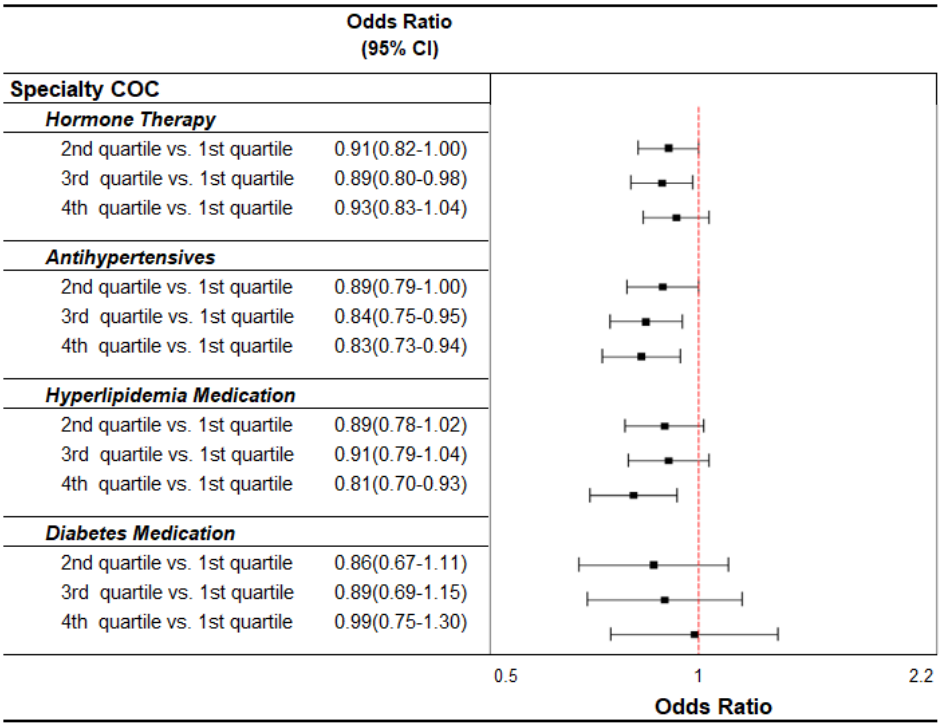
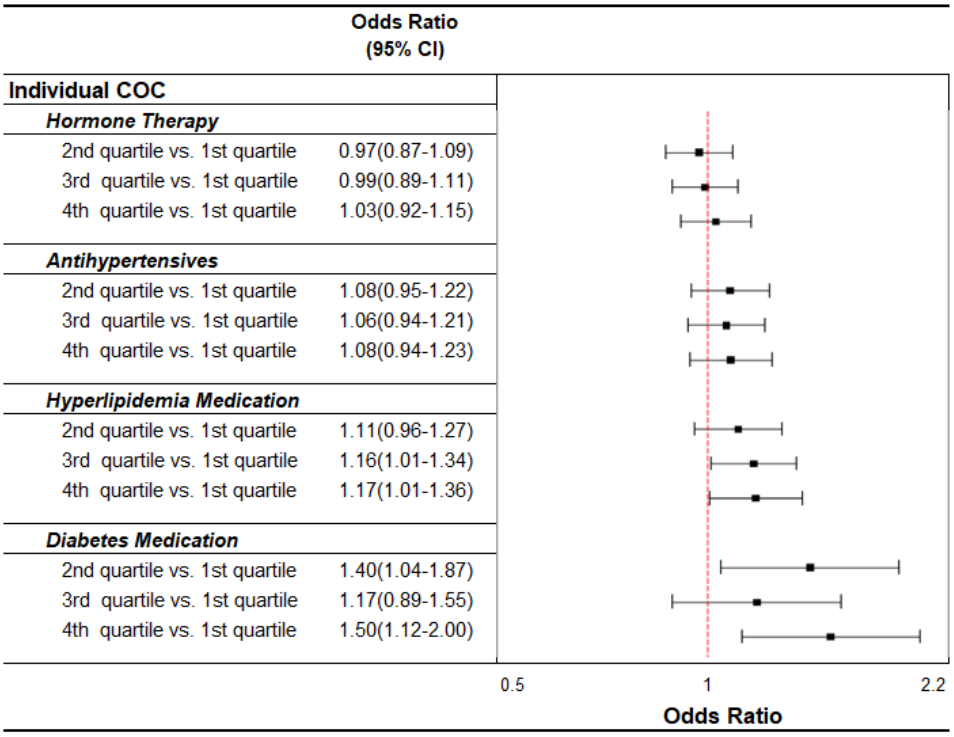


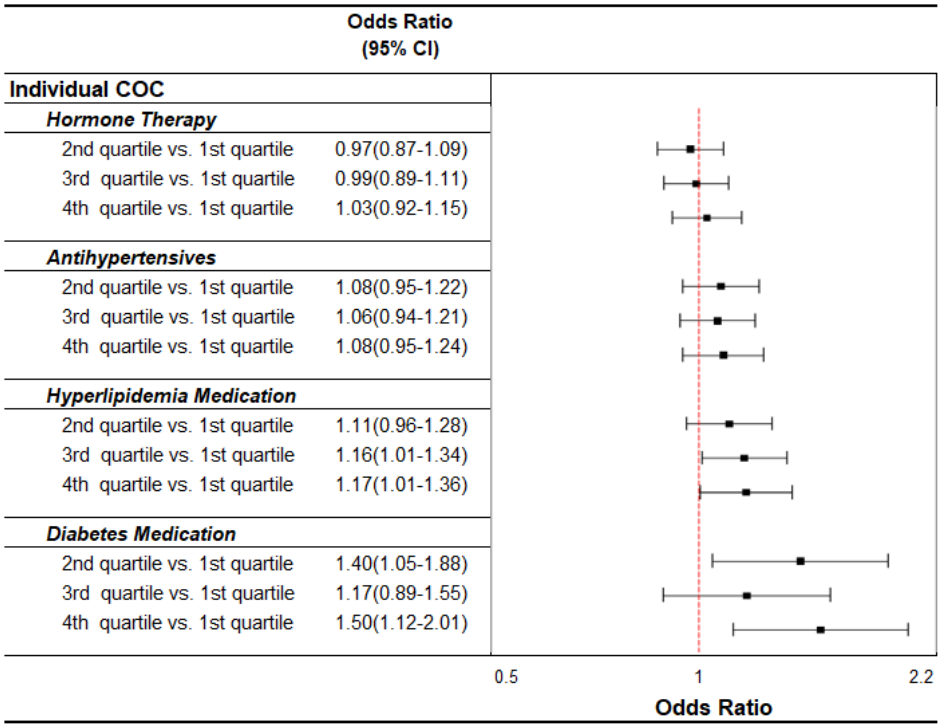
Figure 4.2.4 showed the results of logistic regression for the association of the Specialty COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI. The unadjusted models were adjusted for time only.

Figure 4.2.5 Forest Plot Showing the Association Between Medication Adherence and the Individual COC Index for Breast Cancer Patients after hormone therapy initiation

A. Fully Adjusted Models



B. Partially Adjusted Models



C. Unadjusted Models

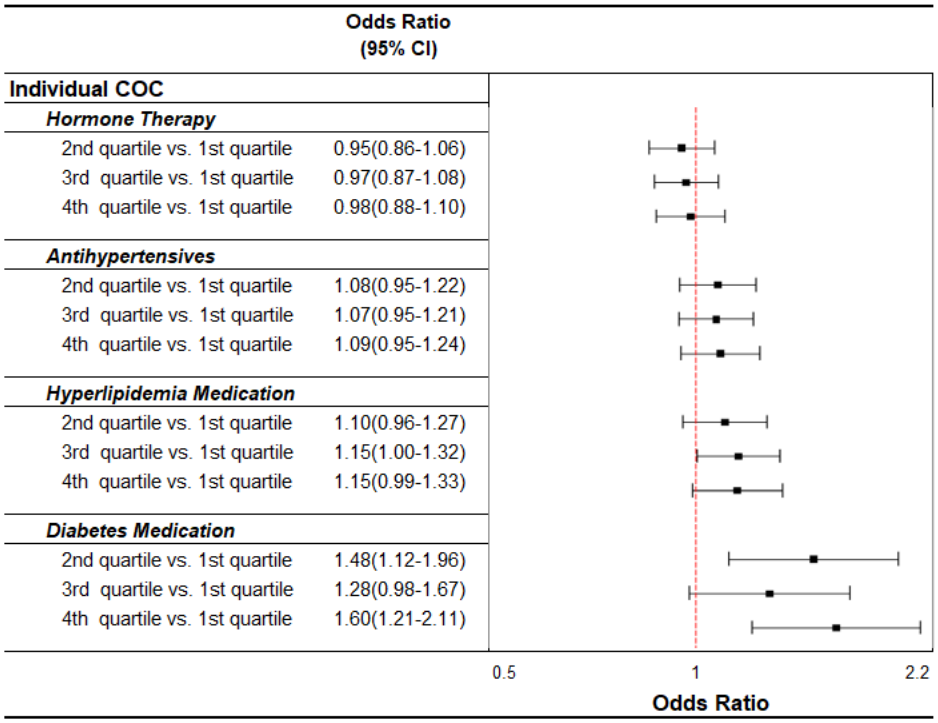


Figure 4.2.5 showed the results of logistic regression for the association of the Individual COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI. The unadjusted models were adjusted for time only.

4.3 Aim 3 Results

4.3.1 Abstract

Objective: To examine the associations between continuity of care (COC) with patient's outcomes including health care service utilization and costs

Methods: A retrospective cohort study identified 8,414 newly diagnosed breast cancer patients with hormone therapy (HT), using the Surveillance, Epidemiology, and End Results-Medicare linked database (2007-2014). Health care service utilization and costs were examined for up to four years after HT initiation. COC Indices were calculated based on provider specialty groups (Specialty COC Index) and individual providers (Individual COC Index) with a scale of 0 (dispersed) to 1 (concentrated), which indicated the frequency and dispersion of patients' healthcare provider visits. Two-stage models including a mixed-effect logistic regression model and a mixed-effect linear regression model (with a log link and a gamma distribution) were used to determine the association between COC indices and health care service (emergency department (ED), inpatient) utilization and costs after HT initiation.

Results: The average COC Indices were lower in patients who had ED or inpatient visits than in the overall population. After controlling for patients' characteristics, patients with intermediate levels of Specialty COC Index were more likely to have ED or inpatient visits (significant in 2nd vs. 1st and 3rd vs. 1st quartile) for all conditions. However, patients with high levels of Individual COC Index were less likely to have ED or inpatient visits (significant in 2nd vs. 1st, 3rd vs. 1st, and 4th vs. 1st quartile) for all conditions. Accordingly, high levels of Specialty COC Index were associated with increased inpatient costs (all-cause, hypertension, hyperlipidemia, and diabetes related $p<0.05$). High levels of Individual COC Index were associated with reduced ED (all-cause related $p<0.05$) and inpatient costs (all-cause, hypertension, and diabetes related $p<0.05$).

Conclusion: High levels of Individual COC Index and intermediate levels of Specialty COC Index were significantly associated with less health care service utilization and costs. The findings of this study provoke the need to optimize continuity of care during the survivorship care for cancer patients with cardiometabolic comorbidities. Strategies for improving the continuity of care could be promoting concentrated individual provider visits and coordinated specialties visits by increasing patients' awareness and improving long term medical facility-based care.

4.3.2 Introduction

The Medicare cost of Breast cancer was $16.5 billion in 2010 and will increase to $20.5 billion in 2020.[183] About 28% of breast cancer patients have cardiometabolic comorbidities.[87,88] Cancer patients with comorbidities have higher health care expenditures and more health care service utilization than those without comorbidities, which places a heavy burden on the health care system.[105] For example, within Medicaid beneficiaries, the additional medical cost for cancer survivors during the 6-month follow-up were $4,584, $13,369, and $25,739 for patients with one, two, and more than three comorbidities.[52] The percentages of Medicare beneficiaries who had at least one inpatient admission were 13%, 30%, and 63% for patients with two to three, four to five, and more than six comorbidities.[51]

Cancer patients with comorbidities need to visit different health care specialists and undertake cancer treatment as well as treatments for their comorbidities.[3,33] In addition, poor coordination and continuity of care have been observed between primary care providers (PCP) and oncologists along the spectrum of acute cancer treatment and survivorship care.[4,8,9] Therefore, cancer patients with comorbidities are often under-treated for their comorbidities following cancer diagnoses,[4,8,9] which can negatively influence cancer patients' health outcomes including costs and service utilization.[10-14] For example, in 2010, 70.4% of health care service utilization were inpatient stays of patients with multiple chronic conditions.[122] Although strategies were developed to promote communication and coordination among health providers for cancer survivorship,[115] limited effects of these strategies on reducing health service utilization and cost were found by researchers.[57] Strategies are needed to address these problematic issues during cancer survivorship care.

Continuity of care indicates the degree of continuity of discrete health care elements during the health care process, which include information continuity, relational continuity, and management continuity.[23]In this study, we measured management continuity by using the Bice-

Boxerman COC Index, which was widely used by previous studies.[25 26] COC Index reflects patients' visit to all providers and is sensitive to the distribution of visits to individual providers.[25,26] Patients with concentrated health care provider visits would have high COC whereas patients with dispersed health care provider visits would have low COC.[125] COC is closely related to patients' satisfaction and their health outcomes.[16,18,19,54] Actually, higher COC would significantly reduce health care cost and service utilization in patients with chronic conditions.[18,19,54,55] For example, a study of elderly adult patients with multiple comorbidities found high COC Index was associated with less inpatient (Hazard Ratio (HR) 0.97 95%CI 0.96-0.99) and ED visits (HR 0.97 95%CI 0.96-0.98).[54] Another study of patients with diabetes found, for every 0.1-unit increase in the COC Index, patients had significantly lower chances of inpatient (Odds Ratio (OR) 0.95 95%CI 0.95-0.96) and ED visit (OR 0.94 95%CI 0.93-0.94), and lower health care cost ($p<0.05$).[19] However, these studies were focused on non-cancer patients. Cancer patients with comorbidities often receive poor continuity of care after cancer diagnoses[1] and have more health care service utilization and costs[105]. This situation is even worse for ER+ breast cancer patients with cardiometabolic comorbidities since they have to undertake long term treatments for cancer and cardiometabolic diseases.[3,33] To our knowledge, very few research studied the relationship between COC and health care expenditures and service utilization for cancer patients.

In this study, we focused on the association between COC and health care service utilization and cost within ER+ breast cancer patients who had cardiometabolic comorbidities. ER+ breast cancer patients with cardiometabolic comorbidities were recommended to take at least five years of hormone therapy and long term cardiometabolic medication treatments.[3,4,8,9,33,40] These patients had to visit multiple provider specialties for their cancer and other chronic conditions.[3,4,8,9,33] The complicated provider visits could be associated with poor continuity of care and negatively influence patients' health care costs and service utilization.[1,4,8-

[14] Studies found, continuity of care to different scopes of medical disciplines would be associated with health outcomes differently.[127,128] However, only limited research focused on this problem. Therefore, the objective of this research is to examine the associations between individual providers and specialty groups based continuity of care (COC) with ER+ breast cancer patient's health outcomes including health care service utilization and costs.

4.3.3 Method

Data sources

This study used the 2006-2014 Surveillance, Epidemiology and End Results (SEER) Program and Medicare claims data. The SEER data includes clinical record (tumor diagnosis, tumor pathology, tumor histology, tumor stage), demographic, and cause of death for cancer patients.[186] The Medicare claims provide information about patients' covered health care services (hospital visit, outpatient, physician office visit, clinic visit, and other health facility utilization, prescription drug usage) from the start of Medicare enrollment until death.[186] The linkage of these two data sources identifies the records of a population subgroup which can be used for epidemiological and healthcare-related research.

Participants and Study Design

We used a new user cohort design to identify female breast cancer patients with hormone therapy (HT) if they: (1) were older than 66 years at their breast cancer diagnoses; (2) were estrogen receptor-positive; (3) started hormone therapy (HT) within 12 months after cancer diagnoses; (4) continuously enrolled in Medicare Part A, B, and D for 12 months before breast cancer diagnoses; (5) continuously enrolled in Medicare Part A, B, and D after breast cancer diagnoses until the end of the study period (Figure 4.3.1). A patient was excluded from the study if her primary cancer was not breast cancer (n=4,262) or she enrolled in managed care (n=75,840). The index date of this study was the date of HT initiation. After HT initiation, each eligible patient was followed for up to 1, 2, 3, or 4 years. Thus, a total of 8,414 patients with 18,203 person-years of observation were included in this study. To allow a homogenized time interval for measuring related variables, this study only included patients with a full year enrollment of each observation year (year 1, 2, 3, or 4). In this longitudinal study, the Continuity of Care (COC) Index, the risk of health care service utilization (Emergency Department (ED)

visit and Inpatient visit), and health care costs (ED costs and Inpatient costs) were measured cross-sectionally within each observation year after the index date.

Breast cancer diagnosis and estrogen receptor status were identified from the SEER registry data using ICD-O-3 codes C500-509.[187] Patients' cardiometabolic diseases were identified from the Medicare claims data as they should have the record of at least one inpatient visit or two outpatient visits during the baseline period. [106,188-190] The ICD-9 codes for identifying breast cancer, hypertension, hyperlipidemia, and diabetes were ICD-9 174-175, 401-405, ICD-9 272, and ICD-9 250 respectively.[106,188-190] The usage of HT was identified from Medicare Part D data using corresponding National Drug Code (NDC) codes.[119,138,191] Medications for HT include oral tamoxifen and aromatase inhibitors (AI) (anastrozole, letrozole, and exemestane).[119,138,191]

Measurement of Continuity of Care

The Continuity of Care (COC) of this study were measured by the Bice-Boxerman COC Index, which is a dispersion measurement with a scale of 0 to 1 and reflects the distribution of visits to different individual providers (or provider groups) during a specified period.[25] The COC Index has been commonly used by previous studies for patients with multiple comorbidities.[125] A COC score of 1 means perfect care continuity. This reflects that across all visits, there is one provider. A COC score of 0 means no care continuity. This reflects a patient that sees a different provider at each visit. The lower COC Index score a patient had, the more dispersed continuity of care that patient might have been received.

In this study, the COC Index was measured based on provider specialty groups and individual providers that a patient visited during each observation year after the index date. Specialty COC Index was calculated based on provider specialty groups. These groups were Primary Care Providers (PCP), Oncologists, and Other specialties. Individual COC Index was calculated based on the overall individual health care providers a patient visited, including PCP,

Oncologists, and Other specialists. The COC Indices were estimated from a patient's annual outpatient records of disease-related (breast cancer, hypertension, hyperlipidemia, and diabetes) health care provider visits. Variable RFR_UPIN in the outpatient file was used to identify individual health care provider. Variable HCFASPEC in the outpatient file was used to determine health care provider specialty. The health care provider specialties included in this study were: Primary Care Provider (PCP) (HCFASPEC: 01, 08, 11, 16, and 38), Oncologist (HCFASPEC: 02, 24, 36, 83, 90, 91, 92, and 98), and all other physician specialists (Other) that a patient visited for conditions related to breast cancer, hypertension, hyperlipidemia, and diabetes in outpatient records.[121,195] According to the suggestion from previous research, a threshold of at least four total visits during the measurement time interval was applied in this study to calculate a stable COC Index.[194]

Covariates

Patients' demographic information (age group, race, marriage status, poverty level, region), and tumor stage were identified from the SEER's registries as of their breast cancer diagnosis. Patients' existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes), and disease burden (Charlson Comorbidity Index (CCI)) were identified from a 12-month baseline period from the Medicare claims. This study used the modified CCI recommended by the National Cancer Institute (NCI) to measure patients' disease burdens, which excluded patients' existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes) during the calculation. [84,190,197,198,210] Breast cancer treatments (hormone therapy, surgery, chemotherapy, and radiation therapy) were measured yearly after HT initiation. Since a small group of patients had surgery (1.43%), chemotherapy (4.67%), and radiation therapy (17.59%) after hormone therapy initiation (Table 4.3.1), we grouped these other treatments into one covariate variable (other cancer treatment). We used ICD-9 codes (surgery, ICD-9 85.2-

85.4; chemotherapy, ICD-9 V58.1, V66.2, V67.2; radiation therapy, ICD-9 V58.0; V66.1; V67.1) to identify other cancer treatments from the Medicare claims data.[42,199]

Outcome Variables

Patients' health outcomes after HT initiation were measured yearly after the index date by health care service utilization and costs. Health care service utilization was determined by whether a patient had an ED visit or an inpatient visit during each follow-up year of the study period. Health care costs were estimated by Medicare costs per patient per year and were adjusted to reflect 2014 dollars using the consumer price index.[205] This study excludes the measurements of outpatient visits and costs to avoid collinear effects between predictor and outcomes, since the COC Indices was estimated by patients' outpatient visits. The health care service utilization (ED visits and inpatient visits) and costs (ED costs and inpatient costs) were measured based on each related condition (breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) as well as all conditions (all-cause) using the Medicare part A and B data. ED visits and inpatient visits were measured from the Medicare inpatient and outpatient files. ED visits included the emergency department visits during inpatient and outpatient visits. Inpatient visits only included the inpatient stays excluding emergency department visits.

Statistical Analysis

Descriptive analyses were conducted to summarize patients' baseline characteristics, health care service utilization, and COC Indices. Patient characteristics included: age groups, race groups, marriage status, poverty levels, regions, tumor stages, other cancer treatments, existing cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes), and CCI. Health care service utilization overtime included ED visit and inpatient visit.

This study used mixed-effect logistic regression models to estimate the associations of COC Indices and the likelihood of ED visit or inpatient visit separately for each related condition (all-cause, breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related). Each COC Index (Specialty COC and Individual COC) was independently served as the primary predictor of the mixed-effect logistic regression models. The random effects caused by repeated measurements of each individual patient were controlled by conducting the mixed-effect models in the analyses. The model looks like equation 1.

Based on previous studies, two-stage models were recommended to estimate the health care cost with a gamma distribution.[206,207] In this study, the distribution of ED cost and inpatient cost both followed gamma distribution (data not shown). Thus, we used two-stage models to estimate the association of COC Indices (Specialty COC and Individual COC) and health care costs for each service type (ED or inpatient) under each related condition (all-cause, breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) separately.[206,207] Random effects caused by repeated measurement of each individual patient was controlled in the mixed effect models. The first part of the models was a logistic regression model estimating the probability of positive health care cost, which was the probability of health care service utilization (equation 1). The second part of the models was a linear regression model with a gamma distribution and log link function estimating the distribution of positive health care cost (equation 2).[206,207] Then the predicted health care cost of each observation was generated by multiplying the probability from the first part of the models and the predicted positive costs from the second part of the models. The 1000 bootstrap samples were used to estimate the effect of The COC Index on the mean and 95% Confident Interval (CI) of health care cost for each health care service type at each condition. The 2-stage models look like:

(1) Logistic regression

$$logit(visit(0/1)) = COC + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment$$ (equation 1)

(2) Linear regression with gamma distribution and log link function:

$$log(cost) = COC + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment$$
(equation 2)

To better interpret COC Indices with clinical meanings, we divided these COC Indices into quartile levels (0-25% as 1st quarter, 26-50% as 2nd quarter, 51-75% as 3rd quarter, and 76-100% as 4th quarter) in regression analyses. The range for each quartile for Specialty COC Index is: 1st quartile: 0-0.33, 2nd quartile: 0.33-0.40, 3rd quartile:0.40-0.49, and 4th quartile: 0.49-1. The range for each quartile for Individual COC Index is: 1st quartile: 0-0.20, 2nd quartile: 0.20-0.32, 3rd quartile:0.32-0.50, and 4th quartile: 0.50-1. All models were adjusted for patients' demographic information (age, race, marriage status, poverty level, region), tumor stage, existing diseases (hypertension, hyperlipidemia, and diabetes), CCI, other cancer treatment, and years after HT initiation.

