Cognitive Impairment and Its Consequences on Health among Breast Cancer Patients

By

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Abstract

Objectives: The purpose of this study was to 1) examine the impact of preexisting cognitive impairment on survival and chronic medication adherence among older adults with breast cancer, 2) examine the association between chemotherapy and cognitive impairment among older adults with breast cancer, and 3) examine the association between antidepressants and cognitive impairment among older adults with breast cancer.

Methods: This retrospective cohort study of female patients aged 67 years or older diagnosed with breast cancer was performed using the Surveillance, Epidemiology, and End Results-Medicare Linked Database of the National Cancer Institute. We examined the risk of mortality from cancer and non-cancer causes in patients with and without a history of cognitive impairment (aim 1). In addition, we examined if chronic medication adherence differ between these groups of patients and if medication adherence mediates or moderates the association between cognitive impairment and non-cancer mortality (aim 1). Furthermore, we examined if chemotherapy (aim 2) or antidepressants (aim 3) were associated with an increased risk of cognitive impairment after breast cancer diagnosis. Difference-in-differences, logistic regression, and Cox proportional hazards regression models were used to assess the outcomes of interest for each aim.

Results: Mortality from cancer-specific and non-cancer causes as well as all-cause mortality was markedly higher in patients with cognitive impairment than in those without cognitive impairment. Both groups showed low adherence levels to chronic medication before and after the

breast cancer diagnosis, but the differences between the groups were not significant. Further analysis did not show that medication adherence mediates or moderates the relationship between cognitive impairment and non-cancer mortality. Chemotherapy was not associated with a statistically significant risk of cognitive impairment. However, Antidepressant use was associated with a significantly increased risk of cognitive impairment.

Conclusion: The results of this study indicate that female patients aged 67 or older with cognitive impairment and a breast cancer diagnosis have a heightened risk of cancer-specific and non-cancer mortality. Our findings did not indicate that medication adherence plays a role in the association between a history of cognitive impairment and mortality. In addition, our findings suggest that there was no increased risk of developing cognitive impairment among older patients with breast cancer after they were exposed to chemotherapy. However, we found that antidepressant use in older adults with breast cancer was associated with a higher risk of cognitive impairment.

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1.1 Overview of Breast Cancer

Breast cancer is a malignant disease in which cells in the breast tissue function abnormally and grow at an uncontrolled rate. It is one of the most prevalent cancers among women in the United States. According to the Centers for Disease Control and Prevention (CDC), the incidence rate of female breast cancer is 123.1 per 100,000,[1] with approximately 231,840 incident diagnoses in 2016.[2] This accounts for 29% of new cancer diagnoses among women.[2] The current improvements in survival and clinical outcomes are attributed to early screening for breast cancer coupled with advances in treatment strategies. Recent statistics showed that the five-year survival rate was 91% in 2004-2010 compared to 75% in 1975-1977.[2]

In 2010, breast cancer cost the United States healthcare system around $16.50 billion, and this figure is projected to increase to $20.50 billion by 2020.[3] The direct costs of patient care range from $20,000 to $100,000.[4] In addition, the indirect costs, such as losses of productivity, increase the economic burden of breast cancer. It is estimated that the indirect costs of breast cancer are around $10 billion, making breast cancer among the most expensive diseases in the United States.[5]

After patients are diagnosed with breast cancer, they usually undergo treatment within a few weeks to a month. The treatment can be complex and may include one or more of the following treatments:

(a) Local treatment: targets a specific area (e.g., breast) and includes radiotherapy and surgery;

(b) Systemic treatment: targets the whole body, for example, chemotherapy; and/or

(c) Biological treatment: uses the body's immune system to fight cancer.

The most appropriate treatment is based on the stage of cancer as well as other risk factors. In the case of local tumors (i.e., located in the breast tissue), it is best to remove the tumor since this has few side effects and a low recurrence rate. However, in more advanced cases, a systemic therapy (i.e., chemotherapy and/or hormone therapy) alone or in combination with surgery is most appropriate to increase survival and reduce recurrence.