Sensitivity analyses were used to test the robustness of this study. To estimate whether our findings were sensitive to our choice of covariates, we conducted sensitivity analyses using models with reduced numbers of variables. First, patients' characteristics, comorbidities, and cancer treatments might influence their health care service utilization and costs. Thus, we used unadjusted models, which only adjusted for the years after HT initiation. Second, out of all covariates, cancer treatments could greatly contribute to patients' health care service utilization and costs. Therefore, we used partially adjusted models, which controlled for all covariates from the fully adjusted models except for the variable 'other cancer treatment'. Third, there might be

uncontrollable changes in COC Indices due to spillover.[125,126] Thus, lagged effects models were used to test models' sensitivity to COC Indices spillover. In the lagged effects models, we added COC Indices from the previous observation year as an additional control variable to baseline characteristics as covariates to the COC Indices from the current observation year. The lagged effect 2-stage models look like:

(3) Logistic regression

$$logit(visit(0/1)) = COC(t) + COC(t-1) + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment$$ (equation 3)

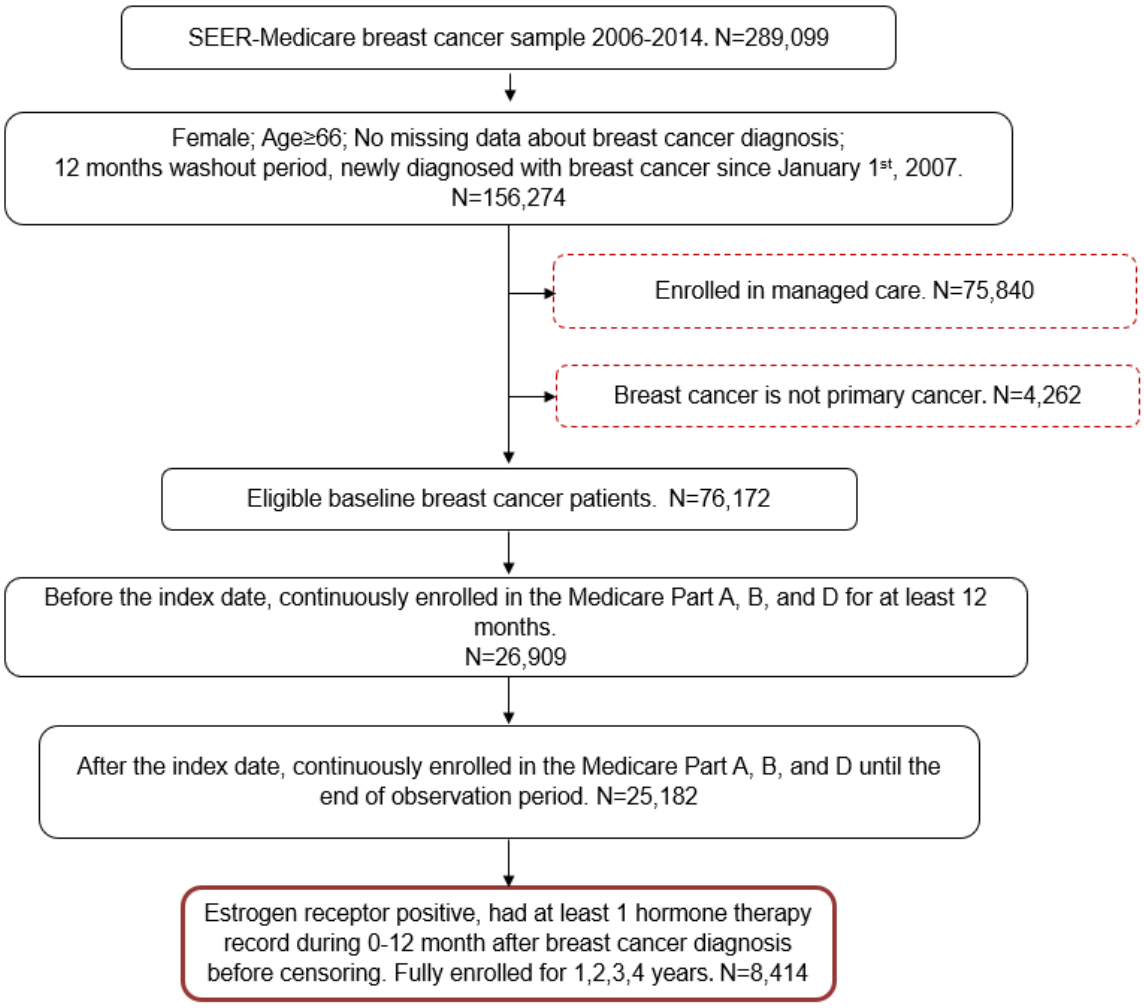
(4) Linear regression with gamma distribution and log link function:

$$log(cost) = COC(t) + COC(t-1) + age + race + marriage + poverty\ level + region + tumor\ stage + hypertension + hyperlipidimia + diabetes + CCI + year + other\ cancer\ treatment$$ (equation 4)

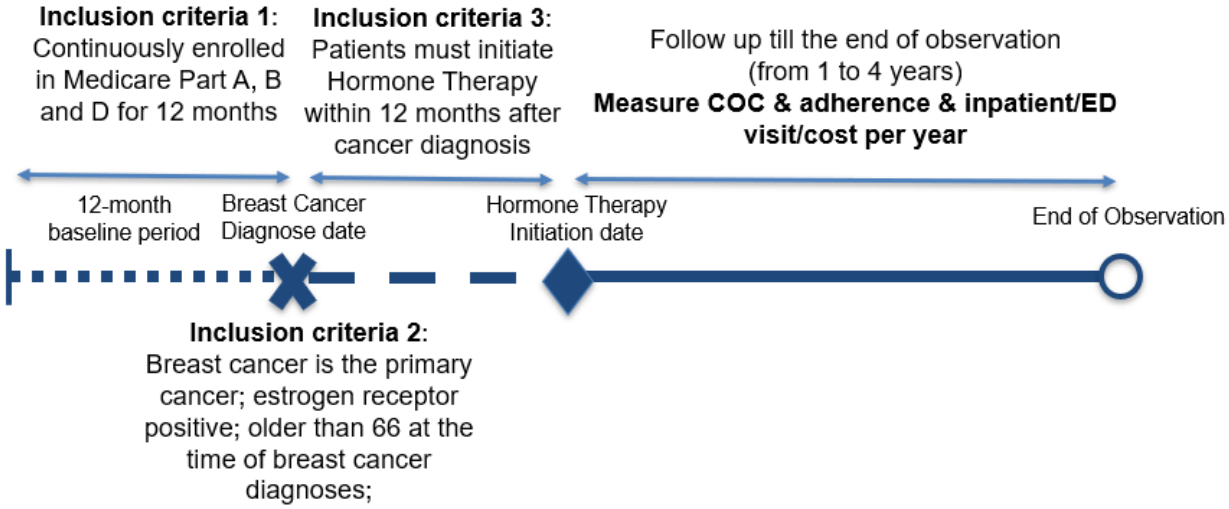
All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary NC).

Figure 4.3.1 Study Sample Flow Chart and Study Design

A. Study sample flow chart



B. Study design



4.3.4 Result

The study sample consisted of 8,414 Medicare beneficiaries diagnosed with estrogen receptor-positive breast cancer and initiated HT within 12 months after cancer diagnoses between 2006 and 2014 (Table 4.3.1). Within the select cohort, 5,309 (63.50%) patients were also diagnosed with hypertension, 4,705 (56.28%) with hyperlipidemia, and 1,779 (21.28%) with diabetes. The numbers and percentages of patients with stage I, II, III, and IV breast cancer were 4,742 (56.36%), 2,478 (29.45%), 558 (6.63%), and 277 (3.29%). The average CCI was 0.44 (Std=0.87) for the whole cohort.

Table 4.3.2 demonstrates the annual health care service utilization and the yearly average COC Indices for breast cancer patients with up to 4 years of HT. The percentage of patients who had at least one all-cause ED visit changed slightly from 25.85% (year 1) to 27.65% (year 4) and the percent of patients who had at least one all-cause inpatient visit changed slightly from 16.50% (year 1) to 15.26% (year 4). All COC Indices had stable average scores during the whole study period. Patients with ED or inpatient visits had lower average scores of Specialty COC Index in year 1 and higher average scores of Specialty COC Index in year 3 and year 4 comparing to overall patients. Patients with ED or inpatient visits had lower average scores of Individual COC Index than total patients during the entire observation period. Total patients included all HT patients with or without visits of ED and inpatient. For example, in year 1, the average scores of Specialty COC Index for patients with ED visits (0.41) and inpatient visits (0.42) were lower than total patients (0.43). However, in year 4, the average scores of Specialty COC Index for patients with ED visits (0.45) and inpatient visits (0.45) were higher than total patients (0.44). From year 1 to year 4, the average scores of Individual COC Index remained 0.38 for total patients but were lower in patients with ED visits (ranged from 0.31 to 0.34) and inpatient visits (ranged from 0.31 to 0.33).

The Odds Ratios (ORs) of health care service utilization (ED visit and inpatient visit) after HT initiation were estimated separately for each condition (all-cause, breast-cancer-related, hypertension-related, hyperlipidemia-related, and diabetes-related) after adjusting for patients' characteristics and years after HT initiation (Figure 4.3.2). In Specialty COC models, the Odds of ED visit (2^{nd} vs. 1^{st} and 3^{rd} vs. 1^{st} quartile) or inpatient visit (2^{nd} vs. 1^{st}, 3^{rd} vs. 1^{st}, 4^{th} vs. 1^{st} quartile) increased significantly at intermediate levels (2^{nd} quartile and 3^{rd} quartile) of Specialty COC Index for all-cause, hypertension, hyperlipidemia, and diabetes related conditions. For example, the ORs for all-cause ED visit were 1.21 (95%CI: 1.10-1.33) at 2^{nd} vs. 1^{st} quartile and 1.30 (95%CI: 1.18-1.43) at 3^{rd} vs. 1^{st} quartile. The ORs for all-cause inpatient visit were 1.56 (95%CI: 1.39-1.76) at 2^{nd} vs. 1^{st} quartile and 1.60 (95%CI: 1.42-1.29) at 3^{rd} vs. 1^{st} quartile. In the Individual COC Index models, the Odds of ED and inpatient visits decreased at higher levels of COC Index (2^{nd} vs. 1^{st}, 3^{rd} vs. 1^{st}, 4^{th} vs. 1^{st} quartile) for all-cause, breast cancer, hypertension, hyperlipidemia, and diabetes related conditions. As Individual COC level increased, the Odds of ED and inpatient visits decreased. For example, the ORs for all-cause ED visit were 0.73 (95%CI 0.66-0.80) at 2^{nd} vs. 1^{st} quartile, 0.50 (95%CI 0.45-0.56) at 3^{rd} vs. 1^{st} quartile, and 0.47 (95%CI 0.42-0.52) at 4^{th} vs. 1^{st} quartile. The ORs for all-cause inpatient visit were 0.79 (95%CI 0.71-0.88) at 2^{nd} vs. 1^{st} quartile, 0.50 (95%CI 0.45-0.56) at 3^{rd} vs. 1^{st} quartile, and 0.43 (95%CI 0.38-0.49) at 3^{rd} vs. 1^{st} quartile.

The associations of COC Indices with ED cost of each related condition are presented in Table 4.3.3. The increased levels of Individual Index (2^{nd} vs. 1^{st}, 3^{rd} vs. 1^{st}, 4^{th} vs. 1^{st} quartile) were significantly associated with reduced all-cause ED cost ($p<0.05$). For example, with the mean cost of $4,473.07, as the levels of Individual COC Index increased, all-cause ED cost reduced from $765.14(95%CI -$1251.96 to -$204.74) at 3^{rd} vs. 1^{st} quartile to $874.00 (95%CI -$1379.87 to -$285.40) at 4^{th} vs. 1^{st} quartile. The Specialty COC Index did not have a significant effect on ED cost.

The associations of COC Indices with inpatient cost for each related condition are presented in Table 4.3.4. The increased levels of Specialty COC Index were significantly associated with increased inpatient costs related to all-cause, hypertension, hyperlipidemia, and diabetes ($p<0.05$). For example, with the mean cost of $13,513.44, all-cause inpatient cost could increase $3,841.63 (95%CI $1,886.51 to $6,044.97) at 2nd vs. 1st quartile, $6,718.95 (95%CI $4,416.31 to $9,321.13) at 3rd vs. 1st quartile, and $5,142.88 (95%CI $2,809.82 to -$7809.39) at 4th vs. 1st quartile. On the contrary, the increased levels of Individual COC Index were significantly associated with reduced inpatient costs related to all-cause, hypertension, and diabetes ($p<0.05$). For instance, with the mean cost of $14,938.73, all-cause inpatient cost decreased from $1,727.63 (95%CI -$3,193.38 to -$78.97) at 3rd vs. 1st quartile to $3,290.47 (95%CI -$4,710.71 to -$1,673.01) at 4th vs. 1st quartile. More details of the models are presented in Table 4.3.4.

The lagged effect service utilization models (Appendix Figure Aim 3.3) got similar results to the original models. The lagged effect costs models (Appendix Table Aim 3.9-10) also got similar results as the original cost models except for hyperlipidemia-related ED cost model. Due to the small sample size, the ED cost model could not be applied for hyperlipidemia-related cohort.

In the sensitivity analyses, the unadjusted models and partially adjusted models got similar results for health care service utilization (Appendix Figure Aim 3.1-2) and health care costs (Appendix Table Aim 3.1-4) of all related conditions.

4.3.5 Discussion

This study analyzed the associations between COC Indices and health care service utilization and cost of breast cancer patients with cardiometabolic diseases. Our longitudinal analyses found significant associations between continuity of care and selected health outcomes. These results differed between the models predicting health service utilization resulting from Individual COC and Specialty COC. High continuity of care to an individual provider was significantly associated with less health care service utilization and costs. However, intermediate continuity of care to a specialty group was significantly associated with more health care service utilization and costs. To the best of our knowledge, this is the first study that analyzed the link between the COC Index and health outcome within breast cancer patients who have cardiometabolic diseases.

In our findings, patients with higher continuity of care to an individual provider had lower likelihoods of ED and inpatient visits for conditions related to all-cause, breast cancer, hypertension, hyperlipidemia, and diabetes. Similarly, these patients had reduced inpatient cost for conditions related to all-cause, hypertension, and diabetes. They also had reduced ED cost for all-cause conditions. These inverse associations between high continuity of care and low health service utilization and cost are consistent with several previous studies within non-cancer patients.[19,54,55,218-221] For instance, Barker et al. found a high level of COC Index could significantly reduce hospital admission by 12.49% compared to a low level of COC Index.[55] Hussey et al. reported that with every 0.1-unit increase in the COC Index, patients with multiple chronic conditions had a significantly lower likelihood of ED or inpatient visits and costs.[19] Chu et al. also found, after controlling for improper medications, patients with high levels of COC Index had lower Odds of ED or inpatient visits and costs.[221] Likewise, our descriptive analyses showed patients with ED or inpatient visits had lower continuity of care to an individual provider than overall patients during the whole observation period.

These inverse associations between high continuity of care to an individual provider and low health service utilization and costs could be explained in different ways. First, continuity of care would reduce the challenges for cancer survivorship care caused by poor coordination. Specialists and PCPs have different roles and responsibilities for the follow-up care of cancer patients with comorbidities.[1] However, they might not share their own treatment decisions.[110] A study found that only 7% of physicians routinely communicated with other physicians in the United States.[112] The poor coordination and information discontinuity could cause challenges for physicians when they prescribed medications to cancer patients with comorbidities.[5-7] Within the health care system, a patient who had a high COC Index would have concentrated visits to one health care provider. Previous research suggested that the individual provider centered care would help to reduce health care providers' concerns during treatment decision making,[109] and help to improve the undertreatment of cancer patients' comorbidities.[4,8,9] Therefore, continuity of care could help to avoid the challenges caused by poor provider coordination and reduce health care service utilization and costs. Second, continuity of care would improve patients' quality of care during cancer survivorship. Continuity of care is an important prerequisite for the quality of care for cancer survivorship care.[21,22] Snyder et al. found cancer patients with more concentrated PCP visits were more likely to receive recommended care during their survivorship.[222,223] Chin et al. also suggested that improving the quality of care would significantly reduce patients' health care service utilization and costs.[224] Thus, continuity of care would reduce patients' health care service utilization and cost by improving the quality of care.

Our findings of continuity of care to a specialty group got different results. Patients with high specialty groups continuity of care had high likelihoods of ED and inpatient visits for conditions related to all-cause, breast cancer, hypertension, hyperlipidemia, and diabetes. Similarly, patients with high specialty groups continuity of care had increased inpatient costs for conditions related to all-cause, hypertension, hyperlipidemia, and diabetes. These proportional

associations found in models of Specialty COC are different from the inverse associations found in models of Individual COC. The controversial results might relate to the various medical disciplines included in the calculations of each COC Index. According to the definition, the COC Index could be calculated based on practice groups or individual providers.[25] Our study estimated the Specialty COC Index based on each patient's visit to three specialty groups (PCP, Oncologist, and Other) which reflected the continuity of care in provider specialties. However, we estimated the Individual COC Index based on each patient's visits to individual health care providers which reflected the continuity of care in individual providers regardless of their specialties. Thus, a patient could have a high Specialty COC Index but a low Individual COC Index at the same time. For example, if a patient visited four different PCP for one year, she would have a high Specialty COC Index (=1), and a low Individual COC Index (=0). Therefore, with the same health outcome, a patient could have different scores of Specialty and Individual COC Indices. Previous studies showed that COC Indices defined by different medical disciplines would have different effects on patients' health outcome.[127,128] For example, Chan et al. found the COC Index based on facility-level and the COC Index based on individual provider level had opposite effects on patients' ED or inpatient visits.[128]

We also observed higher ORs of ED and inpatient visits for the Specialty COC Index at intermediate levels (2nd vs. 1st and 3rd vs. 1st). This could be explained by patients' continuity of care based on specialty groups. Patients with cardiometabolic diseases were more likely to visit multiple specialties and had a low or intermediate specialty groups continuity of care. Therefore, if patients had a more concentrated health care specialty visits to one specialty (e.g. Oncologist), their cardiometabolic diseases might get undertreated. Thus, these patients might have a higher chance to have ED or inpatient visits for their undertreated cardiometabolic diseases. Patients with 4th quartile of Specialty COC Index had the most concentrated health care specialties visits but had slightly lower OR of ED and inpatient visits than patients with 2nd

or 3rd quartile of Specialty COC Index. This might be caused by patients' uncontrollable disease severity. For example, patients with less severe comorbidities only needed to visit their oncologists regularly. Therefore, they would have a higher continuity of care to a specialty group and less likelihood of ED or Inpatient visits.

Our study has several limitations. First, we could not include patients younger than 66 using SEER-Medicare data. Patients in younger age groups might have different associations between COC and health outcome.[42] Future studies need to use alternative medical claims data to include these patients. Second, we could not control for patients' health-seeking behavior. Previous research found patients' health-seeking behavior was closely related to their health care service utilization and costs.[225] Also, patients' preference of health care provider visiting was linked to continuity of care.[125] However, SEER-Medicare data does not have the information for us to control for patients' health-seeking behavior. Future studies could use patients' surveys to study their health-seeking behavior and continuity of care. Third, our study had several uncontrollable confounding factors which could contribute to health care service utilization and costs. These confounding factors were lifestyle modifications, undetected comorbidities, medication adherence, improper medications, adverse drug events, and the Affordable Care Act (ACA). Previous studies proved that these confounding factors had significant influences on patients' health outcomes. [46,161,162,164,196] However, due to the limitations of SEER-Medicare data, we did not control for these factors in our study. Fourth, missing data existed in our longitudinal analyses. However, we applied a reliable imputation method for the missing data during our statistical analyses.[217] Fifth, the COC Index has its limitations. To calculate stable COC Indices, we did not include individuals who had less than four provider visits within that observation year .[194] Also, COC Indices could not provide details of patients' satisfaction and provider coordination. However, measuring the COC Index is a straight forward way to get a timely evaluation of continuity of care at the real-world settings. Thus, this study

used the COC Index to measure the continuity of care. Six, selecting ED and inpatient visits as health outcomes might cause potential bias. On the one hand, some patients might use ED or hospitalization as their source of non-urgent care. Thus, measuring ED or inpatient visits might not reflect the actual disease progress or severe health outcomes. On the other hand, patients who had ED or inpatient visits might already have severe disease conditions than others. Thus, it is no surprise that these patients had more ED or inpatient visits regardless of their COC Indices. To control the bias caused by the uncertain visits of ED and inpatient, in this study, we controlled for patients' breast cancer stage and comorbidities in the analyses. Seven, we did not include patients' health care provider visits to all health care providers. Cancer patients had more severe disease conditions than others and need to have more visits to physicians. Thus, we did not include their visits to non-physicians (e.g., nurse practitioners or physician assistants). Also, we did not include visits to providers without valid HCFASPEC values during the calculations of COC Indices. Therefore, our findings could not reflect the continuity of care based on these providers. Although there are limitations in our study, it provided useful information on continuity of care in a timely way for patients based on the national population. The cohort of our study included a group of breast cancer patients with cardiometabolic diseases who need multiple treatments and faced challenges during their health care management.

This study focused on the association of continuity of care and health outcome within breast cancer patients who had HT and comorbidities. We found high levels of Individual COC was significantly associated with less health care service utilization and costs. However, intermediate levels of Specialty COC was significantly associated with more health care service utilization and costs. These results indicated the protective effects of concentrated individual provider visits and dispersed specialties' visits on health care service utilization and costs. The findings of this study fulfilled a knowledge gap and provided empirical evidence for future

studies. These findings provoke the need to optimize continuity of care during the survivorship care for cancer patients with cardiometabolic comorbidities. Strategies for improving the continuity of care could be promoting concentrated provider visits by increasing patients' awareness and supporting long term individual provider concentrated care. Meanwhile, these strategies should also enhance the coordination among multiple specialties by improving medical faciltiy-based care to patients.

Table 4.3.1 Baseline Characteristics of Breast Cancer Patients with Hormone Therapy

Characteristics	Level	Breast
N (%)		
All		8414 (46.20%)
Age	66-70	2121 (25.21%)
	71-75	2418 (28.74%)
	76-80	1801 (21.40%)
	>80	2074 (24.65%)
Race	Black	224 (2.66%)
	Other	326 (3.87%)
	White	7864 (93.46%)
Marriage	Marriage	4185 (49.74%)
	Other	4229 (50.26%)
Poverty	0-5%	2379 (28.27%)
	5-10%	2547 (30.27%)
	10-20%	2170 (25.79%)
	20-100%	1132 (13.45%)
	unknow	186 (2.21%)
Region	Midwest	1203 (14.30%)
	Northeast	3512 (41.74%)
	South	3011 (35.79%)
	West	688 (8.18%)
Tumor Stage	0	151 (1.79%)
	I	4742 (56.36%)
	II	2478 (29.45%)
	III	558 (6.63%)
	IV	277 (3.29%)
	unknow	208 (2.47%)
Hypertension		
	0	3051 (36.50%)
	1	5309 (63.50%)
Hyperlipidemia		
	0	3655 (43.72%)
	1	4705 (56.28%)
Diabetes		
	0	6581 (78.72%)
	1	1779 (21.28%)
Surgery		

	0	8294 (98.57%)
	1	120 (1.43%)
Chemotherapy		
	0	8021 (95.33%)
	1	393 (4.67%)
Radiationtherapy		
	0	6934 (82.41%)
	1	1480 (17.59%)
CCI (mean(std))		0.44 (0.87)

Table 4.3.1 showed patients' characteristics of the study. Number and percentage of patients in each level of covariates were counted.

Table 4.3.2 Yearly Health Care Service Utilization and the COC Index of Breast Cancer Patients with Hormone Therapy

		Year 1	Year 2	Year 3	Year 4
Number of Patients					
N (%)	All	8414	5447	3058	1284
	ED Visit	2175 (25.85%)	1510 (27.72%)	869 (28.42%)	355 (27.65%)
	Inpatient Visit	1388 (16.50%)	888 (16.30%)	518 (16.94%)	196 (15.26%)
Specialty COC Index					
Mean (Std)	All	0.43(0.15)	0.43(0.15)	0.43(0.15)	0.44(0.16)
	ED Visit	0.41(0.11)	0.42(0.12)	0.45(0.13)	0.45(0.14)
	Inpatient Visit	0.42(0.11)	0.43(0.11)	0.44(0.12)	0.45(0.12)
Individual COC Index					
Mean (Std)	All	0.38(0.22)	0.38(0.23)	0.38(0.24)	0.38(0.24)
	ED Visit	0.34(0.21)	0.33(0.21)	0.34(0.22)	0.31(0.20)
	Inpatient Visit	0.33(0.20)	0.31(0.20)	0.32(0.20)	0.31(0.20)

Table 4.3.2 showed the number (percent) of patients change for different types of health care service (ED and inpatient) utilization. The table also showed the mean (std) COC Index (Specialty, Individual, PCP, Oncologist, and Other) change during the whole study period for different types of health care service (ED and inpatient) utilization.

Table 4.3.3 The Association Between the COC Index and Yearly ED Cost Change after Hormone Therapy Initiation

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	4107.52	12.24%	502.90	-111.66	1211.98	0.0866
3rd qt vs 1st qt		18.07%	742.19	92.52	1492.35	
4th qt vs 1st qt		19.93%	818.44	87.66	1676.52	
Breastcancer-related						
2nd qt vs 1st qt	508.43	-20.09%	-102.16	-202.84	31.70	0.4076
3rd qt vs 1st qt		-15.11%	-76.82	-186.38	70.02	
4th qt vs 1st qt		-21.69%	-110.28	-219.78	40.77	
Hypertension-related						
2nd qt vs 1st qt	2413.59	6.14%	148.30	-295.14	684.56	0.4982
3rd qt vs 1st qt		10.87%	262.39	-202.71	825.33	
4th qt vs 1st qt		17.42%	420.48	-126.92	1098.94	
Hyperlipidemia-related						
2nd qt vs 1st qt	1246.04	-11.44%	-142.56	-411.95	213.85	0.2654
3rd qt vs 1st qt		-8.11%	-101.08	-381.79	270.80	
4th qt vs 1st qt		17.33%	215.91	-188.67	775.30	
Diabetes-related						
2nd qt vs 1st qt	824.50	-10.22%	-84.26	-330.94	285.71	0.5533
3rd qt vs 1st qt		15.27%	125.89	-193.42	606.78	
4th qt vs 1st qt		8.99%	74.14	-253.97	590.97	
Individual COC						
All-cause						
2nd qt vs 1st qt	4473.07	-0.12%	-5.19	-568.20	639.01	**0.0029**
3rd qt vs 1st qt		-17.11%	-765.14	-1251.96	-204.74	
4th qt vs 1st qt		-19.54%	-874.00	-1379.87	-285.40	
Breastcancer-related						
2nd qt vs 1st qt	557.89	20.01%	111.63	-49.43	323.72	0.3759
3rd qt vs 1st qt		-6.71%	-37.41	-163.70	129.35	
4th qt vs 1st qt		6.67%	37.19	-121.98	254.47	
Hypertension-related						
2nd qt vs 1st qt	2646.53	-4.27%	-113.14	-516.29	366.31	0.0930
3rd qt vs 1st qt		-19.05%	-504.30	-862.28	-74.49	
4th qt vs 1st qt		-15.49%	-409.95	-823.46	97.36	
Hyperlipidemia-related						
2nd qt vs 1st qt	1367.78	25.37%	347.01	-44.42	854.21	0.1889
3rd qt vs 1st qt		-5.02%	-68.66	-383.31	346.56	
4th qt vs 1st qt		-4.04%	-55.27	-408.02	427.12	

Diabetes-related						
2nd qt vs 1st qt	906.73	-19.08%	-173.00	-394.05	143.36	0.2330
3rd qt vs 1st qt		-32.95%	-298.81	-490.61	-18.61	
4th qt vs 1st qt		-19.01%	-172.41	-417.02	194.38	

qt, quartile.

Bold, P-value < 0.05

Table 4.3.3 showed the results of two stage models for the association of COC Indices (Specialty and Individual COC) and ED cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of ED visit and a linear regression model for the cost of ED visit. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Table 4.3.4 The Association Between the COC Index and Yearly Inpatient Cost Change after Hormone Therapy Initiation

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	13513.44	28.43%	3841.63	1886.51	6044.97	**<.0001**
3rd qt vs 1st qt		49.72%	6718.95	4413.31	9321.13	
4th qt vs 1st qt		38.06%	5142.88	2809.82	7809.39	
Breastcancer-related						
2nd qt vs 1st qt	2471.49	5.70%	140.89	-354.59	752.34	0.7555
3rd qt vs 1st qt		12.21%	301.76	-232.58	963.63	
4th qt vs 1st qt		4.60%	113.68	-429.74	801.73	
Hypertension-related						
2nd qt vs 1st qt	9751.81	32.91%	3209.29	1562.25	5096.10	**<.0001**
3rd qt vs 1st qt		46.64%	4548.10	2711.37	6655.51	
4th qt vs 1st qt		42.22%	4117.15	2154.01	6403.97	
Hyperlipidemia-related						
2nd qt vs 1st qt	5567.77	28.36%	1579.24	472.50	2888.78	**0.0003**
3rd qt vs 1st qt		38.53%	2145.13	935.70	3579.48	
4th qt vs 1st qt		50.89%	2833.60	1364.70	4613.73	
Diabetes-related						
2nd qt vs 1st qt	3128.79	37.12%	1161.47	221.32	2365.44	**0.0171**
3rd qt vs 1st qt		47.09%	1473.46	467.07	2761.53	
4th qt vs 1st qt		19.99%	625.30	-249.17	1765.33	
Individual COC						
All-cause						
2nd qt vs 1st qt	14938.73	-9.12%	-1362.27	-2758.05	193.44	**0.0026**
3rd qt vs 1st qt		-11.56%	-1727.63	-3193.38	-78.97	
4th qt vs 1st qt		-22.03%	-3290.47	-4710.71	-1673.01	
Breastcancer-related						
2nd qt vs 1st qt	2735.79	8.14%	222.59	-286.80	837.92	0.8236
3rd qt vs 1st qt		8.33%	227.77	-306.39	879.36	
4th qt vs 1st qt		6.96%	190.46	-388.14	911.65	
Hypertension-related						
2nd qt vs 1st qt	10779.26	-9.53%	-1027.73	-2147.97	237.89	**0.0036**
3rd qt vs 1st qt		-13.39%	-1443.76	-2601.92	-121.58	
4th qt vs 1st qt		-24.08%	-2595.73	-3725.26	-1285.33	
Hyperlipidemia-related						
2nd qt vs 1st qt	6145.35	-3.77%	-231.86	-1051.67	719.88	0.2707
3rd qt vs 1st qt		1.67%	102.93	-836.52	1208.62	
4th qt vs 1st qt		-15.38%	-945.16	-1816.18	101.11	

Diabetes-related						
2nd qt vs 1st qt	3474.38	-22.14%	-769.07	-1262.75	-165.19	**0.0090**
3rd qt vs 1st qt		-27.95%	-971.06	-1462.49	-359.61	
4th qt vs 1st qt		-29.55%	-1026.52	-1550.52	-359.78	

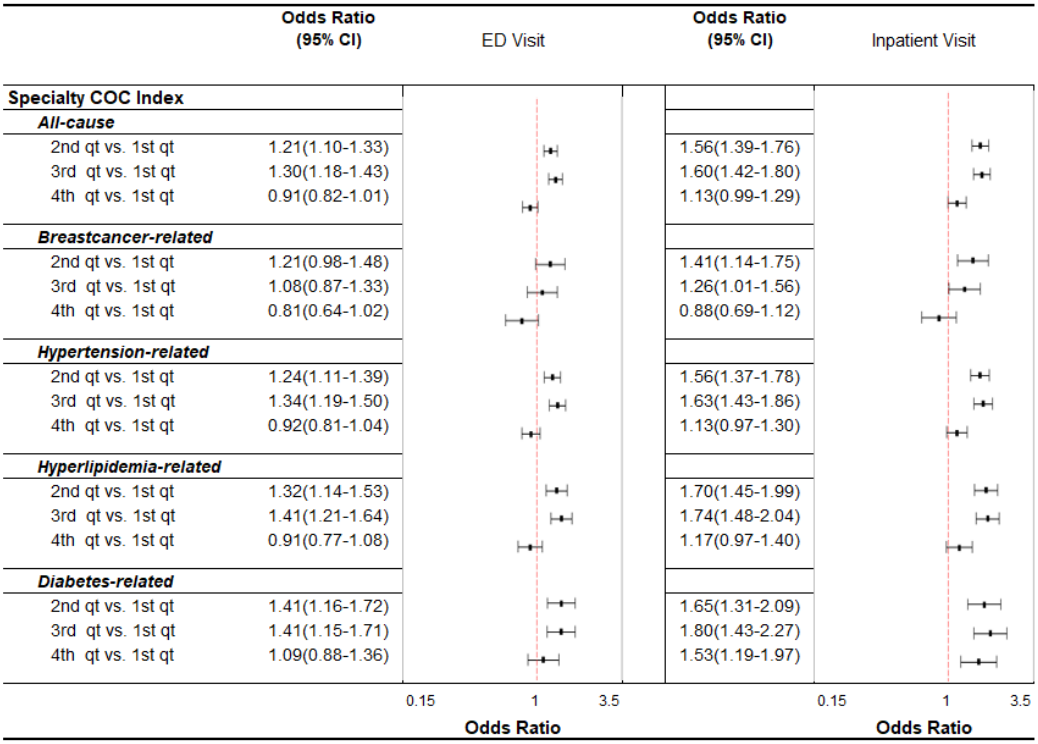
qt, quartile.

Bold, P-value < 0.05

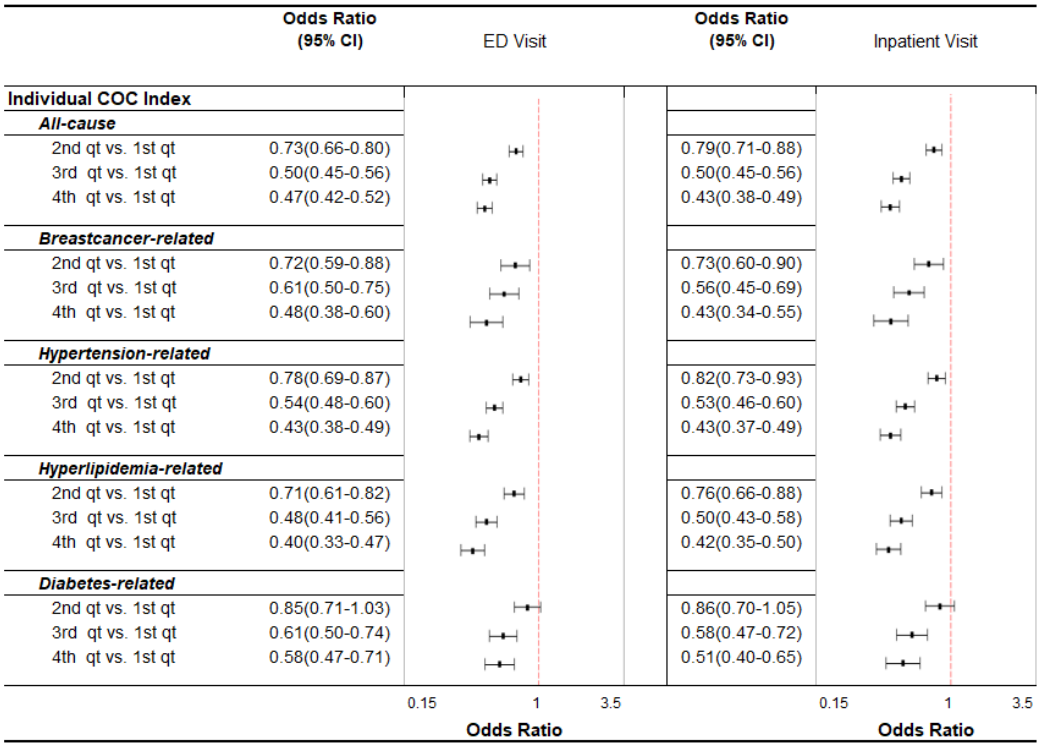
Table 4.3.4 showed the results of two stage models for the association of COC Indices (Specialty and Individual COC) and inpatient cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of inpatient visit and a linear regression model for the cost of inpatient visit. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Figure 4.3.2 Odds of Incidence of Emergency Department visit and Hospitalization among Breast Cancer Patients with Comorbidities Associated with the COC Index, after Hormone Therapy Initiation

A. Specialty COC Index



B. Individual COC Index



qt, quartile.

Figure 4.3.2 showed the results of logistic regression for the association of COC Indices (Specialty and Individual COC) and health care service utilization (ED and inpatient). Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

CHAPTER 5 DISCUSSION AND CONCLUSIONS

Although the five-year survival rate for female breast cancer patients reached 89% in 2012, breast cancer is still the second deadliest cancer for women in the U.S.[27,28] Approximately 68.7% of cancer patients have at least one chronic comorbidity,[29] and 60% of breast cancer survivors die from causes unrelated to cancer.[32] Breast cancer patients with multiple comorbidities are often faced with the need to see multiple health care providers in different specialties.[1] Consequently, health care management for breast cancer survivors with comorbidities can be complicated.[1] Poor continuity of care and coordination among providers have been observed between primary care providers (PCP) and oncologists along the spectrum of acute cancer treatment and survivorship care.[3,4] To promote communication and coordination among health providers for cancer survivorship, the American Society of Clinical Oncology (ASCO) developed cancer survivorship care plan (SCP).[115] However, only limited effects of SCP on health outcomes were found by researchers.[57] The suboptimal comorbidity management following a cancer diagnosis may lead to high mortality risk and increased costs.[10-14] Strategies are needed to address these problematic issues during breast cancer survivorship care.

The definition of Continuity of Care (COC) is the “degree to which a series of discrete healthcare events are experienced as coherent and connected and consistent with the patient ’s medical needs and personal context”.[23] And according to American Academy of Family Physicians, the definition of COC is the cooperation of one patient and his/her physician or care team during the process of health care management aiming at delivering high quality and cost-effective medical care to the patient.[24,25] COC is essential to the health care system since it indicates physicians’ continuity of knowledge about patients’ medical conditions, service provision for patients, and the health care management by multiple providers to the same patient.[23,107] Consequesntly, COC is significantly associated with patients’ satisfaction, quality of care, and their health outcomes including mortality, medication adherence, health care service

utilization, and health care costs.[16-22] Previous research has demonstrated that patients with higher COC were more likely to have a lower risk of mortality.[16,34-36] Patients were more likely to adhere to diabetes medication and statins when they had higher COC.[18,47] In patients with chronic conditions, those with higher COC had significantly less health care cost and service utilization.[18,19,54,55] However, these studies were focused on non-cancer patients. Research is needed to understand the association of COC and health outcomes within breast cancer patients who had comorbidities.

This study focused on breast cancer patients with cardiometabolic diseases (hypertension, hyperlipidemia, and diabetes) since a large proportion of these patients had poor health outcomes[32,37,42,105,136,137] and they were more likely to receive poor continuity of care during their follow-up care after their cancer diagnoses.[1] This situation is even worse for ER+ breast cancer patients who have cardiometabolic comorbidities. The objective of this research is to measure the continuity of care received by breast cancer patients with cardiometabolic comorbidities and the corresponding health outcomes. We included three major aspects of health outcomes for breast cancer patients: (1) mortality, (2) medication adherence, (3) health care service utilization and health care costs. The findings of this research and the implications of the findings are summarized in this chapter.

Aim 1, The Risk of Mortality

The aim 1 study examined the association of continuity of care and the risk of mortality for breast cancer patients with cardiometabolic comorbidities for up to five years of cancer survival. We found that the average scores of the COC Index increased slightly across the entire study period for two COC Indices (Specialty and Individual COC). Patients with stage IV breast cancer had the highest Specialty and Individual COC Indices than others. Patients with advanced cancer stages and more comorbidities had lower survival rates during the whole study period. After controlling for patients' characteristics, we found significant associations between continuity of care and the risk of mortality. These associations were consistent in all

sensitivity analyses with or without lagged effects. However, the results were contradictory among different types of COC. Patients who received high continuity of care to an individual provider had lower risks of mortality compared to those who received low continuity of care. Patients who received high continuity of care to a specialty group had higher risks of mortality compared with those who received low continuity of care.

Aim 2, Mediation adherence

The aim 2 study estimated the association of continuity of care and medication adherence in 8,081 breast cancer patients who had cardiometabolic comorbidities. We compared the effect of two types of COC Indices (Specialty COC and Individual COC) on four therapeutic groups separately (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). The adherence rates for Hormone Therapy from year 1 to year 4 decreased by 10%. The adherence rates for antihypertensives, hyperlipidemia, and diabetes medications from year 1 to year 4 decreased by 6%, 3%, and 12% respectively. Patients who adhered to their medications had a slightly higher continuity of care to an individual provider than those who did not. For the adherence to antihypertensives and hyperlipidemia medication, patients who adhered had a slightly lower continuity of care to a specialty group than patients who did not. After controlling for patients' characteristics, our fully adjusted models found significant associations among COC and medication adherence. Patients with higher continuity of care to a specialty group were less likely to adhere to antihypertensives and hyperlipidemia medications. Patients with higher continuity of care to an individual provider were more likely to adhere to hyperlipidemia and diabetes medications. Similar results were obtained in the sensitivity analyses using unadjusted models and partially adjusted models.

Aim 3, Health care service utilization and costs

The aim 3 study analyzed the associations between continuity of care and health care service utilization and costs of breast cancer patients with cardiometabolic diseases. We found that the average COC Indices were lower in patients who had ED or inpatient visits than in the overall population. After controlling for patients' characteristics, our longitudinal analyses found significant associations between continuity of care and selected health outcomes. These associations were controversial between the Individual COC models and the Specialty COC models. Patients with intermediate continuity of care to a specialty group were more likely to have ED or inpatient visits for all conditions. However, patients with high continuity of care to an individual provider were less likely to have ED or inpatient visits for all conditions. Accordingly, high continuity of care to a specialty group were associated with increased inpatient costs (all-cause, hypertension, hyperlipidemia, and diabetes related). High continuity of care to an individual were associated with reduced ED (all-cause related) and inpatient costs (all-cause, hypertension, and diabetes related).

Conclusions and Implications

To our knowledge, the present study is among the first that focused on the association of continuity of care and health outcomes in breast cancer patients with cardiometabolic comorbidities. This study provided empirical evidence of the associations of continuity of care with selected health outcomes (mortality, medication adherence, and health care service utilization and health care costs) within breast cancer patients who had cardiometabolic comorbidities. We found mixed associations of continuity of care and health outcomes based on different scopes of medical disciplines. These results indicated that concentrated individual provider visits could protect patients from all-cause mortality, medication non-adherence, and health service utilization and costs. In contrast, concentrated visits to specialties could be associated with a high risk of mortality, non-adherence to medication, and more health service

utilization and higher costs in patients. The findings of this study provoked the needs for further research.

First, the contradictory results of different models of COC prompted the necessity of better understanding of the continuity of care based on different medical disciplines. According to the definition, the COC Index could be calculated based on patients' visits to individual health care providers or provider groups. As described by our study (in Chapter 4), breast cancer patients with the same health outcome could have a high Specialty COC Index while still having a low Individual COC Index. Plus, previous studies found strategies of promoting communication and coordination among health providers for cancer survivorship only had limited effects on health outcomes.[57,113,114] Therefore, it could be helpful for future studies to provide more evidence of the association of the COC and health outcomes based on different medical disciplines for breast cancer patients with comorbidities. One way is to investigate the details of visiting patterns to each provider specialty group and the related health outcomes for these patients. Another way is to include multiple types of health care providers (e.g., nurse practitioners, physician assistants, or pharmacists) when estimating continuity of care during cancer patients' survivorship care.

Second, future studies conducted in different settings are needed. Our study provided evidence of the association of continuity of care and health outcomes based on Medicare patients' outpatient physician office visits. Patients from various study settings might have different patterns of visits to health care providers and different continuity of care. For example, patients under different insurance coverage (e.g. private insurance vs. Medicare or Medicaid) or within different health care systems (e.g. European countries vs. the United States) might have different patterns of visits to health care providers due to their access to care. Likewise, patients getting care from medical facilities such as nursing homes might have different continuity of care than patients without nursing home stay. The continuity of care during hospice care for cancer

patients might be different if patients stay at home, or in nursing homes, or assisted living facilities. Further, patients with different diseases might have different patterns of visits to health care providers according to the treatment requirements of each disease type. Thus, it is important to conduct future research under multiple settings for multiple population groups.

Third, it will be helpful to study the association of COC and other aspects of health care management in cancer patients, since our study showed significant associations of COC and health outcomes. These aspects include patients' satisfaction, quality of care, and other types of health care utilization and cost. For example, COC could relate to the quality of care during a patient's survivorship (e.g., hemoglobin A1c test or eye examination for diabetes patients, lipid profile for patients with angina diagnoses). In addition, a patient's home health service, nursing home stay, and assisted living facility utilization and costs might be affected by her COC. Therefore, studies are needed to provide more evidence in these aspects of health care management.

Fourth, the evidence provided by this study should be considered carefully by policymakers and others when guiding future changes in the health care delivery system. Since 2010, policymakers launched multiple renovations to improve coordination and communication of care in the U.S. health care system. For example, from 2010, Medicare fee-for-service beneficiaries could get coordinated care by groups of health care providers through Accountable Care Organizations (ACO).[113] In 2014, the American Society of Clinical Oncology (ASCO) developed a new cancer survivorship care plan (SCP) to promote communication and coordination among health providers for cancer survivorship.[115] Since 2016, the CMS issued new nursing home regulations, which enhanced physician service and promoted communication between pharmacists and physicians.[116] However, limited improvements were found for the health outcomes of cancer patients, and the element of continuity of care was not emphasized in these policy changes.[57,113,114] Our study found that concentrated individual provider visits

could protect patients from all-cause mortality, medication non-adherence, and health service utilization and costs. Whereas, concentrated visits to specialties could be associated with a high risk of mortality, non-adherence to medication, and more health service utilization and higher costs in patients. Therefore, strategies for improving the continuity of care were needed. These strategies include promoting concentrated provider visits by increasing patients' awareness and supporting long term individual provider concentrated care. Meanwhile, these strategies should also optimize the coordination among multiple specialties by providing cancer specified medical facility-based care to patients. For example, build cancer-related medical homes and include patient navigators during survivorship care. The findings of this study could be applied to the health care management of patients with other types of cancers or chronic diseases.

REFERENCE

1. Council NR. *From cancer patient to cancer survivor: lost in transition.* Washington, DC: National Academies Press; 2005.
2. Smith SD, Nicol KM, Devereux J, Cornbleet MA. Encounters with doctors: quantity and quality. *Palliat Med.* 1999;13(3):217-223.
3. Dossett LA, Hudson JN, Morris AM, et al. The primary care provider (PCP)-cancer specialist relationship: A systematic review and mixed-methods meta-synthesis. *CA Cancer J Clin.* 2017;67(2):156-169.
4. Cohen HJ. A model for the shared care of elderly patients with cancer. *Journal of the American Geriatrics Society.* 2009;57(s2):s300-s302.
5. Lee L, Cheung WY, Atkinson E, Krzyzanowska MK. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(1):106-117.
6. Keating NL, Landrum MB, Klabunde CN, et al. Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(15):2532-2537.
7. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA: a cancer journal for clinicians.* 2016.
8. Sada Y, Street Jr RL, Singh H, Shada R, Naik AD. Primary care and communication in shared cancer care: a qualitative study. *The American journal of managed care.* 2011;17(4):259.
9. Klabunde CN, Han PK, Earle CC, et al. Physician roles in the cancer-related follow-up care of cancer survivors. *Family medicine.* 2013;45(7):463.
10. Calip GS, Boudreau DM, Loggers ET. Changes in adherence to statins and subsequent lipid profiles during and following breast cancer treatment. *Breast cancer research and treatment.* 2013;138(1):225-233.
11. Calip GS, Hubbard RA, Stergachis A, Malone KE, Gralow JR, Boudreau DM. Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. *Pharmacoepidemiology and drug safety.* 2015;24(1):75-85.
12. Stuart BC, Davidoff AJ, Erten MZ. Changes in Medication Management After a Diagnosis of Cancer Among Medicare Beneficiaries With Diabetes. *Journal of Oncology Practice.* 2015:JOP. 2014.003046.
13. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *The New England journal of medicine.* 2003;348(26):2635-2645.
14. Institute of Medicine Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington (DC): National Academies Press (US); 2001.
15. Campbell RJ, Jr. Adherence to medication. *The New England journal of medicine.* 2005;353(18):1972-1974; author reply 1972-1974.
16. Worrall G, Knight J. Continuity of care is good for elderly people with diabetes: retrospective cohort study of mortality and hospitalization. *Can Fam Physician.* 2011;57(1):e16-20.
17. Warren JR, Falster MO, Tran B, Jorm L. Association of Continuity of Primary Care and Statin Adherence. *PLoS One.* 2015;10(10):e0140008.
18. Chen CC, Tseng CH, Cheng SH. Continuity of care, medication adherence, and health care outcomes among patients with newly diagnosed type 2 diabetes: a longitudinal analysis. *Medical care.* 2013;51(3):231-237.
19. Hussey PS, Schneider EC, Rudin RS, Fox DS, Lai J, Pollack CE. Continuity and the costs of care for chronic disease. *JAMA Intern Med.* 2014;174(5):742-748.

20. Gulliford M, Naithani S, Morgan M. What is' continuity of care'? *Journal of Health Services Research & Policy.* 2006;11(4):248-250.
21. Sparbel KJ, Anderson MA. A continuity of care integrated literature review, Part 2: Methodological issues. *J Nurs Scholarsh.* 2000;32(2):131-135.
22. Sparbel KJ, Anderson MA. Integrated literature review of continuity of care: Part 1, Conceptual issues. *J Nurs Scholarsh.* 2000;32(1):17-24.
23. Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. *BMJ (Clinical research ed).* 2003;327(7425):1219-1221.
24. American Academy of Family Physicians. Continuity of Care, Definition of. 1983; https://www.aafp.org/about/policies/all/definition-care.html. Accessed 20th, Sep, 2018.
25. Bice TW, Boxerman SB. A quantitative measure of continuity of care. *Medical care.* 1977;15(4):347-349.
26. Steinwachs DM. Measuring provider continuity in ambulatory care: an assessment of alternative approaches. *Medical care.* 1979;17(6):551-565.
27. American Cancer Society. Cancer Facts and Figures 2016. 2016.
28. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review. 2015.
29. Ogle KS, Swanson GM, Woods N, Azzouz F. Cancer and comorbidity. *Cancer.* 2000;88(3):653-663.
30. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel Jr EL. Prognostic importance of comorbidity in a hospital-based cancer registry. *Jama.* 2004;291(20):2441-2447.
31. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JWW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Critical reviews in oncology/hematology.* 2005;55(3):231-240.
32. Chapman J-AW, Meng D, Shepherd L, et al. Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. *Journal of the National Cancer Institute.* 2008;100(4):252-260.
33. Ritchie CS, Kvale E, Fisch MJ. Multimorbidity: an issue of growing importance for oncologists. *J Oncol Pract.* 2011;7(6):371-374.
34. Wolinsky FD, Bentler SE, Liu L, et al. Continuity of care with a primary care physician and mortality in older adults. *J Gerontol A Biol Sci Med Sci.* 2010;65(4):421-428.
35. Damiani G, Federico B, Venditti A, et al. Hospital discharge planning and continuity of care for aged people in an Italian local health unit: does the care-home model reduce hospital readmission and mortality rates? *BMC Health Serv Res.* 2009;9:22.
36. Leleu H, Minvielle E. Relationship between longitudinal continuity of primary care and likelihood of death: analysis of national insurance data. *PLoS One.* 2013;8(8):e71669.
37. Calip GS, Elmore JG, Boudreau DM. Characteristics associated with nonadherence to medications for hypertension, diabetes, and dyslipidemia among breast cancer survivors. *Breast Cancer Res Treat.* 2017;161(1):161-172.
38. Hansen RA, Voils CI, Farley JF, et al. Prescriber continuity and medication adherence for complex patients. *Ann Pharmacother.* 2015;49(3):293-302.
39. Young JM, Walsh J, Butow PN, Solomon MJ, Shaw J. Measuring cancer care coordination: development and validation of a questionnaire for patients. *BMC cancer.* 2011;11(1):1.
40. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *Journal of Clinical Oncology.* 2014;32(21):2255-2269.
41. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687-1717.

42. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(27):4120-4128.
43. Farias AJ, Du XL. Association Between Out-Of-Pocket Costs, Race/Ethnicity, and Adjuvant Endocrine Therapy Adherence Among Medicare Patients With Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(1):86-95.
44. Ebner F, Hancke K, Blettner M, et al. Aggressive Intrinsic Subtypes in Breast Cancer: A Predictor of Guideline Adherence in Older Patients With Breast Cancer? *Clin Breast Cancer.* 2015;15(4):e189-195.
45. Hershman DL, Tsui J, Wright JD, Coromilas EJ, Tsai WY, Neugut AI. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(9):1053-1059.
46. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028-3035.
47. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol.* 2007;166(3):348-354.
48. Uijen AA, Bosch M, van den Bosch WJ, Bor H, Wensing M, Schers HJ. Heart failure patients' experiences with continuity of care and its relation to medication adherence: a cross-sectional study. *BMC Fam Pract.* 2012;13:86.
49. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Arch Intern Med.* 2007;167(8):847-852.
50. Earle CC, Neville BA. Under use of necessary care among cancer survivors. *Cancer.* 2004;101(8):1712-1719.
51. Medicare Cf, Services M. Chronic conditions among Medicare beneficiaries, chartbook, 2012 edition. Baltimore, MD. 2012. 2015.
52. Subramanian S, Tangka FK, Sabatino SA, et al. Impact of chronic conditions on the cost of cancer care for Medicaid beneficiaries. *Medicare Medicaid Res Rev.* 2012;2(4).
53. Maciejewski ML, Powers BJ, Sanders LL, et al. The intersection of patient complexity, prescriber continuity and acute care utilization. *Journal of general internal medicine.* 2014;29(4):594-601.
54. Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Effect of continuity of care on hospital utilization for seniors with multiple medical conditions in an integrated health care system. *Annals of family medicine.* 2015;13(2):123-129.
55. Barker I, Steventon A, Deeny SR. Association between continuity of care in general practice and hospital admissions for ambulatory care sensitive conditions: cross sectional study of routinely collected, person level data. *BMJ (Clinical research ed).* 2017;356:j84.
56. Eichner J, Blumenthal D. Medicare in the 21st century: building a better chronic care system. 2003.
57. Jacobsen PB, DeRosa AP, Henderson TO, et al. Systematic Review of the Impact of Cancer Survivorship Care Plans on Health Outcomes and Health Care Delivery. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2018;36(20):2088-2100.
58. Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. 2017; https://seer.cancer.gov/statfacts/html/breast.html. Accessed April, 23, 2017.
59. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. 2016.

60. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology.* 2010;17(6):1471-1474.
61. breastcancer.org. Hormone Receptor Status. 2017; http://www.breastcancer.org/symptoms/diagnosis/hormone_status. Accessed April, 23, 2017.
62. breastcancer.org. HER2 Status. 2017; http://www.breastcancer.org/symptoms/diagnosis/her2. Accessed April, 23, 2017.
63. Goldman L, Schafer AI. *Goldman's Cecil medicine.* Elsevier Health Sciences; 2011.
64. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. *Breast Cancer Res.* 2007;9(1):R6.
65. breastcancer.org. Male Breast Cancer. 2017; http://www.breastcancer.org/symptoms/types/male_bc. Accessed April, 24, 2017.
66. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer.* 1997;71(5):800-809.
67. National Cancer Institute. Breast Cancer Treatment. 2017; https://www.cancer.gov/types/breast/patient/breast-treatment-pdq#section/_185.
68. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087-2106.
69. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* 2011;378(9793):771-784.
70. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *The New England journal of medicine.* 2005;353(16):1673-1684.
71. Wheeler SB, Kohler RE, Reeder-Hayes KE, et al. Endocrine therapy initiation among Medicaid-insured breast cancer survivors with hormone receptor-positive tumors. *Journal of cancer survivorship : research and practice.* 2014;8(4):603-610.
72. National Cancer Institute. Hormone Therapy for Breast Cancer. 2017; https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet.
73. Chia YH, Ellis MJ, Ma CX. Neoadjuvant endocrine therapy in primary breast cancer: indications and use as a research tool. *Br J Cancer.* 2010;103(6):759-764.
74. National Comprehensive Cancer Network. NCCN Guidelines for Patients. 2016; www.NCCN.org/patients. Accessed April 26, 2017.
75. Brunton LL, Lazo JS, Parker KL. Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 2006.
76. Kluwer W. Lexicomp Online. 2017; http://online.lexi.com/action/home. Accessed April 25, 2017.
77. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *Journal of Clinical Oncology.* 2009;28(3):509-518.
78. National Cancer Institute. Age. 2015; https://www.cancer.gov/about-cancer/causes-prevention/risk/age. Accessed April 26, 2017.
79. Frick KD, Snyder CF, Herbert RJ, et al. Relationship Between Quality of Comorbid Condition Care and Costs for Cancer Survivors. *J Oncol Pract.* 2016;12(6):e734-745.
80. Fortin M, Bravo G, Hudon C, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Quality of Life Research.* 2006;15(1):83-91.
81. Prazeres F, Santiago L. Relationship between health-related quality of life, perceived family support and unmet health needs in adult patients with multimorbidity attending primary care in Portugal: a multicentre cross-sectional study. *Health Qual Life Outcomes.* 2016;14(1):156.

82. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer.* 2014;120(9):1290-1314.
83. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. *J Clin Epidemiol.* 1997;50(6):725-733.
84. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007;17(8):584-590.
85. Centers for Disease Control and Prevention. Strategies for Reducing Health Disparities — Selected CDC-Sponsored Interventions, United States, 2016. 2016; https://www.cdc.gov/mmwr/volumes/65/su/pdfs/su6501.pdf. Accessed April 29, 2017.
86. Rose DP, Haffner SM, Baillargeon J. Adiposity, the metabolic syndrome, and breast cancer in African-American and white American women. *Endocr Rev.* 2007;28(7):763-777.
87. Agnoli C, Berrino F, Abagnato CA, et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. *Nutr Metab Cardiovasc Dis.* 2010;20(1):41-48.
88. Fisher M. Cardiometabolic disease: the new challenge? *Practical Diabetes International.* 2006;23(3):95-97.
89. American Heart Accosiation. About Metabolic Syndrome. https://www.heart.org/HEARTORG/Conditions/More/MetabolicSyndrome/About-Metabolic-Syndrome_UCM_301920_Article.jsp. Accessed April 29, 2017.
90. American Heart Association. High Blood Pressure. 2013; https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319587.pdf. Accessed April 29, 2017.
91. Centers for Disease Control and Prevention. Diabetes Public Health Resource. 2015; https://www.cdc.gov/diabetes/statistics/age/fig1.htm. Accessed April 29, 2017.
92. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation.* 1999;99(9):1165-1172.
93. Castro JP, El-Atat FA, McFarlane SI, Aneja A, Sowers JR. Cardiometabolic syndrome: pathophysiology and treatment. *Curr Hypertens Rep.* 2003;5(5):393-401.
94. Elmer PJ, Obarzanek E, Vollmer WM, et al. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann Intern Med.* 2006;144(7):485-495.
95. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care.* 2007;30(6):1374-1383.
96. Mulrow CD, Lau J, Cornell J, Brand M. Pharmacotherapy for hypertension in the elderly. *The Cochrane Library.* 1998.
97. Broeders N, Knoop C, Abramowicz D. Drug treatment of lipid disorders. *The New England journal of medicine.* 1999;341(26):2020-2021.
98. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England journal of medicine.* 2008;359(15):1577-1589.
99. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama.* 2014;311(5):507-520.

100. American College of Cardiology. 2017 Guideline for High Blood Pressure in Adults. 2017; http://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/11/09/11/41/2017-guideline-for-high-blood-pressure-in-adults.
101. Lambert M. ACC/AHA Release Updated Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD Risk. *American family physician.* 2014;90(4):260.
102. Chamberlain JJ, Herman WH, Leal S, et al. Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med.* 2017;166(8):572-578.
103. Americian Cancer Society. Economic Impact of Cancer. 2017; https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html. Accessed May 31, 2017.
104. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
105. Wells TS, Bhattarai GR, Hawkins K, et al. Care Coordination Challenges Among High-Needs, High-Costs Older Adults in a Medigap Plan. *Prof Case Manag.* 2016;21(6):291-301.
106. Hansen RA, Maciejewski M, Yu-Isenberg K, Farley JF. Adherence to antipsychotics and cardiometabolic medication: association with health care utilization and costs. *Psychiatric Services.* 2012.
107. Johnson S, Prosser D, Bindman J, Szmukler G. Continuity of care for the severely mentally ill: concepts and measures. *Soc Psychiatry Psychiatr Epidemiol.* 1997;32(3):137-142.
108. Pham HH, Schrag D, O'Malley AS, Wu B, Bach PB. Care patterns in Medicare and their implications for pay for performance. *New England Journal of Medicine.* 2007;356(11):1130-1139.
109. Naik AD, Singh H. Electronic health records to coordinate decision making for complex patients: what can we learn from wiki? *Medical Decision Making.* 2010;30(6):722-731.
110. Steinberg ML, Rose CM. Posttreatment follow-up of radiation oncology patients in a managed care environment. *Int J Radiat Oncol Biol Phys.* 1996;35(1):113-116.
111. Snyder CF, Frick KD, Herbert RJ, et al. Comorbid condition care quality in cancer survivors: role of primary care and specialty providers and care coordination. *Journal of cancer survivorship : research and practice.* 2015;9(4):641-649.
112. Audet AM, Doty MM, Peugh J, Shamasdin J, Zapert K, Schoenbaum S. Information technologies: when will they make it into physicians' black bags? *MedGenMed.* 2004;6(4):2.
113. Kaufman BG, Spivack BS, Stearns SC, Song PH, O'Brien EC. Impact of Accountable Care Organizations on Utilization, Care, and Outcomes: A Systematic Review. *Med Care Res Rev.* 2019;76(3):255-290.
114. Herrel LA, Norton EC, Hawken SR, Ye Z, Hollenbeck BK, Miller DC. Early impact of Medicare accountable care organizations on cancer surgery outcomes. *Cancer.* 2016;122(17):2739-2746.
115. Mayer DK, Nekhlyudov L, Snyder CF, Merrill JK, Wollins DS, Shulman LN. American Society of Clinical Oncology clinical expert statement on cancer survivorship care planning. *J Oncol Pract.* 2014;10(6):345-351.
116. Unroe KT, Ouslander JG, Saliba D. Nursing Home Regulations Redefined: Implications for Providers. *J Am Geriatr Soc.* 2018;66(1):191-194.
117. Maciejewski ML, Hammill BG, Bayliss EA, et al. Prescriber Continuity and Disease Control of Older Adults. *Medical care.* 2017;55(4):405-410.
118. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med.* 2011;171(9):814-822.

119. Moon Z, Moss-Morris R, Hunter MS, Carlisle S, Hughes LD. Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review. *Patient Prefer Adherence.* 2017;11:305-322.
120. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2001;19(2):322-328.
121. Pollack CE, Frick KD, Herbert RJ, et al. It's who you know: patient-sharing, quality, and costs of cancer survivorship care. *Journal of cancer survivorship : research and practice.* 2014;8(2):156-166.
122. Gerteis J, Izrael D, Deitz D, et al. Multiple chronic conditions chartbook. *Rockville, MD: Agency for Healthcare Research and Quality.* 2014.
123. Ward BW. Multiple chronic conditions among US adults: a 2012 update. *Preventing chronic disease.* 2014;11.
124. Shortell SM. Continuity of medical care: conceptualization and measurement. *Medical care.* 1976;14(5):377-391.
125. van Walraven C, Oake N, Jennings A, Forster AJ. The association between continuity of care and outcomes: a systematic and critical review. *J Eval Clin Pract.* 2010;16(5):947-956.
126. Hoertel N, Limosin F, Leleu H. Poor longitudinal continuity of care is associated with an increased mortality rate among patients with mental disorders: results from the French National Health Insurance Reimbursement Database. *Eur Psychiatry.* 2014;29(6):358-364.
127. Geroldinger A, Sauter SK, Heinze G, Endel G, Dorda W, Duftschmid G. Mortality and continuity of care - Definitions matter! A cohort study in diabetics. *PLoS One.* 2018;13(1):e0191386.
128. Chan CL, You HJ, Huang HT, Ting HW. Using an integrated COC index and multilevel measurements to verify the care outcome of patients with multiple chronic conditions. *BMC Health Serv Res.* 2012;12:405.
129. Meichenbaum D, Turk DC. *Facilitating treatment adherence: A practitioner's guidebook.* Plenum Press; 1987.
130. Americian Cancer Society. Breast Cancer Hormone Receptor Status. *Understanding A Breast Cancer Diagnosis* 2017; https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html. Accessed April, 03, 2017.
131. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care.* 2005;43(6):521-530.
132. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc.* 2011;86(4):304-314.
133. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26(5):331-342.
134. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care.* 2005;11(7):449-457.
135. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* 2006;40(7-8):1280-1288.
136. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer.* 2008;99(11):1763-1768.
137. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat.* 2012;134(2):459-478.
138. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast cancer research and treatment.* 2011;126(2):529-537.

139. Santorelli ML, Steinberg MB, Hirshfield KM, et al. Effects of breast cancer on chronic disease medication adherence among older women. *Pharmacoepidemiol Drug Saf.* 2016;25(8):898-907.
140. Ferdinand KC, Senatore FF, Clayton-Jeter H, et al. Improving Medication Adherence in Cardiometabolic Disease: Practical and Regulatory Implications. *J Am Coll Cardiol.* 2017;69(4):437-451.
141. Reiner Z, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. *Atherosclerosis.* 2016;246:243-250.
142. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-1913.
143. Shin S, Jang S, Lee TJ, Kim H. Association between non-adherence to statin and hospitalization for cardiovascular disease and all-cause mortality in a national cohort. *Int J Clin Pharmacol Ther.* 2014;52(11):948-956.
144. Herttua K, Martikainen P, Batty GD, Kivimaki M. Poor Adherence to Statin and Antihypertensive Therapies as Risk Factors for Fatal Stroke. *J Am Coll Cardiol.* 2016;67(13):1507-1515.
145. Kirkman MS, Rowan-Martin MT, Levin R, et al. Determinants of adherence to diabetes medications: findings from a large pharmacy claims database. *Diabetes Care.* 2015;38(4):604-609.
146. Garcia-Perez LE, Alvarez M, Dilla T, Gil-Guillen V, Orozco-Beltran D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther.* 2013;4(2):175-194.
147. Goh H, Kwan YH, Seah Y, Low LL, Fong W, Thumboo J. A systematic review of the barriers affecting medication adherence in patients with rheumatic diseases. *Rheumatol Int.* 2017.
148. Lardizabal JA, Deedwania PC. Benefits of statin therapy and compliance in high risk cardiovascular patients. *Vasc Health Risk Manag.* 2010;6:843-853.
149. van der Laan DM, Elders PJM, Boons C, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. *J Hum Hypertens.* 2017.
150. Jaam M, Awaisu A, Mohamed Ibrahim MI, Kheir N. A holistic conceptual framework model to describe medication adherence in and guide interventions in diabetes mellitus. *Res Social Adm Pharm.* 2017.
151. Hyre AD, Krousel-Wood MA, Muntner P, Kawasaki L, DeSalvo KB. Prevalence and predictors of poor antihypertensive medication adherence in an urban health clinic setting. *J Clin Hypertens (Greenwich).* 2007;9(3):179-186.
152. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *J Natl Med Assoc.* 2003;95(1):17-27.
153. Yang Y, Thumula V, Pace PF, Banahan BF, 3rd, Wilkin NE, Lobb WB. Predictors of medication nonadherence among patients with diabetes in Medicare Part D programs: a retrospective cohort study. *Clin Ther.* 2009;31(10):2178-2188; discussion 2150-2171.
154. Holmes HM, Luo R, Hanlon JT, Elting LS, Suarez-Almazor M, Goodwin JS. Ethnic disparities in adherence to antihypertensive medications of medicare part D beneficiaries. *J Am Geriatr Soc.* 2012;60(7):1298-1303.
155. Tinari N, Fanizza C, Romero M, et al. Identification of subgroups of early breast cancer patients at high risk of nonadherence to adjuvant hormone therapy: results of an Italian survey. *Clin Breast Cancer.* 2015;15(2):e131-137.
156. Forsyth J, Schoenthaler A, Chaplin WF, Ogedegbe G, Ravenell J. Perceived discrimination and medication adherence in black hypertensive patients: the role of stress and depression. *Psychosom Med.* 2014;76(3):229-236.

157. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. *Age Ageing.* 2010;39(4):481-487.
158. Griffith S. A review of the factors associated with patient compliance and the taking of prescribed medicines. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 1990;40(332):114-116.
159. Saadat Z, Nikdoust F, Aerab-Sheibani H, et al. Adherence to Antihypertensives in Patients With Comorbid Condition. *Nephrourol Mon.* 2015;7(4):e29863.
160. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol.* 1995;14(1):88-90.
161. Wickersham KE, Sereika SM, Bender CM. Pretreatment predictors of short-term nonadherence to oral hormonal therapy for women with breast cancer. *Nurs Res.* 2013;62(4):243-251.
162. Bender CM, Gentry AL, Brufsky AM, et al. Influence of patient and treatment factors on adherence to adjuvant endocrine therapy in breast cancer. *Oncol Nurs Forum.* 2014;41(3):274-285.
163. Hughes CM. Medication non-adherence in the elderly. *Drugs & aging.* 2004;21(12):793-811.
164. Kruse W, Eggert-Kruse W, Rampmaier J, Runnebaum B, Weber E. Compliance and adverse drug reactions: a prospective study with ethinylestradiol using continuous compliance monitoring. *Clin Investig.* 1993;71(6):483-487.
165. Brito C, Portela MC, de Vasconcellos MT. Adherence to hormone therapy among women with breast cancer. *BMC Cancer.* 2014;14:397.
166. Brito C, Portela MC, Vasconcellos MT. Factors associated to persistence with hormonal therapy in women with breast cancer. *Rev Saude Publica.* 2014;48(2):284-295.
167. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother.* 2011;9(1):11-23.
168. Bardel A, Wallander MA, Svardsudd K. Factors associated with adherence to drug therapy: a population-based study. *Eur J Clin Pharmacol.* 2007;63(3):307-314.
169. Patel BV, Remigio-Baker RA, Mehta D, Thiebaud P, Frech-Tamas F, Preblick R. Effects of initial antihypertensive drug class on patient persistence and compliance in a usual-care setting in the United States. *J Clin Hypertens (Greenwich).* 2007;9(9):692-700.
170. U.S. Department of Health and Human Services. Health Literacy. 2017; https://www.hrsa.gov/publichealth/healthliteracy/.
171. Gazmararian JA, Kripalani S, Miller MJ, Echt KV, Ren J, Rask K. Factors associated with medication refill adherence in cardiovascular-related diseases: a focus on health literacy. *J Gen Intern Med.* 2006;21(12):1215-1221.
172. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychol.* 2004;23(2):207-218.
173. Mojtabai R, Olfson M. Medication costs, adherence, and health outcomes among Medicare beneficiaries. *Health Aff (Millwood).* 2003;22(4):220-229.
174. Wells KJ, Pan TM, Vazquez-Otero C, et al. Barriers and facilitators to endocrine therapy adherence among underserved hormone-receptor-positive breast cancer survivors: a qualitative study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2016;24(10):4123-4130.
175. Osterberg L, Blaschke T. Adherence to medication. *The New England journal of medicine.* 2005;353(5):487-497.
176. Rust C, Davis C. Health literacy and medication adherence in underserved African-american breast cancer survivors: a qualitative study. *Soc Work Health Care.* 2011;50(9):739-761.

177. Liu Y, Malin JL, Diamant AL, Thind A, Maly RC. Adherence to adjuvant hormone therapy in low-income women with breast cancer: the role of provider-patient communication. *Breast Cancer Res Treat.* 2013;137(3):829-836.
178. Turner BJ, Hollenbeak C, Weiner MG, Ten Have T, Roberts C. Barriers to adherence and hypertension control in a racially diverse representative sample of elderly primary care patients. *Pharmacoepidemiol Drug Saf.* 2009;18(8):672-681.
179. Gordon K, Smith F, Dhillon S. Effective chronic disease management: patients' perspectives on medication-related problems. *Patient Educ Couns.* 2007;65(3):407-415.
180. Yam FK, Akers WS, Ferraris VA, et al. Interventions to improve guideline compliance following coronary artery bypass grafting. *Surgery.* 2006;140(4):541-547; discussion 547-552.
181. the official U.S. government site of Medicare. Inpatient or outpatient hospital status affects your costs. 2017; https://www.medicare.gov/what-medicare-covers/part-a/inpatient-or-outpatient.html. Accessed Nov, 10, 2017.
182. Guy GP, Jr., Yabroff KR, Ekwueme DU, Rim SH, Li R, Richardson LC. Economic Burden of Chronic Conditions Among Survivors of Cancer in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(18):2053-2061.
183. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *Journal of the National Cancer Institute.* 2011.
184. Blumen H, Fitch K, Polkus V. Comparison of Treatment Costs for Breast Cancer, by Tumor Stage and Type of Service. *Am Health Drug Benefits.* 2016;9(1):23-32.
185. Americian Cancer Society. The cost of cancer. 2017. Accessed Nov, 10, 2017.
186. Surveillance Epidemiology and End Results. Brief Description of the SEER-Medicare Database. 2018.
187. Surveillance Epidemiology and End Results program. Site Recode ICD-O-3/WHO 2008 Definition. 2008; https://seer.cancer.gov/siterecode/icdo3_dwhoheme/. Accessed March, 01, 2018.
188. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology.* 2011;54(2):463-471.
189. icd9data.com. The Web's Free ICD-9-CM Medical Coding Reference. 2017; http://www.icd9data.com/. Accessed Dec 07, 2017.
190. National Cancer Institute. NCI Comorbidity Index Overview. 2017; https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html. Accessed Nov, 26th, 2017.
191. Balasubramanian BA, Demissie K, Crabtree BF, Strickland PA, Pawlish K, Rhoads GG. Black Medicaid beneficiaries experience breast cancer treatment delays more frequently than whites. *Ethn Dis.* 2012;22(3):288-294.
192. Smedby O, Eklund G, Eriksson EA, Smedby B. Measures of continuity of care. A register-based correlation study. *Medical care.* 1986;24(6):511-518.
193. Chen CC, Cheng SH. Continuity of care and changes in medication adherence among patients with newly diagnosed diabetes. *Am J Manag Care.* 2016;22(2):136-142.
194. Ejlertsson G, Berg S. Continuity-of-care measures. An analytic and empirical comparison. *Medical care.* 1984;22(3):231-239.
195. Brawarsky P, Neville BA, Fitzmaurice GM, Hassett MJ, Haas JS. Use of annual mammography among older women with ductal carcinoma in situ. *J Gen Intern Med.* 2012;27(5):500-505.
196. Griffiths RI, Gleeson ML, Valderas JM, Danese MD. Impact of undetected comorbidity on treatment and outcomes of breast cancer. *Int J Breast Cancer.* 2014;2014:970780.
197. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: an overview. *Medical care.* 2002;40(8):IV-26-IV-35.

198. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol.* 2000;53(12):1258-1267.
199. Silber JH, Rosenbaum PR, Clark AS, et al. Characteristics associated with differences in survival among black and white women with breast cancer. *Jama.* 2013;310(4):389-397.
200. Patel BV, Leslie RS, Thiebaud P, et al. Adherence with single-pill amlodipine/atorvastatin vs a two-pill regimen. *Vasc Health Risk Manag.* 2008;4(3):673-681.
201. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. *Medical care.* 2008;46(11):1125-1133.
202. Choudhry NK, Shrank WH, Levin RL, et al. Measuring concurrent adherence to multiple related medications. *Am J Manag Care.* 2009;15(7):457-464.
203. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *Jama.* 2002;288(4):455-461.
204. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf.* 2006;15(8):565-574; discussion 575-567.
205. FRED Economic Data. Gross Domestic Product: Implicit Price Deflator. *Economic Research Federal Reserve Bank of St. Louis* 2015; https://research.stlouisfed.org/fred2/data/GDPDEF.txt. Accessed September 8 2015.
206. Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs. *Annu Rev Public Health.* 1999;20:125-144.
207. Garrido MM, Deb P, Burgess JF, Jr., Penrod JD. Choosing models for health care cost analyses: issues of nonlinearity and endogeneity. *Health Serv Res.* 2012;47(6):2377-2397.
208. Freeman JL, Zhang D, Freeman DH, Goodwin JS. An approach to identifying incident breast cancer cases using Medicare claims data. *J Clin Epidemiol.* 2000;53(6):605-614.
209. U.S. Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. 2017; https://www.accessdata.fda.gov/scripts/cder/ob/. Accessed Dec 17, 2017.
210. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. *Diabetes Care.* 2012;35(2):299-304.
211. Bentler SE, Morgan RO, Virnig BA, Wolinsky FD. The association of longitudinal and interpersonal continuity of care with emergency department use, hospitalization, and mortality among Medicare beneficiaries. *PLoS One.* 2014;9(12):e115088.
212. Robles S, Anderson GF. Continuity of care and its effect on prescription drug use among Medicare beneficiaries with hypertension. *Medical care.* 2011;49(5):516-521.
213. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ (Clinical research ed).* 2008;336(7653):1114-1117.
214. Ye X, Gross CR, Schommer J, Cline R, St Peter WL. Association between copayment and adherence to statin treatment initiated after coronary heart disease hospitalization: a longitudinal, retrospective, cohort study. *Clin Ther.* 2007;29(12):2748-2757.
215. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence.* 2016;10:1299-1307.
216. Medicare e. Low-Income Subsidy — Medicare Extra Help Program. 2019; https://www.ehealthmedicare.com/medicare-part-d-articles/low-income-subsidy-medicare-extra-help-program/.

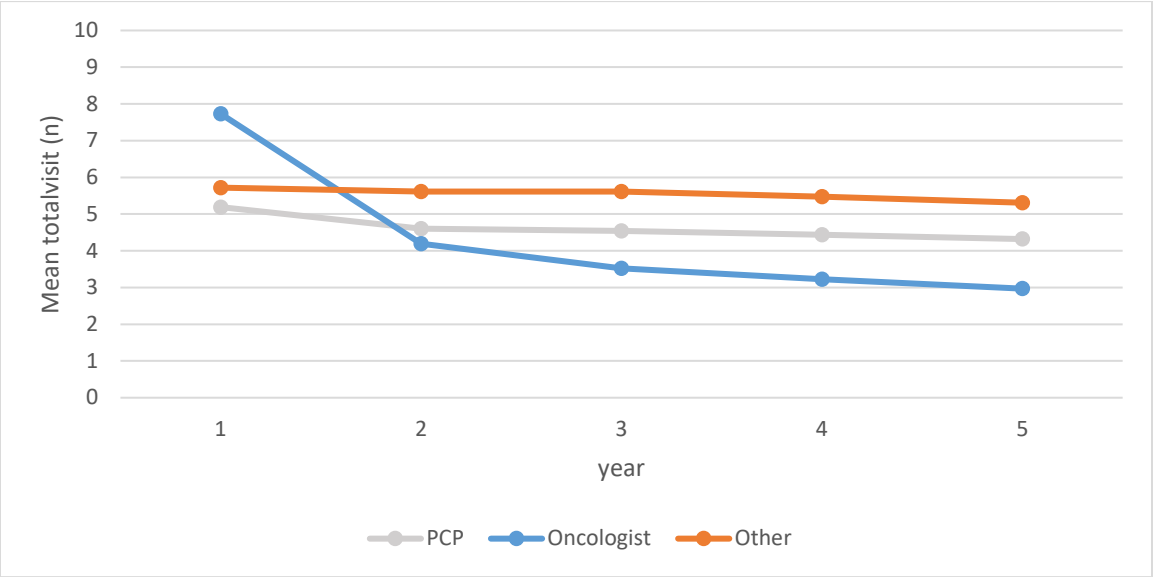
217. Allison PD. Handling Missing Data by Maximum Likelihood 2012; https://statisticalhorizons.com/wp-content/uploads/MissingDataByML.pdf. Accessed Feb, 18th, 2019.
218. Gill JM, Mainous AG, 3rd. The role of provider continuity in preventing hospitalizations. *Arch Fam Med.* 1998;7(4):352-357.
219. Arthur KC, Mangione-Smith R, Burkhart Q, et al. Quality of Care for Children With Medical Complexity: An Analysis of Continuity of Care as a Potential Quality Indicator. *Acad Pediatr.* 2018;18(6):669-676.
220. Christakis DA, Mell L, Koepsell TD, Zimmerman FJ, Connell FA. Association of lower continuity of care with greater risk of emergency department use and hospitalization in children. *Pediatrics.* 2001;107(3):524-529.
221. Chu HY, Chen CC, Cheng SH. Continuity of care, potentially inappropriate medication, and health care outcomes among the elderly: evidence from a longitudinal analysis in Taiwan. *Medical care.* 2012;50(11):1002-1009.
222. Snyder CF, Frick KD, Peairs KS, et al. Comparing care for breast cancer survivors to non-cancer controls: a five-year longitudinal study. *J Gen Intern Med.* 2009;24(4):469-474.
223. Snyder CF, Frick KD, Herbert RJ, et al. Quality of care for comorbid conditions during the transition to survivorship: differences between cancer survivors and noncancer controls. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(9):1140-1148.
224. Chin MH, Zhang JX, Merrell K. Diabetes in the African-American Medicare population. Morbidity, quality of care, and resource utilization. *Diabetes Care.* 1998;21(7):1090-1095.
225. Shaikh BT, Hatcher J. Health seeking behaviour and health service utilization in Pakistan: challenging the policy makers. *J Public Health (Oxf).* 2005;27(1):49-54.