1.2 Breast Cancer and Preexisting Cognitive Impairment

1.2.1 Overview of Cognitive Impairment

The development of effective chemotherapy and endocrine therapy in addition to early screening measures have led to a substantial improvement of survival among breast cancer patients. Therefore, attention is increasingly focused on comorbid conditions such as cognitive impairment.[6-9] Cognitive impairment refers to the disturbance of brain-based processes, including communication, concentration, memory, reasoning, and decision making, which have to be indirectly inferred from behavior.[10] Cognitive impairment is prevalent in the general population, and in particular among older adults, with an estimated prevalence of 5% to 37%.[11] Prior research has estimated the prevalence of cognitive impairment before the initiation of

systemic treatment (i.e., chemotherapy or endocrine therapy) to range from 11% to 35%.[12-16] Cognitive impairment is linked to poor quality of life among survivors and can worsen cancer outcomes.[17]

1.2.2 Impact of Preexisting Cognitive Impairment on Survival

Before starting cancer therapy, it has been recommended to identify sociodemographic factors, medical history, and other relevant risk factors that may increase morbidity and mortality among elderly patients diagnosed with cancer.[18] Risk factors such as dementia have been identified as a predictor of shorter survival among older cancer patients.[19] Some evidence also suggests that cognitive impairment is a predictor of shorter survival among older cancer patients.[20] Although evidence has shown that one-third of older breast cancer patients have signs of cognitive impairment at the initiation of cancer treatment,[21] little is known how cognitive impairment impacts survival of older patients with breast cancer.

1.2.3 Impact of Preexisting Cognitive Impairment on Chronic Medication Adherence

More than 50% of breast cancer survivors in the United States are over 65 years old, and this can be attributed to the success of cancer screening and treatment.[22,23] The improvement of survival in patients with breast cancer has led to enhanced focus on the improvement of chronic condition management.[24] Two prior studies analyzed the Surveillance Epidemiology and End Results (SEER) data and found that 24% of patients with breast cancer had comorbid conditions, and among patients age 66 years or older, nearly 10% had at least two or more comorbid conditions.[25,26]

Chronic conditions such as diabetes and cardiovascular disease are common among breast cancer patients. According to the CDC, approximately 14% of breast cancer patients have diabetes, which is above the national average of 9.3%.[26,27] Also, around 40% of older breast cancer patients have hypertension, and the risk of hypertension in this population is 1.48 times higher compared to the risk in non-cancer patients.[28,29] Furthermore, approximately 6.9%, 2.7%, and 1% of older breast cancer patients have congestive heart failure, peripheral vascular disease, and a history of myocardial infarction, respectively.[30] Both diabetes and cardiovascular disease are leading causes of death in the United States.

Multiple studies have shown that the number and severity of comorbid conditions among early-stage breast cancer were highly associated with non-cancer mortality compared to end-stage breast cancer.[31-36] Patnaik et al. determined the effect of 13 comorbidities on survival and all-cause mortality among Medicare beneficiaries aged 66 years or older. Diabetes and stroke were among those comorbidities. All 13 comorbidities were highly associated with a decreased overall survival. In addition, they found that patients with stage I breast cancer with comorbidities had similar survival to patients with stage II cancer who did not have comorbidities.[36] Successful adherence to chronic medication is important to improve survival from non-cancer mortality.

Evidence supports that medication adherence is a major issue in older populations, and specifically concerning among breast cancer patients who are more vulnerable. The results of an observational study of 4,216 breast cancer patients showed a reduction in oral diabetes medication adherence during and after breast cancer treatment.[37] In another study that utilized SEER-Medicare data, researchers found that patients with breast cancer displayed significantly

lower adherence and persistence to diabetes medication than non-cancer patients, but not to antihypertensive medication.[38] Nonadherence to prescribed medications has adverse effects on health. Despite the significance of this issue, no evidence exists regarding the influence of cognitive impairment on medication adherence for chronic conditions in patients with breast cancer.