APPENDIX

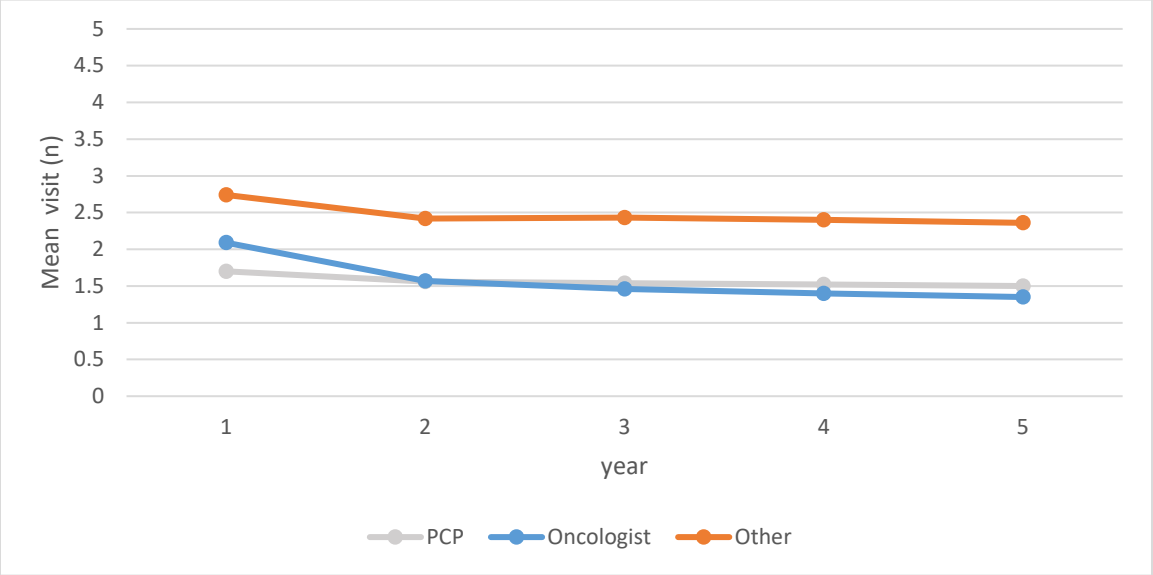
Appendix for Aim 1

Appendix Figure Aim 1.1 Number of Visits During the Whole Study Period for Each Provider Specialty.

A. Total number of visits to each provider type



B. Number of visits to different providers in each type



Appendix Figure Aim 1.1 illustrated the number of provider visits change during the whole study period for each specialty groups (PCP, Oncologist, and Other). Numbers of 1) total visits and 2) unique provider visits were counted and plotted.

Appendix Table Aim 1.1 Average Continuity of Care Index among Breast Cancer Patients at Different Tumor Stage and Numbers of Comorbidities, during the whole study period.

Year	1	2	3	4	5
Specialty COC Index (mean±std)					
Tumor Stage*					
0	0.41±0.13	0.45±0.16	0.46±0.17	0.48±0.18	0.48±0.18
I	0.42±0.13	0.43±0.15	0.44±0.16	0.45±0.17	0.46±0.17
II	0.46±0.15	0.44±0.16	0.44±0.16	0.45±0.17	0.46±0.18
III	0.51±0.16	0.47±0.17	0.46±0.17	0.45±0.17	0.44±0.17
IV	0.48±0.16	0.54±0.20	0.54±0.21	0.53±0.21	0.54±0.23
Number of Comorbidities*					
0	0.47±0.17	0.46±0.18	0.45±0.18	0.45±0.19	0.46±0.19
1	0.44±0.14	0.44±0.16	0.45±0.16	0.46±0.17	0.47±0.18
2	0.43±0.13	0.44±0.15	0.45±0.16	0.46±0.17	0.47±0.17
3	0.42±0.12	0.44±0.15	0.46±0.16	0.46±0.17	0.47±0.17
All	0.44±0.14	0.44±0.16	0.45±0.17	0.46±0.17	0.47±0.18
Individual COC Index (mean±std)					
Tumor Stage*					
0	0.36±0.21	0.40±0.25	0.41±0.26	0.41±0.26	0.42±0.26
I	0.36±0.20	0.38±0.23	0.39±0.24	0.39±0.25	0.40±0.25
II	0.38±0.21	0.39±0.24	0.39±0.24	0.39±0.25	0.39±0.25
III	0.40±0.22	0.40±0.23	0.40±0.24	0.41±0.25	0.40±0.24
IV	0.40±0.24	0.48±0.27	0.49±0.26	0.50±0.26	0.52±0.27
Number of Comorbidities*					
0	0.38±0.21	0.39±0.24	0.38±0.25	0.38±0.25	0.39±0.26
1	0.37±0.21	0.39±0.24	0.39±0.25	0.40±0.25	0.40±0.25
2	0.37±0.20	0.39±0.24	0.40±0.25	0.41±0.25	0.41±0.25
3	0.37±0.20	0.40±0.24	0.41±0.25	0.42±0.25	0.41±0.25
All	0.37±0.21	0.39±0.24	0.40±0.25	0.40±0.25	0.40±0.25

*, $p<0.05$

Appendix Table Aim 1.1 showed the average COC Indices changes during the whole study period (Specialty and Individual COC). ANCOVA analyses were applied to compare the average COC Indices among patients with different tumor stage or number of comorbidities among different years.

Appendix Table Aim 1.2 Full Cox Hazard Model for the Specialty COC Index

		Specialty COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	1.22 (1.18-1.25)	1.23 (1.19-1.27)	1.40 (1.35-1.44)
	3rdqt vs 1stqt	1.38 (1.34-1.42)	1.41 (1.36-1.45)	1.70 (1.65-1.75)
	4thqt vs 1stqt	1.17 (1.14-1.21)	1.22 (1.18-1.25)	1.57 (1.52-1.62)
Age group	66-70 vs >80	0.32 (0.31-0.33)	0.32 (0.31-0.33)	
	71-75 vs >80	0.39 (0.38-0.40)	0.38 (0.37-0.40)	
	76-80 vs >80	0.55 (0.54-0.57)	0.55 (0.53-0.56)	
Race group	Asian vs Other	1.04 (0.91-1.19)	1.02 (0.89-1.17)	
	Black vs Other	1.11 (1.01-1.21)	1.16 (1.06-1.27)	
	White vs Other	1.20 (1.10-1.30)	1.19 (1.10-1.29)	
Poverty level	5-10% vs 0-5%	1.10 (1.07-1.14)	1.11 (1.07-1.14)	
	10-20% vs 0-5%	1.18 (1.14-1.21)	1.18 (1.15-1.22)	
	20-100% vs 0-5%	1.30 (1.25-1.34)	1.29 (1.25-1.34)	
Marriage	Yes vs Other	0.83 (0.81-0.85)	0.83 (0.81-0.85)	
Tumor Stage	I vs 0	1.43 (1.37-1.50)	1.32 (1.27-1.38)	
	II vs 0	2.47 (2.36-2.59)	2.28 (2.18-2.38)	
	III vs 0	5.02 (4.78-5.28)	4.62 (4.40-4.85)	
	IV vs 0	15.86 (15.12-16.63)	15.83 (15.10-16.59)	
Hypertension	1 vs 0	1.12 (1.09-1.14)	1.11 (1.08-1.14)	
Hyperlipidemia	1 vs 0	0.72 (0.70-0.73)	0.71 (0.69-0.73)	
Diabetes	1 vs 0	1.30 (1.27-1.33)	1.29 (1.26-1.33)	
Region	Midwest vs West	0.95 (0.91-1.00)	0.96 (0.92-1.00)	
	Northeast vs West	0.93 (0.89-0.97)	0.94 (0.90-0.98)	
	South vs West	0.92 (0.89-0.96)	0.94 (0.90-0.97)	
Surgery	1 vs 0	0.76 (0.72-0.79)		
Chemotherapy	1 vs 0	1.46 (1.41-1.52)		
Radiation	1 vs 0	0.70 (0.67-0.73)		
Hormone	1 vs 0	0.38 (0.37-0.40)		
Charlson Index	1 unit change from mean	1.35 (1.34-1.36)	1.35 (1.34-1.36)	

Appendix Table Aim 1.2 showed the full Cox Hazard models of the association of the Specialty COC Index with patients' mortality risk. The unadjusted models used the COC indices as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.3 Full Cox Hazard Model for the Individual COC Index

		Individual COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	0.65 (0.63-0.67)	0.65 (0.63-0.67)	0.67 (0.65-0.69)
	3rdqt vs 1stqt	0.57 (0.55-0.59)	0.58 (0.56-0.59)	0.63 (0.61-0.65)
	4thqt vs 1stqt	0.55 (0.53-0.56)	0.56 (0.54-0.58)	0.68 (0.66-0.70)
Age group	66-70 vs >81	0.32 (0.31-0.33)	0.32 (0.31-0.33)	
	71-75 vs >81	0.40 (0.38-0.41)	0.39 (0.38-0.41)	
	76-80 vs >81	0.55 (0.53-0.57)	0.55 (0.53-0.56)	
Race group	Asian vs Other	1.05 (0.90-1.22)	1.05 (0.90-1.21)	
	Black vs Other	1.07 (0.97-1.19)	1.13 (1.02-1.24)	
	White vs Other	1.18 (1.08-1.28)	1.17 (1.07-1.27)	
Poverty level	5-10% vs 0-5%	1.12 (1.09-1.15)	1.13 (1.09-1.16)	
	10-20% vs 0-5%	1.21 (1.17-1.25)	1.22 (1.18-1.26)	
	20-100% vs 0-5%	1.34 (1.29-1.39)	1.33 (1.28-1.38)	
Marriage	Yes vs Other	0.83 (0.81-0.85)	0.84 (0.82-0.86)	
Tumor Stage	I vs 1	1.44 (1.37-1.51)	1.32 (1.26-1.39)	
	II vs 1	2.47 (2.36-2.60)	2.28 (2.17-2.39)	
	III vs 1	5.03 (4.77-5.31)	4.65 (4.41-4.90)	
	IV vs 1	16.75 (15.91-17.63)	16.81 (15.99-17.68)	
Hypertension	1 vs 0	1.13 (1.10-1.16)	1.12 (1.09-1.15)	
Hyperlipidemia	1 vs 0	0.73 (0.71-0.75)	0.72 (0.70-0.74)	
Diabetes	1 vs 0	1.31 (1.27-1.34)	1.30 (1.27-1.33)	
Region	Midwest vs West	0.94 (0.90-0.99)	0.95 (0.90-0.99)	
	Northeast vs West	0.92 (0.88-0.96)	0.92 (0.88-0.96)	
	South vs West	0.92 (0.88-0.96)	0.94 (0.90-0.98)	
Surgery	1 vs 0	0.80 (0.77-0.84)		
Chemotherapy	1 vs 0	1.53 (1.47-1.59)		
Radiation	1 vs 0	0.70 (0.67-0.73)		
Hormone	1 vs 0	0.38 (0.36-0.40)		
Charlson Index	1 unit change from mean	1.35 (1.34-1.36)	1.35 (1.34-1.36)	

Appendix Table Aim 1.3 showed the full Cox Hazard models of the association of the Individual COC Index with patients' mortality risk. The unadjusted models used the COC indices as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.4 Full Cox Hazard Model for the Specialty COC Index, with lagged effects

		Specialty COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	1.34 (1.28-1.39)	1.37 (1.31-1.42)	1.54 (1.48-1.60)
	3rdqt vs 1stqt	1.59 (1.52-1.65)	1.61 (1.54-1.67)	1.91 (1.84-1.99)
	4thqt vs 1stqt	1.34 (1.29-1.40)	1.37 (1.31-1.43)	1.70 (1.63-1.77)
COC_lag	2ndqt vs 1stqt	1.18 (1.14-1.23)	1.19 (1.15-1.24)	1.32 (1.27-1.37)
	3rdqt vs 1stqt	1.39 (1.34-1.45)	1.40 (1.34-1.46)	1.61 (1.55-1.67)
	4thqt vs 1stqt	1.43 (1.37-1.49)	1.48 (1.41-1.54)	1.78 (1.71-1.86)
Age group	66-70 vs >80	0.31 (0.30-0.33)	0.33 (0.31-0.34)	
	71-75 vs >80	0.37 (0.35-0.38)	0.38 (0.36-0.39)	
	76-80 vs >80	0.53 (0.51-0.54)	0.54 (0.52-0.56)	
Race group	Asian vs Other	1.07 (0.91-1.26)	1.06 (0.90-1.25)	
	Black vs Other	1.14 (1.02-1.28)	1.18 (1.05-1.32)	
	White vs Other	1.20 (1.09-1.32)	1.20 (1.08-1.32)	
Poverty level	5-10% vs 0-5%	1.11 (1.07-1.15)	1.11 (1.07-1.15)	
	10-20% vs 0-5%	1.18 (1.13-1.22)	1.18 (1.14-1.22)	
	20-100% vs 0-5%	1.25 (1.20-1.31)	1.26 (1.20-1.31)	
Marriage	Yes vs Other	0.85 (0.83-0.87)	0.86 (0.84-0.89)	
Tumor Stage	I vs 0	1.33 (1.27-1.40)	1.30 (1.23-1.36)	
	II vs 0	2.13 (2.03-2.24)	2.11 (2.01-2.22)	
	III vs 0	3.88 (3.67-4.11)	4.01 (3.79-4.24)	
	IV vs 0	8.02 (7.54-8.53)	9.52 (8.97-10.11)	
Hypertension	1 vs 0	1.14 (1.10-1.18)	1.14 (1.10-1.18)	
Hyperlipidemia	1 vs 0	0.72 (0.70-0.75)	0.72 (0.70-0.74)	
Diabetes	1 vs 0	1.35 (1.31-1.40)	1.34 (1.30-1.38)	
Region	Midwest vs West	0.99 (0.94-1.05)	1.00 (0.94-1.06)	
	Northeast vs West	0.96 (0.91-1.01)	0.95 (0.91-1.00)	
	South vs West	0.96 (0.91-1.01)	0.97 (0.92-1.02)	
Surgery	1 vs 0	1.00 (0.82-1.22)		
Chemotherapy	1 vs 0	2.27 (2.16-2.38)		
Radiation	1 vs 0	1.16 (1.09-1.23)		
Hormone	1 vs 0	0.63 (0.60-0.66)		
Charlson Index	1 unit change from mean	1.34 (1.33-1.36)	1.34 (1.32-1.35)	

Appendix Table Aim 1.4 showed the full Cox Hazard models of the association of the Specialty COC Index with patients' mortality risk, adjusting for the lagged COC Index from the previous year. The unadjusted models used the COC indices as the predictor. The partially adjusted models were also adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were also adjusted

for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.5 Full Cox Hazard Model for the Individual COC Index, with lagged effects

		Individual COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	0.67 (0.64-0.69)	0.67 (0.65-0.69)	0.68 (0.66-0.71)
	3rdqt vs 1stqt	0.57 (0.55-0.59)	0.57 (0.55-0.59)	0.63 (0.60-0.65)
	4thqt vs 1stqt	0.53 (0.51-0.54)	0.54 (0.52-0.56)	0.63 (0.61-0.65)
COC_lag	2ndqt vs 1stqt	0.98 (0.94-1.01)	0.99 (0.95-1.02)	1.03 (1.00-1.07)
	3rdqt vs 1stqt	1.10 (1.06-1.14)	1.10 (1.06-1.14)	1.17 (1.13-1.21)
	4thqt vs 1stqt	1.22 (1.17-1.26)	1.23 (1.18-1.27)	1.42 (1.37-1.48)
Age group	66-70 vs >80	0.32 (0.31-0.33)	0.33 (0.31-0.34)	
	71-75 vs >80	0.39 (0.38-0.41)	0.40 (0.38-0.41)	
	76-80 vs >80	0.54 (0.53-0.56)	0.55 (0.53-0.57)	
Race group	Asian vs Other	0.97 (0.82-1.14)	0.96 (0.81-1.13)	
	Black vs Other	1.01 (0.91-1.13)	1.06 (0.95-1.18)	
	White vs Other	1.10 (1.00-1.21)	1.09 (1.00-1.20)	
Poverty level	5-10% vs 0-5%	1.13 (1.09-1.17)	1.14 (1.10-1.17)	
	10-20% vs 0-5%	1.20 (1.16-1.24)	1.21 (1.17-1.25)	
	20-100% vs 0-5%	1.31 (1.26-1.37)	1.31 (1.25-1.36)	
Marriage	Yes vs Other	0.84 (0.81-0.86)	0.84 (0.82-0.86)	
Tumor Stage	I vs 0	1.42 (1.35-1.50)	1.33 (1.26-1.40)	
	II vs 0	2.38 (2.26-2.50)	2.23 (2.11-2.34)	
	III vs 0	4.72 (4.46-5.00)	4.47 (4.22-4.72)	
	IV vs 0	14.67 (13.87-15.53)	15.16 (14.35-16.02)	
Hypertension	1 vs 0	1.14 (1.10-1.17)	1.14 (1.10-1.17)	
Hyperlipidemia	1 vs 0	0.72 (0.70-0.74)	0.71 (0.69-0.73)	
Diabetes	1 vs 0	1.34 (1.30-1.38)	1.33 (1.29-1.37)	
Region	Midwest vs West	0.99 (0.94-1.04)	0.99 (0.94-1.05)	
	Northeast vs West	0.97 (0.92-1.01)	0.97 (0.92-1.01)	
	South vs West	0.98 (0.93-1.03)	0.99 (0.95-1.04)	
Surgery	1 vs 0	0.77 (0.72-0.81)		
Chemotherapy	1 vs 0	1.72 (1.64-1.79)		
Radiation	1 vs 0	0.76 (0.72-0.80)		
Hormone	1 vs 0	0.43 (0.41-0.45)		
Charlson Index	1 unit change from mean	1.35 (1.34-1.37)	1.35 (1.34-1.36)	

Appendix Table Aim 1.5 showed the full Cox Hazard models of the association of the Individual COC Index with patients' mortality risk, adjusting for the lagged COC Index from the previous year. The unadjusted models used the COC indices as the predictor. The partially adjusted models were also adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were also adjusted

for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.6 Cox Hazard Ratio for Mortality, predicted by the first year Specialty COC Index.

		Specialty COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	1.10 (1.08-1.12)	1.10 (1.08-1.11)	1.18 (1.16-1.19)
	3rdqt vs 1stqt	1.15 (1.13-1.17)	1.16 (1.14-1.17)	1.28 (1.26-1.30)
	4thqt vs 1stqt	1.16 (1.14-1.18)	1.19 (1.17-1.21)	1.31 (1.29-1.33)
Age group	66-70 vs >80	0.26 (0.26-0.27)	0.27 (0.26-0.27)	
	71-75 vs >80	0.33 (0.32-0.33)	0.33 (0.32-0.33)	
	76-80 vs >80	0.51 (0.50-0.51)	0.50 (0.50-0.51)	
Race group	Asian vs Other	1.14 (1.07-1.21)	1.12 (1.05-1.19)	
	Black vs Other	1.13 (1.08-1.18)	1.18 (1.12-1.23)	
	White vs Other	1.26 (1.21-1.31)	1.24 (1.20-1.29)	
Poverty level	5-10% vs 0-5%	1.07 (1.05-1.08)	1.07 (1.05-1.08)	
	10-20% vs 0-5%	1.16 (1.14-1.17)	1.16 (1.14-1.17)	
	20-100% vs 0-5%	1.17 (1.15-1.19)	1.17 (1.15-1.19)	
Marriage	Yes vs Other	0.82 (0.81-0.83)	0.82 (0.81-0.83)	
Tumor Stage	I vs 0	1.28 (1.25-1.30)	1.20 (1.18-1.22)	
	II vs 0	1.91 (1.88-1.95)	1.84 (1.80-1.87)	
	III vs 0	3.45 (3.38-3.53)	3.45 (3.38-3.53)	
	IV vs 0	10.17 (9.93-10.42)	10.12 (9.89-10.36)	
Hypertension	1 vs 0	1.17 (1.15-1.18)	1.17 (1.15-1.18)	
Hyperlipidemia	1 vs 0	0.74 (0.73-0.75)	0.74 (0.73-0.74)	
Diabetes	1 vs 0	1.28 (1.26-1.30)	1.28 (1.26-1.29)	
Region	Midwest vs West	1.03 (1.01-1.05)	1.05 (1.02-1.07)	
	Northeast vs West	0.99 (0.97-1.01)	0.99 (0.97-1.01)	
	South vs West	0.98 (0.96-1.00)	0.99 (0.97-1.01)	
Surgery	1 vs 0	1.47 (1.44-1.49)		
Chemotherapy	1 vs 0	1.43 (1.40-1.46)		
Radiation	1 vs 0	0.94 (0.92-0.95)		
Hormone	1 vs 0	0.50 (0.49-0.51)		
Charlson Index	1 unit change from mean	1.36 (1.35-1.36)	1.36 (1.35-1.37)	

Appendix Table Aim 1.6 showed the result of Cox Hazard models of the association of the Specialty COC Index with patients' mortality, using the first year Specialty COC Index as the primary predictor for each model. The unadjusted models used the COC Index as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were

adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.7 Cox Hazard Ratio for Mortality, predicted by the first year Individual COC Index.

		Individual COC, HR (95%CI)		
		Adjusted model with treatment	Adjusted model	Unadjusted model
COC	2ndqt vs 1stqt	0.88 (0.87-0.90)	0.88 (0.86-0.89)	0.92 (0.91-0.93)
	3rdqt vs 1stqt	0.91 (0.89-0.92)	0.91 (0.89-0.92)	0.94 (0.92-0.95)
	4thqt vs 1stqt	1.02 (1.00-1.03)	1.04 (1.02-1.05)	1.16 (1.14-1.17)
Age group	66-70 vs >81	0.27 (0.27-0.28)	0.27 (0.27-0.28)	
	71-75 vs >81	0.34 (0.33-0.34)	0.34 (0.33-0.34)	
	76-80 vs >81	0.52 (0.51-0.52)	0.52 (0.51-0.53)	
Race group	Asian vs Other	1.16 (1.09-1.24)	1.14 (1.07-1.22)	
	Black vs Other	1.12 (1.06-1.17)	1.16 (1.11-1.22)	
	White vs Other	1.25 (1.20-1.30)	1.24 (1.19-1.29)	
Poverty level	5-10% vs 0-5%	1.17 (1.15-1.18)	1.17 (1.15-1.18)	
	10-20% vs 0-5%	1.18 (1.16-1.21)	1.18 (1.16-1.20)	
	20-100% vs 0-5%	1.08 (1.06-1.09)	1.08 (1.06-1.09)	
Marriage	Yes vs Other	0.82 (0.81-0.83)	0.83 (0.82-0.83)	
Tumor Stage	I vs 1	1.27 (1.25-1.30)	1.20 (1.17-1.22)	
	II vs 1	1.92 (1.88-1.95)	1.84 (1.81-1.88)	
	III vs 1	3.48 (3.40-3.56)	3.51 (3.43-3.59)	
	IV vs 1	10.16 (9.91-10.41)	10.23 (9.99-10.48)	
Hypertension	1 vs 0	1.16 (1.15-1.18)	1.16 (1.15-1.18)	
Hyperlipidemia	1 vs 0	0.74 (0.73-0.75)	0.74 (0.73-0.74)	
Diabetes	1 vs 0	1.29 (1.27-1.30)	1.28 (1.27-1.30)	
Region	Midwest vs West	1.05 (1.02-1.07)	1.07 (1.04-1.09)	
	Northeast vs West	1.00 (0.98-1.02)	1.01 (0.99-1.03)	
	South vs West	0.99 (0.97-1.01)	1.00 (0.98-1.02)	
Surgery	1 vs 0	1.48 (1.45-1.51)		
Chemotherapy	1 vs 0	1.47 (1.44-1.50)		
Radiation	1 vs 0	0.95 (0.93-0.96)		
Hormone	1 vs 0	0.51 (0.50-0.52)		
Charlson Index	1 unit change from mean	1.36 (1.35-1.37)	1.36 (1.35-1.37)	

Appendix Table Aim 1.7 showed the result of Cox Hazard models of the association of the Individual COC Index with patients' mortality, using the first year Individual COC Index as the primary predictor for each model. The unadjusted models used the COC Index as the predictor. The partially adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, and CCI. The fully adjusted models were adjusted for age group, race, marriage, poverty level, region, tumor stage, hypertension, hyperlipidemia, diabetes, cancer treatments, and CCI.

Appendix Table Aim 1.8 Percentage of visits to each provider type by Specialty COC Index levels across survival years.