1.3 Chemotherapy and Cognitive Impairment

An increasing body of evidence suggests that breast cancer patients, post-treatment, experience a decline in cognitive function more than the general population.[12,39,40] Patients commonly refer to this condition as "chemo brain" or "chemo fog." Chemotherapy-related cognitive impairment refers to the decline in cognitive function associated with the beginning of cancer therapy and is a serious problem facing 15% to 61% of breast cancer survivors each year.[12,41] Other researchers found that cognitive impairment associated with cancer treatment, specifically chemotherapy, can last for years after completion of treatment.[42,43] Studies have found chemotherapy and endocrine therapy, or endocrine therapy alone, to be associated with cognitive impairments.[44,45] Most prior research has focused on chemotherapy as a possible cause for this condition.[46,47]

Some cross-sectional studies have found that 17% to 75% of breast cancer patients experience cognitive impairments.[48-50] The absence of pre-treatment baseline assessments of cognitive function limits the inferences that can be drawn from these studies. Consequently, an increasing number of longitudinal neuropsychological studies have included pre- and post-assessments of cognitive function. Many demonstrate a decline in cognitive functions in breast cancer patients who have been treated with chemotherapy compared to disease-free or non-chemotherapy

groups.[12,39,40,42] However, other studies found no association between cancer treatments and cognitive function.[51-53]

Moreover, the results of several studies showed that 11% to 35% of breast cancer patients have a decline in cognitive performance before starting cancer treatment.[15 16] However, only a small portion of the cognitive decline can be attributed to age, education, depression, anxiety, and surgery/anesthesia.[16] No explanation exists why breast cancer patients are at higher risk for cognitive impairment than the general population. Two hypotheses have been indicated in the literature: (a) the biology of cancer cells may trigger an inflammatory response that releases neurotoxic cytokines, and/or poor DNA repair may result in neurodegenerative diseases; and (b) exposures to chemotherapy or endocrine therapy through various mechanisms may result in cognitive decline.[54-56] For instance, it has been proposed that adjuvant chemotherapy such as doxorubicin increases free radicals in the brain, which damage the brain cells and adversely impact cognitive function.[54,55]

Chemotherapy-related cognitive impairment can have a serious negative impact on health outcomes and quality of life.[57] Because of mixed results from prior studies, it is critical to examine chemotherapy-related cognitive impairment and identify risk factors that contribute to cognitive change in older adults with breast cancer.

1.4 Antidepressants and Cognitive Impairment

The association of antidepressants and cognitive impairment risk is of particular interest, as depression is known as a risk factor for cognitive decline.[58-61] To date, the association between

depression and cognitive impairment remains unclear; nonetheless, several mechanisms have been hypothesized. These hypotheses include depression as a factor in inflammatory changes, increased deposition of B-amyloid plaques, vascular disease, and nerve growth factor deficits.[60] At this time, it is unclear whether antidepressants can alter the risk for developing cognitive impairment. It is possible that antidepressants might alter the risk for cognitive impairment in patients with depression by virtue of altering the pathological pathway between depression and cognitive impairment.

However, this might not be the case in patients who use antidepressants for reasons other than depression. Antidepressants are among the most commonly prescribed medication in the United States.[62] It is estimated that approximately 15% of older adults (over the age of 50 years) use antidepressants.[62,63] Few studies have directly investigated the association between antidepressant use and the risk for cognitive impairment. In a retrospective cohort study of older adults, researchers found that antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), were associated with a higher incidence of cognitive impairment.[64] Another study of postmenopausal women found that SSRIs and tricyclic antidepressants (TCAs) were associated with an increased risk of mild cognitive impairment.[65] In the Health and Retirement Study, researchers did not observe any difference in the incidence of cognitive impairment among antidepressant users after six years of follow-up.[66]

Insufficient and conflicting evidence exists on the association between antidepressant use and the risk for cognitive impairment. There is a need for research into the association between antidepressants and the risk for cognitive impairment in older adults with breast cancer.