		Specialty COC Index				
	total visit%	1st qt	2nd qt	3rd qt	4th qt	All
1stYear	PCP	32%	31%	29%	21%	29%
	Oncologist	35%	36%	40%	55%	40%
	Other	32%	33%	31%	24%	31%
2ndYear	PCP	34%	34%	34%	28%	33%
	Oncologist	34%	30%	25%	27%	30%
	Other	33%	36%	41%	45%	37%
3rdYear	PCP	35%	36%	36%	28%	35%
	Oncologist	33%	27%	20%	22%	27%
	Other	33%	38%	44%	49%	39%
4thYear	PCP	35%	37%	35%	29%	35%
	Oncologist	32%	25%	19%	20%	25%
	Other	33%	39%	46%	51%	40%
5thYear	PCP	35%	37%	36%	27%	35%
	Oncologist	32%	24%	18%	20%	25%
	Other	33%	40%	46%	53%	40%

Appendix Table Aim 1.8 showed the average percentage of visits to each provider type by Specialty COC Index levels across survival years.

Appendix for Aim 2

Appendix Table Aim 2.1 The COC Index of Breast Cancer Patients, who Receive Hormone Therapy, Antihypertensives, Hyperlipidemia Medications, and Diabetes Medications

Mean (Std)	Year	Hormone Therapy only	Antihypertensives	Hyperlipidemia Medications	Diabetes Medications
Specialty COC Index					
adherence					
	Year1	0.44 (0.15)	0.43 (0.14)	0.42 (0.13)	0.43 (0.14)
	Year2	0.42 (0.15)	0.42 (0.14)	0.42 (0.14)	0.43 (0.15)
	Year3	0.42 (0.15)	0.42 (0.14)	0.42 (0.14)	0.44 (0.14)
	Year4	0.43 (0.15)	0.43 (0.15)	0.45 (0.17)	0.49 (0.18)
nonadherence					
	Year1	0.44 (0.14)	0.43 (0.14)	0.43 (0.13)	0.42 (0.13)
	Year2	0.42 (0.14)	0.42 (0.13)	0.42 (0.14)	0.43 (0.13)
	Year3	0.42 (0.15)	0.43 (0.14)	0.43 (0.14)	0.44 (0.14)
	Year4	0.43 (0.16)	0.45 (0.15)	0.44 (0.15)	0.42 (0.12)
Individual COC Index					
adherence					
	Year1	0.38 (0.22)	0.38 (0.22)	0.38 (0.21)	0.41 (0.23)
	Year2	0.37 (0.23)	0.37 (0.23)	0.37 (0.23)	0.41 (0.23)
	Year3	0.37 (0.23)	0.38 (0.23)	0.37 (0.23)	0.43 (0.25)
	Year4	0.38 (0.24)	0.39 (0.24)	0.39 (0.24)	0.49 (0.29)
nonadherence					
	Year1	0.38 (0.22)	0.37 (0.21)	0.37 (0.22)	0.39 (0.22)
	Year2	0.38 (0.24)	0.37 (0.22)	0.38 (0.24)	0.39 (0.24)
	Year3	0.37 (0.24)	0.38 (0.24)	0.36 (0.21)	0.41 (0.25)
	Year4	0.38 (0.23)	0.36 (0.21)	0.34 (0.21)	0.39 (0.25)

Appendix Table Aim 2.1 showed the mean (std) COC Index (Specialty and Individual COC Indices) change during the whole study period for each therapeutic group (HT, antihypertensives, hyperlipidemia medications, and diabetes medications).

Appendix Table Aim 2.2 Full Model of Logistic Regression Showing the Association Between Medication Adherence and the Specialty COC Index for Breast Cancer Patients after hormone therapy initiated, fully adjusted model.

OR (95% CI)	Level	Hormone Therapy	Antihypertensives	Hyperlipidemia Medications	Diabetes Medications
Specialty COC	2ndqt vs 1stqt	0.92(0.83-1.01)	0.89(0.79-1.01)	0.89(0.78-1.01)	0.90(0.70-1.16)
	3rdqt vs 1stqt	0.91(0.82-1.01)	0.86(0.76-0.97)	0.91(0.79-1.04)	0.94(0.72-1.22)
	4thqt vs 1stqt	0.97(0.87-1.08)	0.86(0.76-0.98)	0.81(0.70-0.94)	1.07(0.80-1.43)
Year	2 vs 1	1.21(1.10-1.32)	1.05(0.94-1.16)	1.19(1.06-1.34)	0.83(0.67-1.04)
	3 vs 1	0.96(0.86-1.07)	0.85(0.75-0.96)	1.00(0.87-1.15)	0.65(0.50-0.85)
	4 vs 1	0.60(0.52-0.70)	0.71(0.59-0.84)	0.93(0.76-1.14)	0.58(0.39-0.86)
Other cancer treatment	1 vs 0	0.96(0.86-1.07)	0.85(0.75-0.96)	1.01(0.88-1.16)	0.93(0.71-1.21)
Region	Midwest vs West	1.05(0.89-1.24)	0.88(0.73-1.07)	1.08(0.87-1.34)	0.37(0.23-0.58)
	Northeast vs West	0.98(0.85-1.13)	0.97(0.82-1.15)	0.90(0.74-1.08)	0.66(0.44-0.98)
	South vs West	1.02(0.88-1.18)	1.01(0.85-1.20)	0.95(0.78-1.15)	0.64(0.43-0.97)
Age group	66-70 vs >80	1.25(1.12-1.39)	0.97(0.85-1.10)	0.75(0.64-0.86)	0.80(0.61-1.06)
	71-75 vs >80	1.22(1.10-1.35)	1.07(0.95-1.21)	0.81(0.70-0.93)	1.01(0.77-1.33)
	76-80 vs >80	1.07(0.96-1.20)	1.21(1.06-1.37)	0.77(0.67-0.90)	1.07(0.80-1.44)
Race group	Black vs Other	0.63(0.51-0.78)	0.86(0.67-1.09)	0.63(0.48-0.84)	0.47(0.30-0.73)
	White vs Other	0.97(0.80-1.17)	0.85(0.68-1.05)	0.74(0.57-0.94)	0.63(0.42-0.95)
Poverty level	5-10% vs 0-5%	0.97(0.87-1.07)	1.04(0.92-1.17)	1.07(0.93-1.22)	0.98(0.75-1.27)
	10-20% vs 0-5%	0.88(0.77-0.99)	0.93(0.80-1.07)	1.07(0.91-1.27)	1.00(0.74-1.34)
	20-100% vs 0-5%	0.89(0.81-0.98)	1.04(0.93-1.17)	1.14(1.00-1.29)	0.80(0.62-1.04)
Marriage	Yes vs Other	1.05(0.97-1.13)	0.81(0.74-0.88)	0.96(0.87-1.06)	1.07(0.88-1.29)
Tumor Stage	I vs 0	1.18(0.88-1.58)	0.91(0.63-1.32)	0.87(0.61-1.23)	1.25(0.67-2.34)
	II vs 0	1.16(0.86-1.56)	0.77(0.53-1.12)	0.76(0.53-1.08)	1.07(0.56-2.03)
	III vs 0	0.98(0.71-1.36)	0.75(0.50-1.13)	0.85(0.57-1.27)	0.72(0.36-1.45)
	IV vs 0	0.80(0.56-1.15)	0.69(0.44-1.09)	0.55(0.35-0.89)	0.82(0.36-1.85)
Hypertension	1 vs 0	0.98(0.90-1.07)	0.00(0.00-0.00)	1.15(1.02-1.28)	1.04(0.81-1.35)
Hyperlipidemia	1 vs 0	1.17(1.08-1.26)	1.15(1.05-1.26)	0.00(0.00-0.00)	1.13(0.90-1.41)
Diabetes	1 vs 0	0.97(0.89-1.07)	1.16(1.05-1.29)	0.96(0.86-1.08)	0.00(0.00-0.00)

CCI	1 unit change from mean	0.97(0.93-1.02)	0.92(0.88-0.97)	0.97(0.92-1.02)	0.89(0.80-0.98)

Appendix Table Aim 2.2 showed the full models of logistic regression for the association of the Specialty COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 2.3 Full Model of Logistic Regression Showing the Association Between Medication Adherence and the Individual COC Index for Breast Cancer Patients after hormone therapy initiated, fully adjusted model.

OR (95% CI)	Level	Hormone Therapy	Antihypertensives	Hyperlipidemia Medications	Diabetes Medications
Individual COC	2ndqt vs 1stqt	0.97(0.87-1.09)	1.08(0.95-1.22)	1.11(0.96-1.27)	1.40(1.04-1.87)
	3rdqt vs 1stqt	0.99(0.89-1.11)	1.06(0.94-1.21)	1.16(1.01-1.34)	1.17(0.89-1.55)
	4thqt vs 1stqt	1.03(0.92-1.15)	1.08(0.94-1.23)	1.17(1.01-1.36)	1.50(1.12-2.00)
Year	2 vs 1	1.21(1.10-1.33)	1.01(0.91-1.13)	1.25(1.11-1.41)	0.82(0.65-1.04)
	3 vs 1	0.98(0.87-1.10)	0.83(0.73-0.95)	1.04(0.89-1.21)	0.66(0.50-0.88)
	4 vs 1	0.59(0.50-0.69)	0.68(0.56-0.82)	0.96(0.77-1.19)	0.51(0.33-0.81)
Other cancer treatment	1 vs 0	0.96(0.86-1.07)	0.83(0.73-0.94)	1.05(0.91-1.22)	0.93(0.71-1.23)
Region	Midwest vs West	1.04(0.88-1.24)	0.84(0.69-1.03)	1.01(0.81-1.27)	0.37(0.23-0.61)
	Northeast vs West	0.97(0.84-1.13)	0.94(0.78-1.12)	0.82(0.67-1.00)	0.69(0.45-1.06)
	South vs West	1.03(0.89-1.20)	0.93(0.78-1.12)	0.89(0.73-1.09)	0.65(0.42-1.01)
Age group	66-70 vs >80	1.27(1.13-1.43)	0.92(0.81-1.06)	0.75(0.64-0.87)	0.90(0.67-1.20)
	71-75 vs >80	1.19(1.06-1.32)	1.05(0.93-1.20)	0.80(0.69-0.93)	1.04(0.78-1.39)
	76-80 vs >80	1.07(0.95-1.20)	1.16(1.02-1.33)	0.78(0.67-0.91)	1.19(0.87-1.62)
Race group	Black vs Other	0.70(0.55-0.89)	0.99(0.75-1.30)	0.68(0.50-0.92)	0.46(0.27-0.76)
	White vs Other	0.94(0.77-1.16)	0.89(0.70-1.13)	0.71(0.54-0.93)	0.68(0.44-1.05)
Poverty level	5-10% vs 0-5%	0.99(0.89-1.11)	1.04(0.92-1.19)	1.05(0.91-1.21)	1.01(0.77-1.34)
	10-20% vs 0-5%	0.88(0.77-1.00)	0.96(0.82-1.11)	1.06(0.89-1.27)	0.99(0.72-1.36)
	20-100% vs 0-5%	0.90(0.81-1.00)	1.01(0.90-1.14)	1.17(1.02-1.34)	0.76(0.58-1.00)
Marriage	Yes vs Other	1.07(0.99-1.16)	0.85(0.77-0.93)	1.00(0.90-1.11)	1.07(0.88-1.31)
Tumor Stage	I vs 0	1.13(0.83-1.55)	0.89(0.60-1.32)	0.97(0.67-1.40)	1.25(0.63-2.48)
	II vs 0	1.11(0.81-1.53)	0.73(0.49-1.08)	0.83(0.57-1.21)	1.04(0.52-2.10)
	III vs 0	0.94(0.67-1.33)	0.72(0.47-1.10)	0.94(0.62-1.43)	0.72(0.34-1.55)
	IV vs 0	0.78(0.53-1.15)	0.64(0.40-1.02)	0.60(0.37-0.98)	0.97(0.40-2.32)
Hypertension	1 vs 0	0.95(0.87-1.04)	0.00(0.00-0.00)	1.13(1.00-1.28)	1.07(0.82-1.40)
Hyperlipidemia	1 vs 0	1.17(1.07-1.27)	1.19(1.08-1.31)	0.00(0.00-0.00)	1.16(0.92-1.47)
Diabetes	1 vs 0	0.97(0.88-1.07)	1.15(1.03-1.29)	0.91(0.81-1.03)	0.00(0.00-0.00)

CCI	1 unit change from mean	0.98(0.94-1.03)	0.93(0.88-0.97)	0.97(0.92-1.03)	0.88(0.79-0.98)

Appendix Table Aim 2.3 showed the full models of logistic regression for the association of the Individual COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 2.4 Full Model of Logistic Regression Showing the Association Between Medication Adherence and the Specialty COC Index for Breast Cancer Patients after hormone therapy initiated, partially adjusted model

	Specialty COC Index	HT OR (95% CI)	Antihypertensives OR (95% CI)	Hyperlipidemia Medications OR (95% CI)	Diabetes Medications OR (95% CI)
COC	2ndqt vs 1stqt	0.92(0.83-1.01)	0.89(0.79-1.00)	0.89(0.78-1.01)	0.90(0.69-1.16)
	3rdqt vs 1stqt	0.91(0.82-1.01)	0.86(0.76-0.97)	0.91(0.79-1.04)	0.94(0.72-1.22)
	4thqt vs 1stqt	0.97(0.87-1.08)	0.86(0.75-0.98)	0.81(0.70-0.94)	1.07(0.80-1.42)
Year	2 vs 1	1.21(1.11-1.32)	1.07(0.97-1.19)	1.19(1.06-1.33)	0.84(0.68-1.04)
	3 vs 1	0.97(0.87-1.07)	0.87(0.77-0.99)	1.00(0.87-1.15)	0.66(0.51-0.86)
	4 vs 1	0.61(0.53-0.70)	0.72(0.61-0.86)	0.93(0.76-1.14)	0.59(0.40-0.87)
Region	Midwest vs West	1.05(0.89-1.24)	0.88(0.72-1.06)	1.08(0.87-1.34)	0.37(0.23-0.58)
	Northeast vs West	0.98(0.85-1.13)	0.96(0.81-1.14)	0.90(0.74-1.08)	0.66(0.44-0.99)
	South vs West	1.02(0.88-1.18)	1.00(0.85-1.19)	0.95(0.78-1.15)	0.65(0.43-0.97)
Age group	66-70 vs >80	1.24(1.12-1.39)	0.95(0.84-1.08)	0.75(0.64-0.86)	0.79(0.60-1.05)
	71-75 vs >80	1.21(1.09-1.35)	1.06(0.94-1.20)	0.81(0.70-0.93)	1.01(0.77-1.32)
	76-80 vs >80	1.07(0.96-1.19)	1.20(1.05-1.36)	0.77(0.67-0.90)	1.06(0.79-1.43)
Race group	Black vs Other	0.63(0.50-0.78)	0.86(0.67-1.10)	0.63(0.48-0.84)	0.47(0.30-0.73)
	White vs Other	0.97(0.80-1.17)	0.85(0.68-1.06)	0.74(0.57-0.94)	0.63(0.42-0.95)
Poverty level	5-10% vs 0-5%	0.96(0.87-1.07)	1.04(0.92-1.17)	1.07(0.93-1.22)	0.98(0.75-1.27)
	10-20% vs 0-5%	0.88(0.77-0.99)	0.93(0.80-1.07)	1.07(0.91-1.27)	1.00(0.74-1.35)
	20-100% vs 0-5%	0.89(0.81-0.98)	1.04(0.93-1.17)	1.14(1.00-1.29)	0.80(0.62-1.04)
Marriage	Yes vs Other	1.05(0.97-1.13)	0.81(0.74-0.88)	0.96(0.87-1.06)	1.07(0.88-1.29)
Tumor Stage	I vs 0	1.18(0.88-1.58)	0.91(0.62-1.31)	0.87(0.61-1.23)	1.24(0.66-2.33)
	II vs 0	1.16(0.86-1.56)	0.76(0.52-1.11)	0.76(0.53-1.08)	1.06(0.56-2.01)
	III vs 0	0.98(0.71-1.35)	0.74(0.49-1.10)	0.85(0.57-1.27)	0.71(0.36-1.43)
	IV vs 0	0.79(0.56-1.14)	0.66(0.42-1.03)	0.56(0.35-0.89)	0.80(0.36-1.80)
Hypertension	1 vs 0	0.98(0.90-1.07)	0.00(0.00-0.00)	1.15(1.02-1.28)	1.04(0.81-1.34)
Hyperlipidemia	1 vs 0	1.17(1.08-1.26)	1.16(1.06-1.27)	0.00(0.00-0.00)	1.13(0.91-1.41)
Diabetes	1 vs 0	0.97(0.89-1.07)	1.16(1.04-1.29)	0.96(0.86-1.08)	0.00(0.00-0.00)
CCI	1 unit change from mean	0.98(0.93-1.02)	0.92(0.88-0.97)	0.97(0.92-1.02)	0.89(0.80-0.98)

Appendix Table Aim 2.4 showed the full models of logistic regression for the association of the Specialty COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI.

Appendix Table Aim 2.5 Full Model of Logistic Regression Showing the Association Between Medication Adherence and the Individual COC Index for Breast Cancer Patients after hormone therapy initiated, partially adjusted model.

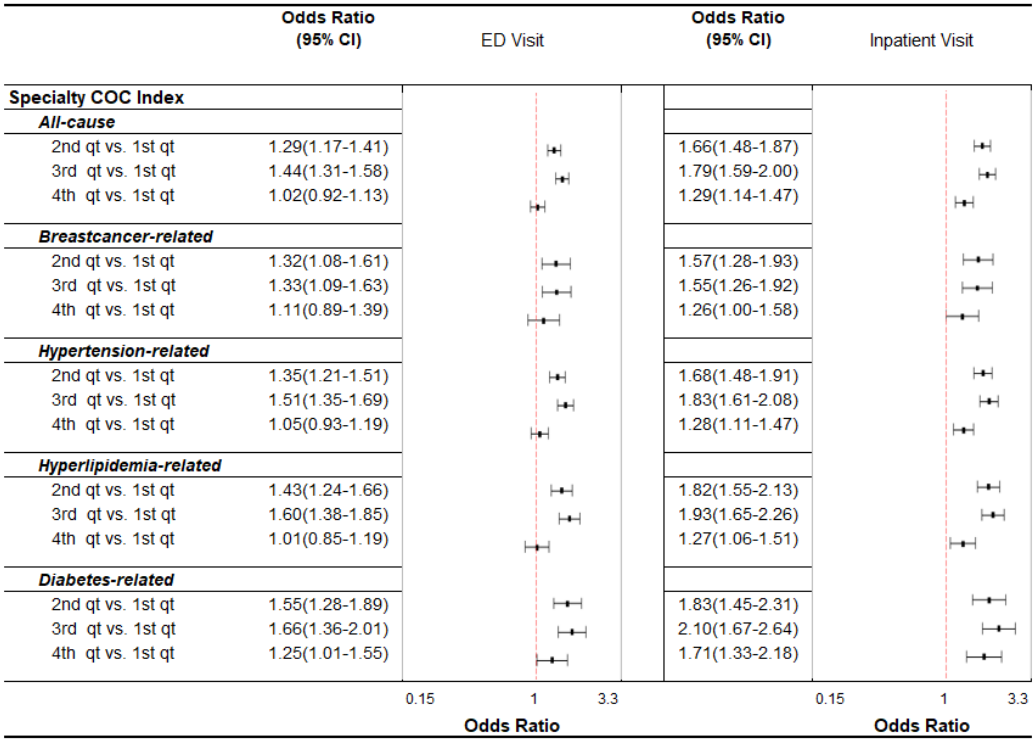
	Individual COC Index	HT	Antihypertensives	Hyperlipidemia Medications	Diabetes Medications
COC	2ndqt vs 1stqt	0.97(0.87-1.09)	1.08(0.95-1.22)	1.11(0.96-1.28)	1.40(1.05-1.88)
	3rdqt vs 1stqt	0.99(0.89-1.11)	1.06(0.94-1.21)	1.16(1.01-1.34)	1.17(0.89-1.55)
	4thqt vs 1stqt	1.03(0.92-1.15)	1.08(0.95-1.24)	1.17(1.01-1.36)	1.50(1.12-2.01)
Year	2 vs 1	1.21(1.10-1.33)	1.04(0.93-1.16)	1.24(1.10-1.40)	0.83(0.66-1.04)
	3 vs 1	0.98(0.88-1.10)	0.86(0.75-0.98)	1.03(0.89-1.20)	0.67(0.50-0.89)
	4 vs 1	0.59(0.51-0.70)	0.70(0.58-0.84)	0.95(0.76-1.18)	0.52(0.33-0.82)
Region	Midwest vs West	1.04(0.88-1.24)	0.84(0.68-1.03)	1.01(0.81-1.28)	0.37(0.23-0.61)
	Northeast vs West	0.97(0.84-1.13)	0.93(0.78-1.12)	0.82(0.67-1.00)	0.69(0.45-1.06)
	South vs West	1.03(0.88-1.20)	0.93(0.77-1.11)	0.89(0.73-1.09)	0.65(0.43-1.01)
Age group	66-70 vs >80	1.26(1.12-1.42)	0.91(0.79-1.04)	0.75(0.64-0.87)	0.89(0.67-1.19)
	71-75 vs >80	1.18(1.06-1.32)	1.04(0.92-1.18)	0.80(0.69-0.93)	1.03(0.78-1.38)
	76-80 vs >80	1.07(0.95-1.20)	1.15(1.01-1.32)	0.78(0.67-0.91)	1.18(0.86-1.61)
Race group	Black vs Other	0.70(0.55-0.89)	0.99(0.75-1.30)	0.68(0.50-0.92)	0.45(0.27-0.76)
	White vs Other	0.94(0.77-1.16)	0.89(0.70-1.13)	0.71(0.54-0.92)	0.69(0.45-1.05)
Poverty level	5-10% vs 0-5%	0.99(0.89-1.11)	1.04(0.92-1.18)	1.05(0.91-1.21)	1.01(0.77-1.34)
	10-20% vs 0-5%	0.87(0.77-1.00)	0.95(0.82-1.11)	1.06(0.89-1.27)	1.00(0.72-1.37)
	20-100% vs 0-5%	0.90(0.81-1.00)	1.02(0.90-1.15)	1.17(1.02-1.34)	0.76(0.58-1.00)
Marriage	Yes vs Other	1.07(0.99-1.16)	0.85(0.77-0.93)	1.00(0.90-1.11)	1.07(0.88-1.31)
Tumor Stage	I vs 0	1.13(0.83-1.55)	0.89(0.60-1.32)	0.97(0.67-1.40)	1.25(0.63-2.48)
	II vs 0	1.11(0.80-1.52)	0.72(0.48-1.08)	0.83(0.57-1.21)	1.04(0.52-2.09)
	III vs 0	0.93(0.66-1.32)	0.70(0.46-1.07)	0.95(0.62-1.44)	0.71(0.33-1.53)
	IV vs 0	0.77(0.53-1.13)	0.60(0.38-0.97)	0.61(0.37-0.99)	0.95(0.40-2.26)
Hypertension	1 vs 0	0.95(0.87-1.04)	0.00(0.00-0.00)	1.13(1.00-1.28)	1.07(0.82-1.40)
Hyperlipidemia	1 vs 0	1.17(1.07-1.27)	1.19(1.08-1.31)	0.00(0.00-0.00)	1.16(0.92-1.47)
Diabetes	1 vs 0	0.97(0.88-1.07)	1.15(1.03-1.28)	0.91(0.81-1.03)	0.00(0.00-0.00)
CCI	1 unit change from mean	0.98(0.94-1.03)	0.93(0.88-0.97)	0.97(0.92-1.03)	0.88(0.79-0.98)

Appendix Table Aim 2.5 showed the full models of logistic regression for the association of the Individual COC Index and medication adherence (HT, antihypertensives, hyperlipidemia medications, and diabetes medications). Mix-effect logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI.

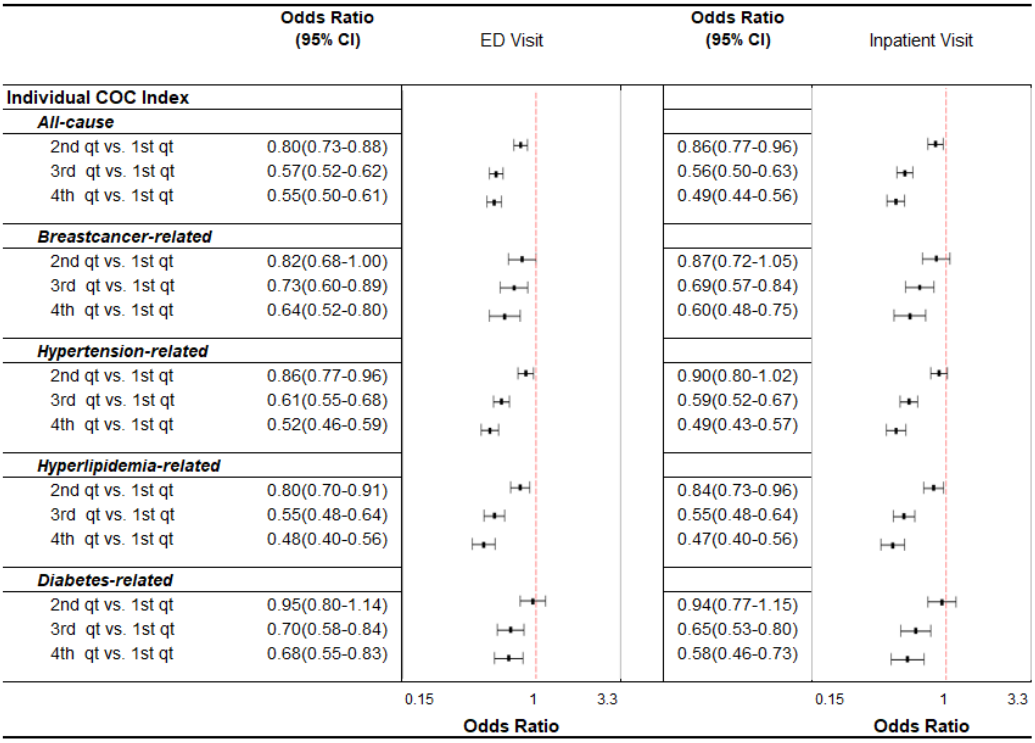
Appendix for Aim 3

Appendix Figure Aim 3.1 Odds of Incidence of Emergency Department visit and Hospitalization among Breast Cancer Patients with Comorbidities Associated with the COC Index, after Hormone Therapy Initiation, unadjusted models.