1.5 Study Objectives

The current project addresses several issues: (a) the need for population-based research to examine the impact of cognitive impairment on the health outcomes of patients with breast cancer, (b) the need for better understanding of the association between chemotherapy and cognitive impairment in patients with breast cancer, and (c) an exploration of the association between antidepressant use and the risk for cognitive impairment in patients with breast cancer. To address these issues, we used SEER-Medicare data to examine three specific aims:

Aim 1: Assess the impact of cognitive impairment on cancer survival and chronic medication adherence in older adults with breast cancer,

Aim 2: Assess the association between chemotherapy and the risk for cognitive impairment in older adults with breast cancer,

Aim 3: Assess the association between antidepressant use and the risk for cognitive impairment in older adults with breast cancer.

1.6 Study Significance

Attention is increasingly focused on the health of breast cancer survivors after the completion of cancer treatment due to the significant improvement in survival. Several studies have explored the impact of cognitive impairment on survival and adherence. However, the majority of these studies were small clinical trials that used a variety of study designs and assessment methodologies. Our approach to explore these issues using SEER-Medicare data will enable a population-level assessment of the three specific aims.

This study will fill the gap in our knowledge about the potential impact of cognitive impairment on survival and chronic medication adherence in breast cancer patients. This study will also examine the association between breast cancer treatment, particularly chemotherapy, and the risk for cognitive impairment development. In addition, this study will explore the association between antidepressant use and the risk for cognitive impairment.

The results obtained from this study could guide clinical practice and improve the health of breast cancer patients. Our findings will provide more information for physicians on the incidence of and factors associated with cognitive impairment and its impact on health outcomes. As a result, physicians may be able to optimize treatments or health services. From a public health perspective, understanding these issues could improve patients' health and reduce healthcare costs. Healthcare costs can be reduced by identifying high-risk patients and implementing cost-effective therapeutic strategies.

Chapter Two | Literature Review

The aim of this review chapter is to provide background information relating to breast cancer and cognitive impairment, its impact on survival, and chronic medication adherence. Furthermore, we will discuss in detail the controversy around the association of cancer chemotherapy and the development of cognitive impairment among patients with breast cancer. The chapter will conclude with an overview of the association of antidepressants with the risk of cognitive impairment.

2.1 Breast Cancer Literature Review

2.1.1 Breast Cancer Incidence and Survival

Breast cancer is a malignant disease in which cells in the breast tissue function abnormally and grow at an uncontrolled rate. In the United States, approximately 810,170 new cancer cases are diagnosed annually in women.[67] Although there are more than 200 different types of cancer, breast, lung, and colon cancers are the most prevalent cancers among women. According to the CDC, the incidence rate of female breast cancer is 123.1 per 100,000,[68] with approximately 231,840 incident diagnoses in 2016.[2] This accounts for 29% of new cancer diagnoses among women.[69] It is estimated that one in eight (12.4%) women born in the United States will develop breast cancer during their lifetime.[70]

In the past, breast cancer was usually terminal. However, recent advances in the medical field and an increase in public awareness about breast cancer (e.g., early screening) have led to substantial improvements in the diagnosis and treatment of breast cancer. Subsequently, survival rates have increased due to early detection and effective treatment. Among women, the overall cancer incidence rates declined slightly from 2003 to 2012 in all racial and ethnic groups combined; however, this decline was not statistically significant for most groups. Whereas breast cancer incidence rates remained stable during this period for women overall, the rate increased slightly among black women (0.2% per year).

The five-year relative survival rate for breast cancer patients improved from 75% in 1975-1977 to 91% in 2004-2010.[2] Recent published evidence estimates that the five-year survival rate for non-Hispanic white women with breast cancer and black women are 92% and 80%, respectively.[2] Survival varies by cancer grade and stage at diagnosis. An estimated 61% of breast cancer patients are diagnosed at an early stage, for which the five-year survival rate is approximately 99%. If the breast cancer has spread to lymph nodes or surrounding tissues, the survival rate is 85%.[69] Survival falls dramatically to 25% if cancer is diagnosed at a late stage.[69] Death rates in women have declined since 1989, with a larger decrease in women under 50 years old. The death rate decreased by 2.4% to 3.2% per year for women under 50 years old compared to 1.1% to 1.8% for women older than 50 years.[69]

2.1.2 Economic Burden of Breast Cancer

The United States cancer care expenditure has increased substantially in the last decade. In 2010, the healthcare costs of all cancer types were estimated to be $124 billion. Breast cancer had the

highest healthcare cost, estimated to be $16.50 billion in 2010.[3] The total expenditure for cancer care will continue to increase over the next few years. By 2020, healthcare costs are projected to rise to $173 billion for all cancers and $20.5 billion for breast cancer alone.[22] At the patient-level, the lifetime costs per-patient range from $20,000 to $100,000.[4] In addition, the indirect costs, such as losses of productivity, increase the economic burden of breast cancer. In fact, it is estimated that the indirect costs of breast cancer are $10 billion and it is ranked among the top most expensive diseases in the United States.[71]

2.1.3 Risk Factors for Breast Cancer

The risk factors for developing breast cancer involve a combination of age, geographic location, genetics, and lifestyle factors. Older age is considered one of the main risk factors for breast cancer. Based on statistics from the National Cancer Institute's SEER program, the average age at breast cancer diagnosis is around 63 years, and the disease incidence increases with age.[72] Where people reside can also be influential, as evidence suggests a higher incidence of breast cancer for western countries than in the rest of the world.[73] Previous history or/and family history of the disease can also increase the risk of developing breast cancer.[73] Furthermore, lifestyle factors such as obesity, alcohol consumption, physical inactivity, and hormone replacement therapy has been shown to increase the risk for this disease.[74]

2.1.4 Diagnosing Breast Cancer

Since breast cancer can metastasize, it is important that it is detected at an early stage to improve the likelihood of survival. Breast cancer can be detected through self-examination or mammography. One of the main symptoms that can be detected during self-examination is an

isolated, painless lump/mass in the breast.[75] However, breast cancer development involves several stages; thus, it takes time before cancer cells develop into a noticeable tumor that can be detected by hand.[75] Further, the tumor can grow and attach to the skin or thoracic wall. It is usually associated with painful ulceration or inflammation symptoms, and there is a possibility for discharge or bleeding from the nipple.[75] Typically, women seek medical care upon recognition of these symptoms. Physicians' first resource is physical examination and mammography to make a breast cancer diagnosis.[75]

Physicians commonly determine the grade and stage of cancer to tailor the treatment. A biopsy of the cancer cells is examined by a specialist, who evaluates the degree of similarity between the cancer cells and normal cells in terms of appearance and growth patterns. When the biopsy sample appears similar to normal cells, the grade of cancer is low; whereas, the higher the degree of abnormality, the higher the grade of breast cancer.[76] Breast cancer is graded as I (low), II (intermediate), and III (high).[76] For instance, a high-grade tumor is faster-growing and faster-metastasizing than a low-grade tumor, and it may require complex invasive treatment.[76] The stage of cancer describes the advancement of cancer development in the patient and can be used to determine a patient's prognosis.[77] Stage is expressed numerically, where stage 0 means non-invasive cancer and stage IV means invasive cancer that has spread outside the breast tissue.[77] The prognosis of breast cancer is an important factor in determining the most appropriate treatment strategy.[78]

2.1.5 Treatment for Breast Cancer

After patients are diagnosed with breast cancer, they usually undergo treatment within a few weeks to a month. The treatment can be complex and may include one or more of the following treatments:

(a) Local treatment: targets a specific area (e.g., breast) and includes radiotherapy and surgery;

(b) Systemic treatment: targets the whole body, for example, chemotherapy; and/or

(c) Biological treatment: uses the immune system to fight cancer.