A. Specialty COC Index



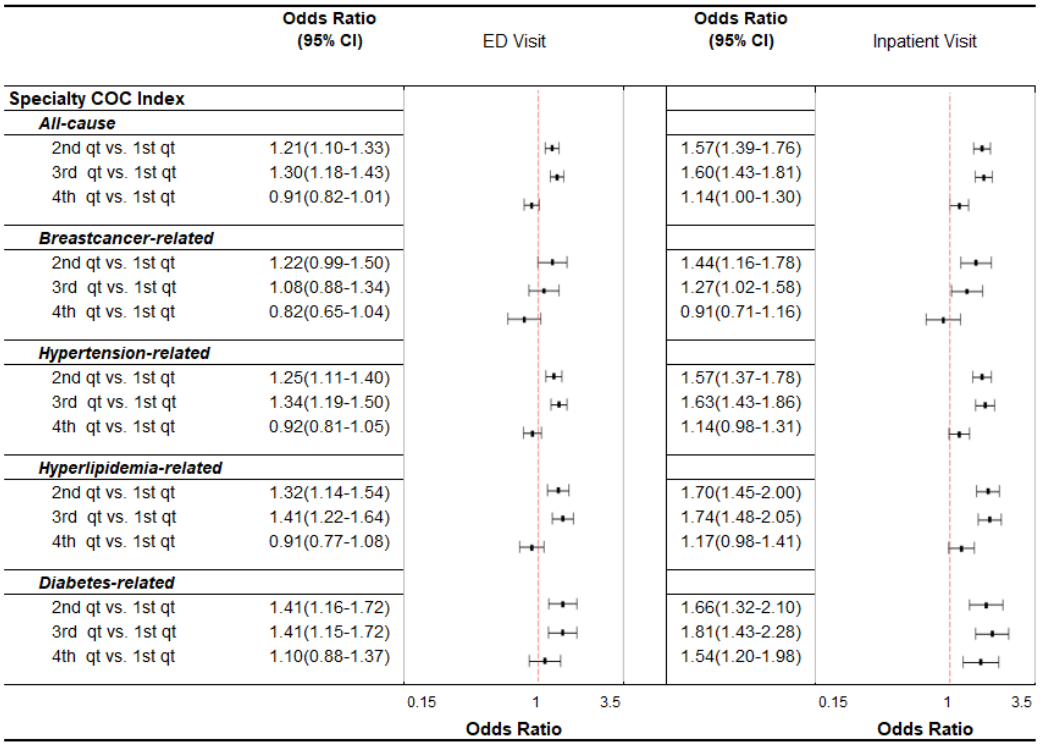
B. Individual COC Index



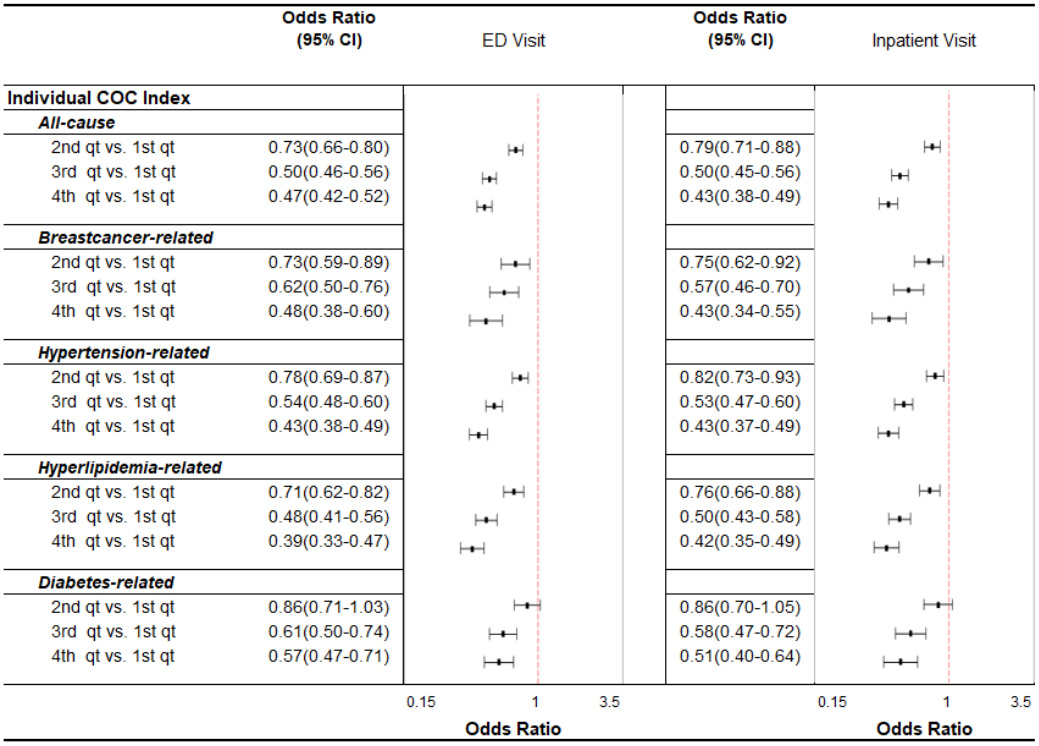
Appendix Figure Aim 3.1 showed the results of logistic regression for the association of COC Indices (Specialty and Individual COC) and health care service utilization (ED and inpatient). Logistic regressions generated the results. The analyses were adjusted for time.

Appendix Figure Aim 3.2 Odds of Incidence of Emergency Department visit and Hospitalization among Breast Cancer Patients with Comorbidities Associated with The COC Index, after Hormone Therapy Initiation, partially adjusted models.

A. Specialty COC Index



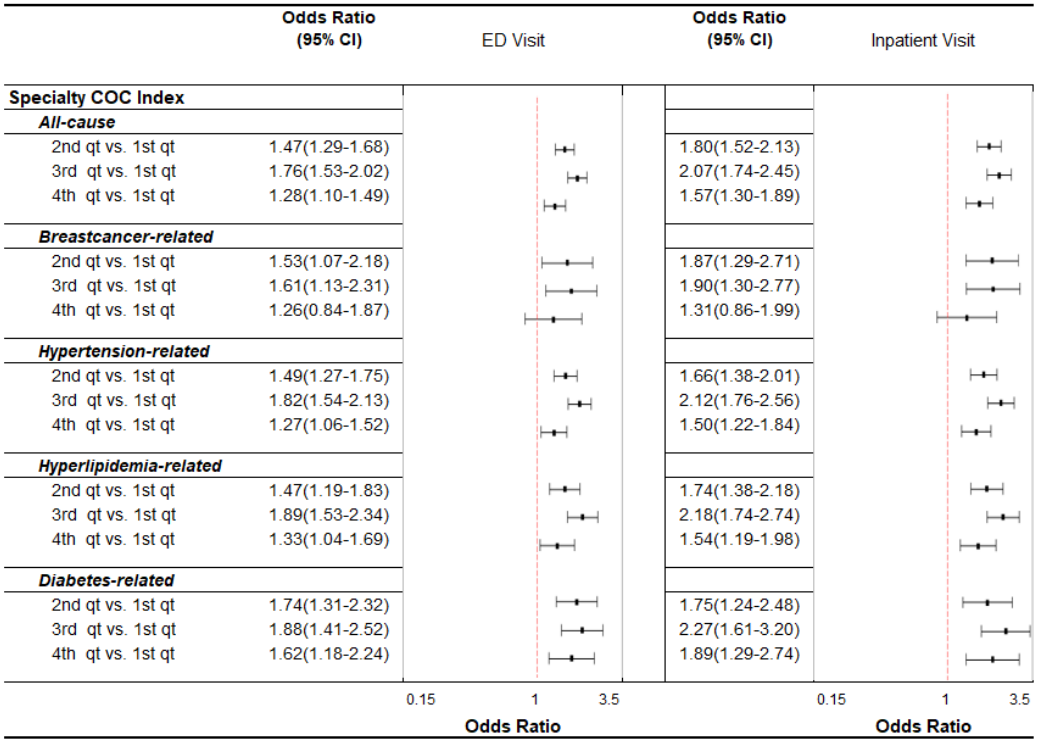
B. Individual COC Index



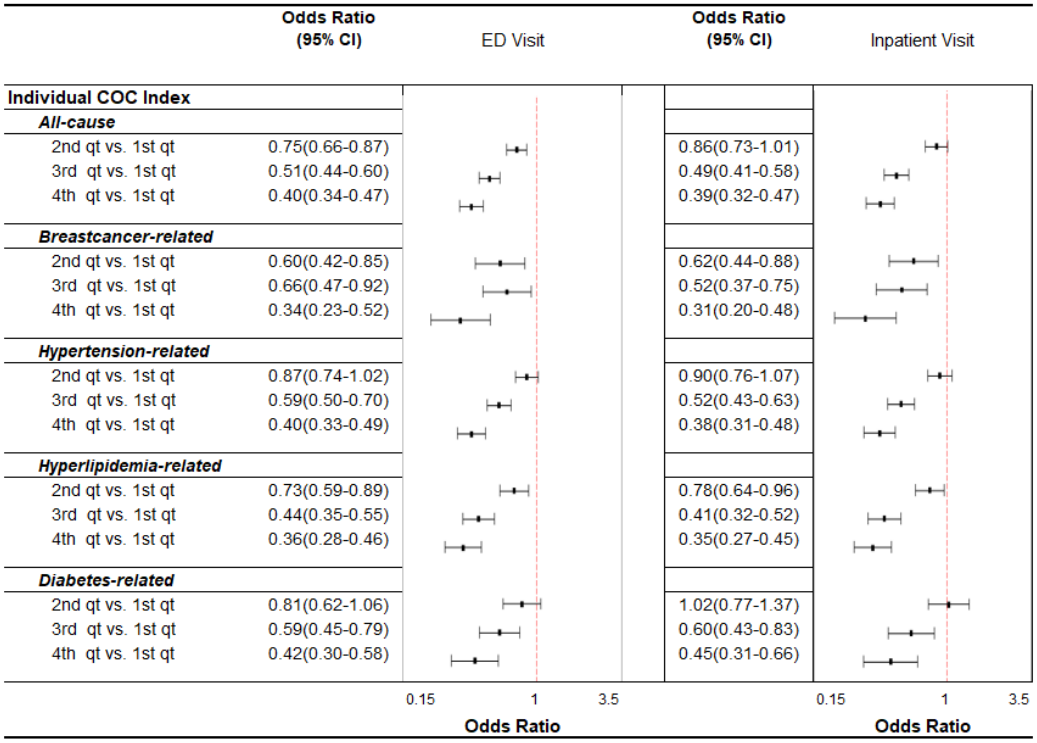
Appendix Figure Aim 3.2 showed the results of logistic regression for the association of COC Indices (Specialty and Individual COC) and health care service utilization (ED and inpatient). Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI.

Appendix Figure Aim 3.3 Odds of Incidence of Emergency Department visit and Hospitalization among Breast Cancer Patients with Comorbidities Associated with The COC Index, after Hormone Therapy Initiation, lagged effect fully adjusted models.

A. Specialty COC Index



B. Individual COC Index



Appendix Figure Aim 3.3 showed the results of logistic regression for the association of COC Indices (Specialty and Individual COC) and health care service utilization (ED and inpatient). Logistic regressions generated the results. The analyses were adjusted for lagged COC Index, age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.1 The Association Between the COC Index and Yearly ED Cost Change after Hormone Therapy Initiation, unadjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	4118.44	15.20%	626.00	-144.76	1546.27	**0.0463**
3rd qt vs 1st qt		22.86%	941.60	119.48	1923.20	
4th qt vs 1st qt		30.15%	1241.62	278.96	2415.01	
Breast cancer-related						
2nd qt vs 1st qt	507.43	-18.56%	-94.18	-206.96	60.93	0.5439
3rd qt vs 1st qt		-14.50%	-73.55	-193.81	92.81	
4th qt vs 1st qt		-21.35%	-108.31	-227.62	61.87	
Hypertension-related						
2nd qt vs 1st qt	2435.19	8.66%	210.80	-392.38	992.08	0.2262
3rd qt vs 1st qt		16.28%	396.36	-247.84	1230.28	
4th qt vs 1st qt		34.59%	842.45	15.23	1948.93	
Hyperlipidemia-related						
2nd qt vs 1st qt	1275.44	-4.78%	-60.99	-481.41	582.04	0.1894
3rd qt vs 1st qt		-0.67%	-8.52	-445.97	659.64	
4th qt vs 1st qt		52.04%	663.79	-88.35	1892.48	
Diabetes-related						
2nd qt vs 1st qt	853.37	1.92%	16.42	-386.64	767.55	0.5033
3rd qt vs 1st qt		30.42%	259.61	-258.01	1227.25	
4th qt vs 1st qt		53.20%	454.02	-200.12	1763.23	
Individual COC						
All-cause						
2nd qt vs 1st qt	4495.44	-2.41%	-108.19	-798.17	710.56	**0.0207**
3rd qt vs 1st qt		-18.80%	-845.31	-1442.01	-132.00	
4th qt vs 1st qt		-21.16%	-951.06	-1568.81	-202.91	
Breast cancer-related						
2nd qt vs 1st qt	558.16	15.70%	87.61	-81.11	316.00	0.3920
3rd qt vs 1st qt		-12.58%	-70.24	-198.14	103.10	
4th qt vs 1st qt		4.64%	25.89	-141.90	261.32	
Hypertension-related						
2nd qt vs 1st qt	2677.62	-8.86%	-237.30	-770.94	445.69	0.1913
3rd qt vs 1st qt		-23.44%	-627.64	-1096.82	-19.22	
4th qt vs 1st qt		-19.30%	-516.71	-1059.87	208.81	
Hyperlipidemia-related						
2nd qt vs 1st qt	1403.90	16.88%	237.02	-340.88	1129.07	0.5221
3rd qt vs 1st qt		-17.12%	-240.38	-673.27	449.01	
4th qt vs 1st qt		-12.93%	-181.58	-678.33	655.28	

Diabetes-related						
2nd qt vs 1st qt	946.75	-14.96%	-141.68	-498.18	498.15	0.4112
3rd qt vs 1st qt		-40.36%	-382.08	-641.84	98.97	
4th qt vs 1st qt		-26.97%	-255.34	-590.07	393.52	

Bold, P-value < 0.05

Appendix Table Aim 3.1 showed the results of two stage models for the association of the COC Indices (Specialty and Individual COC) and ED cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of ED visit and a linear regression model for the cost of ED visit. The analyses were adjusted for time.

Appendix Table Aim 3.2 The Association Between the COC Index and Yearly Inpatient Cost Change after Hormone Therapy Initiation, unadjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	13506.48	30.75%	4152.94	2149.41	6412.88	**<.0001**
3rd qt vs 1st qt		52.56%	7099.26	4750.00	9750.82	
4th qt vs 1st qt		41.95%	5665.88	3261.06	8415.60	
Breast cancer-related						
2nd qt vs 1st qt	2482.83	13.88%	344.69	-231.66	1068.59	0.5682
3rd qt vs 1st qt		18.06%	448.33	-160.09	1216.13	
4th qt vs 1st qt		12.14%	301.48	-322.25	1105.27	
Hypertension-related						
2nd qt vs 1st qt	9746.47	32.76%	3193.30	1540.56	5088.04	**<.0001**
3rd qt vs 1st qt		45.31%	4416.14	2602.13	6496.63	
4th qt vs 1st qt		43.36%	4226.23	2245.83	6533.67	
Hyperlipidemia-related						
2nd qt vs 1st qt	5544.72	28.49%	1579.83	440.08	2936.62	**0.0008**
3rd qt vs 1st qt		34.51%	1913.72	714.92	3342.11	
4th qt vs 1st qt		51.26%	2841.97	1334.40	4679.94	
Diabetes-related						
2nd qt vs 1st qt	3105.88	34.86%	1082.85	181.02	2232.11	**0.0284**
3rd qt vs 1st qt		44.82%	1391.96	427.04	2620.42	
4th qt vs 1st qt		24.06%	747.29	-132.25	1886.98	
Individual COC						
All-cause						
2nd qt vs 1st qt	14938.43	-8.20%	-1224.84	-2658.33	375.97	**0.0058**
3rd qt vs 1st qt		-12.26%	-1831.55	-3300.80	-176.81	
4th qt vs 1st qt		-20.60%	-3077.65	-4540.13	-1409.48	
Breast cancer-related						
2nd qt vs 1st qt	2748.52	11.65%	320.21	-254.99	1028.09	0.7589
3rd qt vs 1st qt		7.87%	216.29	-356.84	926.76	
4th qt vs 1st qt		8.43%	231.84	-405.24	1042.12	
Hypertension-related						
2nd qt vs 1st qt	10784.41	-8.72%	-940.12	-2081.42	350.85	**0.0032**
3rd qt vs 1st qt		-13.83%	-1491.04	-2647.63	-170.04	
4th qt vs 1st qt		-24.22%	-2611.69	-3746.77	-1293.54	
Hyperlipidemia-related						
2nd qt vs 1st qt	6127.18	-4.13%	-253.13	-1097.92	733.56	0.2625
3rd qt vs 1st qt		0.58%	35.43	-922.45	1169.60	
4th qt vs 1st qt		-16.50%	-1010.86	-1894.71	57.56	

Diabetes-related						
2nd qt vs 1st qt	3455.23	-21.62%	-747.02	-1239.93	-144.43	**0.0173**
3rd qt vs 1st qt		-26.32%	-909.32	-1403.88	-295.52	
4th qt vs 1st qt		-26.61%	-919.48	-1458.78	-234.50	

Bold, P-value < 0.05

Appendix Table Aim 3.2 showed the results of two stage models for the association of the COC Indices (Specialty and Individual COC) and inpatient cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of inpatient visit and a linear regression model for the cost of inpatient visit. The analyses were adjusted for time.

Appendix Table Aim 3.3 The Association Between the COC Index and Yearly ED Cost Change after Hormone Therapy Initiation, partially adjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	4088.14	12.24%	500.53	-110.82	1205.85	0.0875
3rd qt vs 1st qt		18.05%	737.73	91.58	1483.76	
4th qt vs 1st qt		19.84%	811.15	84.74	1664.02	
Breast cancer-related						
2nd qt vs 1st qt	507.53	-19.97%	-101.37	-201.90	32.24	0.4129
3rd qt vs 1st qt		-14.92%	-75.73	-185.21	70.94	
4th qt vs 1st qt		-21.54%	-109.33	-218.79	41.63	
Hypertension-related						
2nd qt vs 1st qt	2400.80	6.08%	145.96	-296.22	681.05	0.4709
3rd qt vs 1st qt		10.90%	261.80	-202.31	823.88	
4th qt vs 1st qt		18.10%	434.65	-114.81	1116.19	
Hyperlipidemia-related						
2nd qt vs 1st qt	1239.95	-11.57%	-143.51	-412.00	212.05	0.2460
3rd qt vs 1st qt		-8.43%	-104.58	-383.94	265.96	
4th qt vs 1st qt		17.90%	222.00	-183.62	783.37	
Diabetes-related						
2nd qt vs 1st qt	813.98	-10.15%	-82.60	-326.23	282.73	0.5515
3rd qt vs 1st qt		15.35%	124.95	-189.90	598.64	
4th qt vs 1st qt		9.23%	75.17	-248.93	585.16	
Individual COC						
All-cause						
2nd qt vs 1st qt	4447.10	-0.06%	-2.58	-561.97	637.35	**0.0028**
3rd qt vs 1st qt		-17.08%	-759.59	-1243.47	-202.61	
4th qt vs 1st qt		-19.55%	-869.29	-1371.93	-284.49	
Breast cancer-related						
2nd qt vs 1st qt	551.59	20.24%	111.63	-47.43	320.86	0.3701
3rd qt vs 1st qt		-6.59%	-36.36	-161.23	128.44	
4th qt vs 1st qt		6.72%	37.08	-120.20	251.70	
Hypertension-related						
2nd qt vs 1st qt	2628.19	-4.75%	-124.95	-524.87	351.00	0.0913
3rd qt vs 1st qt		-19.47%	-511.83	-866.91	-85.18	
4th qt vs 1st qt		-15.30%	-401.99	-815.36	105.64	
Hyperlipidemia-related						
2nd qt vs 1st qt	1352.87	24.41%	330.21	-55.50	830.60	0.1992
3rd qt vs 1st qt		-6.05%	-81.92	-391.07	326.60	
4th qt vs 1st qt		-4.26%	-57.63	-407.40	421.55	

Diabetes-related						
2nd qt vs 1st qt	888.64	-19.05%	-169.26	-386.08	141.11	0.2328
3rd qt vs 1st qt		-32.99%	-293.15	-481.10	-18.50	
4th qt vs 1st qt		-18.93%	-168.25	-408.22	191.59	

Bold, P-value < 0.05

Appendix Table Aim 3.3 showed the results of two stage models for the association of the COC Indices (Specialty and Individual COC) and ED cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of ED visit and a linear regression model for the cost of ED visit. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI.

Appendix Table Aim 3.4 The Association Between the COC Index and Yearly Inpatient Cost Change after Hormone Therapy Initiation, partially adjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	13650.67	28.52%	3892.92	1914.73	6122.52	**<.0001**
3rd qt vs 1st qt		49.63%	6774.92	4445.14	9404.66	
4th qt vs 1st qt		37.84%	5164.97	2810.06	7856.79	
Breast cancer-related						
2nd qt vs 1st qt	2478.04	5.91%	146.48	-351.72	761.40	0.7416
3rd qt vs 1st qt		12.60%	312.31	-225.77	978.94	
4th qt vs 1st qt		4.99%	123.75	-423.97	817.51	
Hypertension-related						
2nd qt vs 1st qt	9791.92	32.94%	3225.10	1570.51	5120.63	**<.0001**
3rd qt vs 1st qt		46.57%	4559.62	2716.26	6674.64	
4th qt vs 1st qt		42.08%	4120.16	2150.69	6414.42	
Hyperlipidemia-related						
2nd qt vs 1st qt	5646.07	29.02%	1638.51	508.17	2976.46	**0.0003**
3rd qt vs 1st qt		39.25%	2216.08	980.64	3681.84	
4th qt vs 1st qt		50.65%	2859.83	1369.91	4666.15	
Diabetes-related						
2nd qt vs 1st qt	3192.37	37.12%	1185.07	227.16	2411.31	**0.0157**
3rd qt vs 1st qt		47.92%	1529.78	501.50	2844.29	
4th qt vs 1st qt		20.70%	660.67	-235.11	1827.80	
Individual COC						
All-cause						
2nd qt vs 1st qt	15087.02	-9.14%	-1378.54	-2788.61	193.21	**0.0025**
3rd qt vs 1st qt		-11.55%	-1742.11	-3222.71	-76.75	
4th qt vs 1st qt		-22.12%	-3337.24	-4770.47	-1704.89	
Breast cancer-related						
2nd qt vs 1st qt	2742.09	7.41%	203.18	-303.66	815.37	0.8540
3rd qt vs 1st qt		7.67%	210.29	-320.90	858.01	
4th qt vs 1st qt		6.68%	183.28	-395.60	904.97	
Hypertension-related						
2nd qt vs 1st qt	10827.05	-9.54%	-1033.27	-2158.53	238.06	**0.0035**
3rd qt vs 1st qt		-13.33%	-1443.60	-2607.38	-115.04	
4th qt vs 1st qt		-24.14%	-2613.81	-3747.44	-1298.65	
Hyperlipidemia-related						
2nd qt vs 1st qt	6236.28	-3.76%	-234.69	-1068.43	733.55	0.2399
3rd qt vs 1st qt		2.19%	136.36	-823.06	1265.83	
4th qt vs 1st qt		-15.75%	-982.31	-1864.31	77.62	

Diabetes-related						
2nd qt vs 1st qt	3546.59	-21.85%	-774.82	-1279.74	-157.43	**0.0094**
3rd qt vs 1st qt		-28.09%	-996.35	-1496.18	-374.68	
4th qt vs 1st qt		-29.14%	-1033.57	-1570.75	-350.34	

Bold, P-value < 0.05

Appendix Table Aim 3.4 showed the results of two stage models for the association of the COC Indices (Specialty and Individual COC) and inpatient cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of inpatient visit and a linear regression model for the cost of inpatient visit. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, and CCI.

Appendix Table Aim 3.5 The Association Between the Specialty COC Index and ED Visit after Hormone Therapy Initiation, full model of fully adjusted models

Specialty COC		All-cause	Breast cancer-related	Hypertension-related	Hyperlipidemia-related	Diabetes-related
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
COC Index						
	2ndqt vs 1stqt	1.21(1.10-1.33)	1.21(0.98-1.48)	1.24(1.11-1.39)	1.32(1.14-1.53)	1.41(1.16-1.72)
	3rdqt vs 1stqt	1.30(1.18-1.43)	1.08(0.87-1.33)	1.34(1.19-1.50)	1.41(1.21-1.64)	1.41(1.15-1.71)
	4thqt vs 1stqt	0.91(0.82-1.01)	0.81(0.64-1.02)	0.92(0.81-1.04)	0.91(0.77-1.08)	1.09(0.88-1.36)
Year						
	2 vs 1	1.20(1.10-1.30)	0.73(0.61-0.86)	1.21(1.10-1.34)	1.18(1.04-1.34)	1.09(0.93-1.29)
	3 vs 1	1.32(1.20-1.46)	0.63(0.50-0.80)	1.44(1.28-1.61)	1.31(1.13-1.53)	1.34(1.10-1.62)
	4 vs 1	1.31(1.14-1.51)	0.51(0.35-0.76)	1.53(1.31-1.80)	1.52(1.24-1.87)	1.42(1.09-1.86)
Treatment						
	1 vs 0	1.11(1.01-1.23)	1.67(1.39-1.99)	1.23(1.09-1.38)	1.32(1.14-1.53)	1.38(1.15-1.65)
Region						
	Midwest vs West	0.78(0.67-0.90)	0.94(0.69-1.30)	0.94(0.79-1.13)	0.74(0.59-0.93)	1.21(0.88-1.67)
	Northeast vs West	0.83(0.73-0.95)	0.92(0.70-1.22)	0.92(0.78-1.07)	0.82(0.68-1.00)	1.03(0.77-1.37)
	South vs West	0.83(0.72-0.95)	0.92(0.70-1.22)	0.97(0.82-1.13)	0.80(0.66-0.98)	1.15(0.86-1.54)
Age group						
	66-70 vs >80	0.52(0.47-0.58)	0.70(0.56-0.87)	0.46(0.41-0.52)	0.62(0.53-0.73)	1.03(0.84-1.27)
	71-75 vs >80	0.58(0.52-0.63)	0.65(0.53-0.80)	0.53(0.48-0.60)	0.68(0.59-0.79)	0.93(0.77-1.13)
	76-80 vs >80	0.71(0.65-0.79)	0.90(0.73-1.09)	0.72(0.65-0.81)	0.88(0.76-1.02)	1.16(0.96-1.40)
Race group						
	Black vs Other	1.20(0.90-1.61)	1.64(0.93-2.91)	1.51(1.09-2.10)	0.93(0.62-1.41)	1.47(0.93-2.34)
	White vs Other	1.29(1.06-1.56)	1.16(0.76-1.77)	1.25(0.99-1.57)	0.94(0.72-1.25)	0.89(0.63-1.26)
Poverty level						
	5-10% vs 0-5%	1.09(1.00-1.20)	0.85(0.70-1.04)	1.00(0.89-1.11)	1.05(0.91-1.21)	1.06(0.87-1.29)
	10-20% vs 0-5%	1.19(1.08-1.31)	1.09(0.89-1.33)	1.18(1.05-1.32)	1.14(0.99-1.32)	1.55(1.28-1.89)

	20-100% vs 0-5%	1.25(1.11-1.40)	0.90(0.70-1.16)	1.23(1.08-1.41)	0.96(0.80-1.15)	1.78(1.43-2.22)
Marriage						
	Yes vs Other	0.92(0.86-0.99)	0.88(0.76-1.03)	0.89(0.82-0.97)	0.89(0.80-0.99)	0.98(0.85-1.13)
Tumor Stage						
	I vs 0	1.25(0.91-1.71)	0.91(0.45-1.86)	1.03(0.72-1.48)	0.84(0.55-1.30)	0.58(0.36-0.93)
	II vs 0	1.35(0.99-1.86)	1.49(0.73-3.05)	1.16(0.80-1.67)	0.96(0.62-1.49)	0.70(0.43-1.14)
	III vs 0	1.63(1.17-2.28)	2.24(1.07-4.69)	1.38(0.94-2.03)	1.03(0.64-1.65)	1.05(0.62-1.78)
	IV vs 0	2.21(1.53-3.19)	8.93(4.25-18.74)	1.73(1.14-2.64)	1.52(0.91-2.52)	1.43(0.81-2.52)
Hypertension						
	1 vs 0	1.25(1.15-1.35)	1.36(1.13-1.63)	-	1.85(1.62-2.12)	2.25(1.85-2.75)
Hyperlipidemia						
	1 vs 0	0.87(0.80-0.94)	0.79(0.67-0.93)	1.08(0.99-1.18)	-	1.56(1.33-1.83)
Diabetes						
	1 vs 0	1.23(1.13-1.34)	1.22(1.02-1.45)	1.47(1.34-1.62)	1.42(1.26-1.60)	-
CCI						
	1 unit change from mean	1.39(1.34-1.45)	1.35(1.27-1.45)	1.43(1.37-1.49)	1.38(1.31-1.45)	1.50(1.42-1.59)

Appendix Table Aim 3.5 showed the results of logistic regression for the association of the Specialty COC Index and ED visit. Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.6 The Association Between the Individual COC Index and ED Visit after Hormone Therapy Initiation, full model of fully adjusted models

Individual COC		All-cause	Breast cancer-related	Hypertension-related	Hyperlipidemia-related	Diabetes-related
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
COC Index						
	2ndqt vs 1stqt	0.73(0.66-0.80)	0.72(0.59-0.88)	0.78(0.69-0.87)	0.71(0.61-0.82)	0.85(0.71-1.03)
	3rdqt vs 1stqt	0.50(0.45-0.56)	0.61(0.50-0.75)	0.54(0.48-0.60)	0.48(0.41-0.56)	0.61(0.50-0.74)
	4thqt vs 1stqt	0.47(0.42-0.52)	0.48(0.38-0.60)	0.43(0.38-0.49)	0.40(0.33-0.47)	0.58(0.47-0.71)
Year						
	2 vs 1	1.21(1.11-1.32)	0.74(0.62-0.89)	1.23(1.11-1.37)	1.18(1.04-1.35)	1.11(0.94-1.31)
	3 vs 1	1.37(1.23-1.52)	0.64(0.50-0.82)	1.51(1.34-1.71)	1.34(1.14-1.57)	1.36(1.12-1.67)
	4 vs 1	1.37(1.18-1.60)	0.56(0.38-0.83)	1.62(1.37-1.92)	1.53(1.23-1.90)	1.42(1.07-1.88)
Treatment						
	1 vs 0	1.11(1.00-1.23)	1.70(1.41-2.04)	1.23(1.09-1.39)	1.33(1.14-1.55)	1.38(1.14-1.66)
Region						
	Midwest vs West	0.72(0.62-0.85)	0.91(0.65-1.26)	0.89(0.74-1.07)	0.66(0.52-0.84)	1.16(0.84-1.61)
	Northeast vs West	0.79(0.69-0.90)	0.88(0.66-1.17)	0.88(0.75-1.04)	0.77(0.63-0.95)	1.02(0.76-1.38)
	South vs West	0.80(0.70-0.92)	0.91(0.68-1.22)	0.95(0.81-1.12)	0.77(0.62-0.94)	1.12(0.83-1.52)
Age group						
	66-70 vs >80	0.51(0.46-0.57)	0.69(0.55-0.86)	0.44(0.39-0.50)	0.63(0.53-0.74)	1.04(0.84-1.28)
	71-75 vs >80	0.57(0.51-0.63)	0.65(0.53-0.81)	0.51(0.46-0.58)	0.69(0.59-0.80)	0.90(0.74-1.10)
	76-80 vs >80	0.71(0.64-0.79)	0.88(0.71-1.08)	0.72(0.64-0.81)	0.91(0.78-1.05)	1.17(0.96-1.42)
Race group						
	Black vs Other	1.07(0.78-1.46)	1.47(0.81-2.67)	1.31(0.93-1.86)	0.79(0.51-1.23)	1.49(0.92-2.42)
	White vs Other	1.16(0.95-1.43)	1.05(0.67-1.62)	1.09(0.85-1.39)	0.84(0.63-1.13)	0.84(0.58-1.21)
Poverty level						
	5-10% vs 0-5%	1.25(1.13-1.39)	1.15(0.94-1.42)	1.22(1.09-1.38)	1.18(1.01-1.37)	1.59(1.30-1.94)
	10-20% vs 0-5%	1.33(1.18-1.51)	0.92(0.71-1.19)	1.32(1.14-1.52)	1.04(0.86-1.26)	1.87(1.49-2.35)
	20-100% vs 0-5%	1.11(1.01-1.23)	0.88(0.71-1.08)	1.01(0.90-1.13)	1.09(0.94-1.26)	1.08(0.88-1.33)

Marriage						
	Yes vs Other	0.90(0.83-0.97)	0.85(0.72-0.99)	0.86(0.79-0.94)	0.84(0.75-0.94)	0.94(0.82-1.09)
Tumor Stage						
	I vs 0	1.12(0.81-1.55)	0.85(0.41-1.75)	0.91(0.63-1.32)	0.74(0.48-1.16)	0.52(0.32-0.84)
	II vs 0	1.24(0.89-1.71)	1.36(0.66-2.81)	1.03(0.71-1.49)	0.86(0.55-1.35)	0.64(0.39-1.04)
	III vs 0	1.52(1.07-2.15)	2.04(0.96-4.31)	1.23(0.83-1.82)	0.92(0.57-1.49)	0.98(0.58-1.66)
	IV vs 0	2.13(1.46-3.12)	8.81(4.16-18.65)	1.65(1.07-2.55)	1.54(0.92-2.59)	1.42(0.80-2.52)
Hypertension						
	1 vs 0	1.26(1.16-1.38)	1.38(1.15-1.67)	-	1.85(1.61-2.13)	2.20(1.79-2.69)
Hyperlipidemia						
	1 vs 0	0.85(0.79-0.92)	0.77(0.65-0.91)	1.04(0.95-1.14)	-	1.57(1.33-1.85)
Diabetes						
	1 vs 0	1.27(1.16-1.39)	1.25(1.05-1.50)	1.53(1.38-1.69)	1.49(1.32-1.69)	-
CCI						
	1 unit change from mean	1.38(1.32-1.44)	1.32(1.23-1.41)	1.42(1.36-1.48)	1.38(1.31-1.45)	1.48(1.39-1.57)

Appendix Table Aim 3.6 showed the results of logistic regression for the association of the Individual COC Index and ED visit. Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.7 The Association Between the Specialty COC Index and Inpatient Visit after Hormone Therapy Initiation, full model of fully adjusted models

Specialty COC		All-cause	Breast cancer-related	Hypertension-related	Hyperlipidemia-related	Diabetes-related
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
COC Index						
	2ndqt vs 1stqt	1.56(1.39-1.76)	1.41(1.14-1.75)	1.56(1.37-1.78)	1.70(1.45-1.99)	1.65(1.31-2.09)
	3rdqt vs 1stqt	1.60(1.42-1.80)	1.26(1.01-1.56)	1.63(1.43-1.86)	1.74(1.48-2.04)	1.80(1.43-2.27)
	4thqt vs 1stqt	1.13(0.99-1.29)	0.88(0.69-1.12)	1.13(0.97-1.30)	1.17(0.97-1.40)	1.53(1.19-1.97)
Year						
	2 vs 1	1.13(1.02-1.24)	0.74(0.62-0.89)	1.17(1.05-1.30)	1.21(1.06-1.37)	1.05(0.88-1.26)
	3 vs 1	1.28(1.14-1.43)	0.70(0.55-0.89)	1.31(1.16-1.50)	1.34(1.15-1.56)	1.17(0.94-1.46)
	4 vs 1	1.13(0.95-1.34)	0.49(0.32-0.74)	1.29(1.07-1.55)	1.31(1.05-1.63)	1.04(0.75-1.44)
Treatment						
	1 vs 0	1.52(1.36-1.70)	3.11(2.64-3.68)	1.52(1.34-1.72)	1.42(1.23-1.65)	1.61(1.32-1.95)
Region						
	Midwest vs West	1.09(0.91-1.31)	1.02(0.74-1.40)	1.07(0.88-1.31)	0.98(0.77-1.25)	1.29(0.89-1.87)
	Northeast vs West	1.02(0.87-1.20)	0.89(0.67-1.18)	0.97(0.82-1.16)	0.96(0.78-1.19)	1.26(0.90-1.76)
	South vs West	0.96(0.82-1.13)	0.99(0.74-1.31)	0.94(0.78-1.12)	0.90(0.73-1.11)	1.23(0.88-1.72)
Age group						
	66-70 vs >80	0.68(0.60-0.77)	0.56(0.45-0.70)	0.58(0.51-0.66)	0.74(0.63-0.87)	1.11(0.88-1.40)
	71-75 vs >80	0.75(0.67-0.84)	0.66(0.54-0.81)	0.72(0.64-0.81)	0.81(0.70-0.94)	1.03(0.83-1.27)
	76-80 vs >80	0.83(0.74-0.93)	0.73(0.59-0.90)	0.82(0.72-0.93)	0.90(0.77-1.05)	1.17(0.94-1.45)
Race group						
	Black vs Other	1.17(0.82-1.68)	1.76(0.90-3.44)	1.31(0.89-1.93)	1.31(0.81-2.11)	1.27(0.75-2.16)
	White vs Other	1.49(1.16-1.90)	1.73(1.05-2.86)	1.44(1.10-1.90)	1.55(1.10-2.18)	0.91(0.61-1.35)
Poverty level						
	5-10% vs 0-5%	0.95(0.85-1.06)	0.89(0.73-1.09)	0.98(0.86-1.11)	0.97(0.84-1.12)	0.87(0.69-1.08)
	10-20% vs 0-5%	1.12(1.00-1.25)	0.99(0.81-1.22)	1.13(1.00-1.28)	1.02(0.88-1.19)	1.32(1.07-1.63)
	20-100% vs 0-5%	1.18(1.03-1.36)	0.96(0.75-1.23)	1.27(1.09-1.47)	0.96(0.80-1.16)	1.56(1.23-1.98)

Marriage						
	Yes vs Other	0.88(0.81-0.95)	0.88(0.76-1.03)	0.88(0.80-0.97)	0.90(0.80-1.00)	0.94(0.80-1.10)
Tumor Stage						
	I vs 0	1.12(0.77-1.62)	0.98(0.45-2.10)	1.07(0.71-1.60)	0.99(0.62-1.59)	0.87(0.47-1.61)
	II vs 0	1.27(0.87-1.85)	1.39(0.65-3.01)	1.21(0.80-1.82)	1.07(0.66-1.71)	1.09(0.58-2.03)
	III vs 0	1.62(1.09-2.41)	2.55(1.16-5.61)	1.54(1.00-2.37)	1.28(0.78-2.13)	1.58(0.81-3.05)
	IV vs 0	2.50(1.64-3.82)	8.36(3.79-18.45)	1.87(1.18-2.99)	1.52(0.88-2.63)	1.71(0.84-3.48)
Hypertension						
	1 vs 0	1.19(1.08-1.31)	1.26(1.05-1.52)	-	1.75(1.53-2.01)	2.31(1.85-2.88)
Hyperlipidemia						
	1 vs 0	0.93(0.85-1.02)	0.79(0.67-0.93)	1.10(1.00-1.21)	-	1.51(1.27-1.81)
Diabetes						
	1 vs 0	1.13(1.02-1.25)	1.15(0.96-1.38)	1.33(1.19-1.47)	1.31(1.15-1.48)	-
CCI						
	1 unit change from mean	1.42(1.37-1.49)	1.38(1.29-1.48)	1.45(1.39-1.52)	1.36(1.29-1.43)	1.50(1.41-1.60)

Appendix Table Aim 3.7 showed the results of logistic regression for the association of the Specialty COC Index and inpatient visit. Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.8 The Association Between the Individual COC Index and Inpatient Visit after Hormone Therapy Initiation, full model of fully adjusted models

Individual COC		All-cause OR (95%CI)	Breast cancer-related OR (95%CI)	Hypertension-related OR (95%CI)	Hyperlipidemia-related OR (95%CI)	Diabetes-related OR (95%CI)
COC Index						
	2ndqt vs 1stqt	0.79(0.71-0.88)	0.73(0.60-0.90)	0.82(0.73-0.93)	0.76(0.66-0.88)	0.86(0.70-1.05)
	3rdqt vs 1stqt	0.50(0.45-0.56)	0.56(0.45-0.69)	0.53(0.46-0.60)	0.50(0.43-0.58)	0.58(0.47-0.72)
	4thqt vs 1stqt	0.43(0.38-0.49)	0.43(0.34-0.55)	0.43(0.37-0.49)	0.42(0.35-0.50)	0.51(0.40-0.65)
Year						
	2 vs 1	1.16(1.05-1.28)	0.76(0.63-0.91)	1.19(1.07-1.33)	1.20(1.05-1.38)	1.07(0.89-1.29)
	3 vs 1	1.32(1.17-1.49)	0.74(0.58-0.95)	1.35(1.18-1.55)	1.36(1.16-1.60)	1.22(0.98-1.53)
	4 vs 1	1.22(1.02-1.46)	0.54(0.35-0.83)	1.39(1.15-1.68)	1.38(1.10-1.73)	1.11(0.80-1.56)
Treatment						
	1 vs 0	1.52(1.35-1.70)	3.14(2.64-3.73)	1.49(1.31-1.69)	1.40(1.20-1.63)	1.58(1.29-1.93)
Region						
	Midwest vs West	0.99(0.82-1.19)	0.88(0.63-1.24)	0.98(0.80-1.21)	0.87(0.68-1.11)	1.22(0.83-1.79)
	Northeast vs West	0.97(0.82-1.15)	0.82(0.61-1.11)	0.93(0.78-1.12)	0.90(0.73-1.12)	1.25(0.88-1.76)
	South vs West	0.95(0.80-1.13)	0.98(0.73-1.32)	0.95(0.79-1.14)	0.88(0.71-1.10)	1.25(0.88-1.78)
Age group						
	66-70 vs >80	0.66(0.58-0.75)	0.56(0.44-0.71)	0.56(0.48-0.64)	0.74(0.62-0.88)	1.12(0.89-1.42)
	71-75 vs >80	0.72(0.64-0.81)	0.62(0.51-0.77)	0.69(0.60-0.78)	0.78(0.67-0.91)	0.97(0.78-1.22)
	76-80 vs >80	0.83(0.74-0.94)	0.71(0.57-0.89)	0.81(0.71-0.92)	0.90(0.77-1.05)	1.19(0.95-1.48)
Race group						
	Black vs Other	1.10(0.75-1.62)	1.78(0.89-3.56)	1.22(0.81-1.84)	1.15(0.69-1.93)	1.23(0.71-2.13)
	White vs Other	1.40(1.07-1.82)	1.57(0.93-2.65)	1.36(1.01-1.82)	1.49(1.03-2.15)	0.82(0.54-1.25)
Poverty level						
	5-10% vs 0-5%	0.98(0.87-1.10)	0.91(0.74-1.12)	1.02(0.90-1.16)	1.02(0.88-1.18)	0.94(0.75-1.18)
	10-20% vs 0-5%	1.18(1.05-1.33)	1.04(0.84-1.29)	1.20(1.06-1.37)	1.08(0.93-1.27)	1.39(1.12-1.74)
	20-100% vs 0-5%	1.33(1.15-1.53)	1.02(0.79-1.32)	1.43(1.22-1.66)	1.09(0.91-1.32)	1.73(1.35-2.22)

Marriage						
	Yes vs Other	0.85(0.77-0.92)	0.86(0.73-1.01)	0.86(0.78-0.95)	0.86(0.77-0.97)	0.88(0.75-1.04)
Tumor Stage						
	I vs 0	1.00(0.68-1.46)	0.89(0.41-1.93)	0.96(0.64-1.44)	0.88(0.55-1.42)	0.78(0.42-1.45)
	II vs 0	1.14(0.78-1.66)	1.30(0.59-2.83)	1.07(0.71-1.63)	0.93(0.58-1.51)	0.98(0.52-1.83)
	III vs 0	1.51(1.01-2.25)	2.45(1.10-5.46)	1.42(0.92-2.21)	1.16(0.70-1.94)	1.46(0.75-2.85)
	IV vs 0	2.52(1.64-3.89)	8.75(3.91-19.61)	1.81(1.12-2.91)	1.55(0.89-2.70)	1.76(0.86-3.63)
Hypertension						
	1 vs 0	1.18(1.07-1.31)	1.30(1.08-1.58)	-	1.74(1.51-2.00)	2.22(1.77-2.78)
Hyperlipidemia						
	1 vs 0	0.91(0.83-1.00)	0.77(0.65-0.92)	1.07(0.97-1.18)	-	1.49(1.24-1.79)
Diabetes						
	1 vs 0	1.16(1.04-1.28)	1.16(0.96-1.40)	1.36(1.22-1.52)	1.34(1.18-1.53)	-
CCI						
	1 unit change from mean	1.41(1.35-1.47)	1.34(1.25-1.44)	1.44(1.37-1.51)	1.36(1.29-1.44)	1.48(1.39-1.58)

Appendix Table Aim 3.8 showed the results of logistic regression for the association of the Individual COC Index and inpatient visit. Logistic regressions generated the results. The analyses were adjusted for age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.9 The Association Between the COC Index and Yearly ED Cost Change after Hormone Therapy Initiation, lagged effect fully adjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	4446.63	25.28%	1124.21	135.99	2325.54	0.0235
3rd qt vs 1st qt		33.38%	1484.10	429.36	2766.98	
4th qt vs 1st qt		32.84%	1460.42	299.88	2904.71	
Breast cancer-related						
2nd qt vs 1st qt	410.23	22.37%	91.78	-105.51	416.79	0.5353
3rd qt vs 1st qt		42.29%	173.49	-60.12	562.96	
4th qt vs 1st qt		5.36%	22.01	-161.96	342.31	
Hypertension-related						
2nd qt vs 1st qt	2648.21	20.57%	544.86	-197.48	1512.08	0.1870
3rd qt vs 1st qt		26.01%	688.83	-82.47	1691.99	
4th qt vs 1st qt		37.69%	997.98	70.28	2242.28	
Hyperlipidemia-related						
2nd qt vs 1st qt	1391.88	5.21%	72.58	-442.80	867.82	0.6266
3rd qt vs 1st qt		-10.86%	-151.21	-580.07	504.22	
4th qt vs 1st qt		14.98%	208.52	-399.83	1189.94	
Diabetes-related						
2nd qt vs 1st qt	958.11	18.42%	176.52	-302.18	1004.59	0.4675
3rd qt vs 1st qt		51.97%	497.91	-113.75	1552.65	
4th qt vs 1st qt		25.65%	245.72	-296.76	1233.16	
Individual COC						
All-cause						
2nd qt vs 1st qt	4917.80	-9.53%	-468.88	-1221.68	437.24	**0.0175**
3rd qt vs 1st qt		-14.45%	-710.75	-1470.38	216.26	
4th qt vs 1st qt		-30.40%	-1494.99	-2177.14	-643.05	
Breast cancer-related						
2nd qt vs 1st qt	458.97	30.41%	139.56	-77.78	480.84	0.6504
3rd qt vs 1st qt		18.21%	83.58	-109.28	382.81	
4th qt vs 1st qt		-1.78%	-8.17	-200.04	325.90	
Hypertension-related						
2nd qt vs 1st qt	2950.37	-12.81%	-377.99	-915.14	300.92	0.1042
3rd qt vs 1st qt		-15.15%	-447.02	-1008.19	276.30	
4th qt vs 1st qt		-31.30%	-923.42	-1440.92	-228.51	
Hyperlipidemia-related						
2nd qt vs 1st qt	-	-	-	-	-	-
3rd qt vs 1st qt		-	-	-	-	
4th qt vs 1st qt		-	-	-	-	

Diabetes-related						
2nd qt vs 1st qt	1083.01	-35.31%	-382.44	-631.29	3.52	0.2427
3rd qt vs 1st qt		-28.23%	-305.73	-600.06	167.98	
4th qt vs 1st qt		-32.09%	-347.55	-648.49	161.83	

Bold, P-value < 0.05

Appendix Table Aim 3.9 showed the results of two stage models for the association of the COC Indices (Specialty and Individual COC) and ED cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of ED visit and a linear regression model for the cost of ED visit. The analyses were adjusted for lagged COC Index, age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.

Appendix Table Aim 3.10 The Association Between the COC Index and Yearly Inpatient Cost Change after Hormone Therapy Initiation, lagged effect fully adjusted models.

	Mean Cost ($)	Estimated Cost Change (percent)	Estimated Cost Change ($)	95%CI Low	95%CI High	Pr > |t|
Specialty COC						
All-cause						
2nd qt vs 1st qt	14102.54	28.44%	4010.91	1246.83	7272.75	**<.0001**
3rd qt vs 1st qt		65.50%	9237.14	5677.86	13436.87	
4th qt vs 1st qt		48.48%	6837.33	3409.41	10936.26	
Breast cancer-related						
2nd qt vs 1st qt	1654.75	3.63%	60.02	-472.91	833.26	0.9778
3rd qt vs 1st qt		7.65%	126.56	-427.29	930.31	
4th qt vs 1st qt		2.64%	43.66	-517.88	882.54	
Hypertension-related						
2nd qt vs 1st qt	10500.07	30.38%	3190.15	887.48	5958.45	**<.0001**
3rd qt vs 1st qt		55.16%	5792.06	3097.24	9020.95	
4th qt vs 1st qt		57.43%	6030.01	3071.89	9632.88	
Hyperlipidemia-related						
2nd qt vs 1st qt	6081.64	30.70%	1866.79	276.47	3854.90	**0.0091**
3rd qt vs 1st qt		42.86%	2606.63	886.01	4752.15	
4th qt vs 1st qt		51.35%	3122.69	1138.18	5652.69	
Diabetes-related						
2nd qt vs 1st qt	3182.04	13.80%	439.22	-755.67	2222.56	0.4108
3rd qt vs 1st qt		35.08%	1116.27	-261.10	3143.14	
4th qt vs 1st qt		12.04%	383.17	-845.56	2258.07	
Individual COC						
All-cause						
2nd qt vs 1st qt	15704.75	-9.92%	-1558.31	-3527.59	729.44	0.0902
3rd qt vs 1st qt		-14.96%	-2348.78	-4420.33	103.05	
4th qt vs 1st qt		-20.36%	-3196.82	-5350.27	-595.50	
Breast cancer-related						
2nd qt vs 1st qt	1822.01	20.80%	379.05	-215.02	1192.75	0.4580
3rd qt vs 1st qt		25.65%	467.28	-154.87	1321.59	
4th qt vs 1st qt		44.01%	801.83	-44.54	2051.23	
Hypertension-related						
2nd qt vs 1st qt	11706.73	-10.84%	-1268.62	-2862.50	612.51	**0.0466**
3rd qt vs 1st qt		-19.94%	-2334.38	-3916.45	-431.02	
4th qt vs 1st qt		-23.52%	-2753.06	-4466.88	-633.53	
Hyperlipidemia-related						
2nd qt vs 1st qt	6670.73	-5.11%	-340.99	-1474.74	1040.14	0.5122
3rd qt vs 1st qt		4.89%	326.25	-1104.34	2124.52	
4th qt vs 1st qt		-14.23%	-949.24	-2236.17	711.16	

Diabetes-related						
2nd qt vs 1st qt	3626.65	-20.37%	-738.81	-1496.23	287.90	0.0621
3rd qt vs 1st qt		-28.79%	-1044.28	-1798.05	20.21	
4th qt vs 1st qt		-43.71%	-1585.10	-2246.63	-606.47	

Bold, P-value < 0.05

Appendix Table Aim 3.10 showed the results of two stage models for the association of the COC Indices (Specialty and Individual) and inpatient cost. Two-stage models were conducted for the analyses, which include a logistic regression model for the risk of inpatient visit and a linear regression model for the cost of inpatient visit. The analyses were adjusted for lagged COC Index, age group, race, marriage, poverty level, region, tumor stage, time, hypertension, hyperlipidemia, diabetes, other cancer treatments, and CCI.