The most appropriate treatment is based on the stage of cancer as well as other risk factors. In the case of local tumors (i.e., located in the breast tissue), it is best to remove the tumor since this has few side effects and a low recurrence rate. However, in metastatic cancer cases, a systemic therapy (i.e., chemotherapy and/or hormone therapy) alone or in combination with surgery is most appropriate to increase survival and reduce recurrence. In some severe cases where cancer is incurable, the goal of treatment is palliative. Neoadjuvant therapy includes chemotherapy, hormone therapy, and/or radiotherapy pre-surgery with the goal of shrinking the tumor size to make surgery more effective. Alternatively, these therapies can be used post-surgery (known as adjuvant therapy) to target any remaining cancer cells.

Surgery

The aim of surgery is to remove the cancer. There are many types of surgery depending on the disease prognosis.[79] For example, patients with a lower stage of cancer are offered breast-conserving surgery which involves removing the tumor and partially removing healthy breast tissue. Mastectomy may be necessary for patients with a higher stage of breast cancer. This

surgery can be further classified as total mastectomy (complete removal of the entire breast tissue) or radical mastectomy (complete removal of the entire breast tissue, muscle, and lymph nodes near the breast).[79]

Radiotherapy

Radiotherapy uses high-energy rays to destroy cells by damaging their DNA and prevent/reduce the growth and reproduction of the affected cells.[80] Healthy cells can recover but cancer cells cannot. It can be administered pre-surgery to shrink the tumor size, thus improving the success of surgery.[80] Furthermore, radiotherapy can be administered post-surgery to reduce the risk of the cancer recurring.[80]

Hormone Therapy

Breast cancer cells are occasionally sensitive to estrogen, which means that estrogen facilitates cancer cell growth.[81,82] Hormone therapy can reduce the levels of estrogen and thus block its effects.[82] Three types of hormone therapies are available and each function differently:

(a) drugs that block estrogen's effect, for example tamoxifen, raloxifene, and toremifene (known as selective estrogen receptor modulators), bind to estrogen receptor-positive cells to block the attachment of endogenous estrogen thereby decreasing cancer cell growth. Fulvestrant works differently through binding to the estrogen receptor and functioning as an antagonist,

(b) drugs that prevent estrogen production, for example aromatase inhibitors such as anastrozole, exemestane, and letrozole, prevent estrogen production in post-menopausal women, and,

(c) drugs that suppress ovarian function. Ovarian function can be suppressed by a drug called luteinizing hormone-releasing hormone blockers, such as goserelin and leuprolide. These drugs

temporally suppress ovarian function and thus reduce estrogen level.[82] Hormone therapy can be used pre-surgery to shrink breast tumors with estrogen receptor-positive cells. However, it is commonly used up to five years post-surgery to help prevent the recurrence of breast cancer.[82]

Chemotherapy

Chemotherapy is a drug treatment involving chemicals cytotoxic to cancer cells.[83] Chemotherapeutic agents interfere with the cell division process by damaging the cell's DNA. There are multiple routes of chemotherapy administration including injection, infusion pumps, or orally. These chemotherapeutic agents then circulate in the body, targeting and destroying fast dividing cells. The systemic nature of this treatment means that it can effectively target cancer cells in multiple locations, including potential metastases to other organs. Chemotherapy also adversely affects healthy fast-dividing cells, such as immune, bone marrow, and hair follicle cells. Chemotherapy is usually administered in cycles that vary in time between one and five days, followed by a break of four weeks. In general, the chemotherapy can last for eight cycles.[83] There are many different types of chemotherapy drugs and multiple factors determine the type of agent administered to a patient, such as the type of cancer, its grade, and its stage. It is commonly administered as a combination with the aim to maximize the effectiveness of the treatment. The drugs function using different mechanisms to kill the cancer cells. Examples of the most commonly used regimens include:[83]

1. First-generation chemotherapy regimens
    (a) Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)
    (b) Doxorubicin and cyclophosphamide (AC)
    (c) 5-Fluorouracil, epirubicin, and cyclophosphamide (FEC)

2. Second-generation chemotherapy regimens
    (a) Cyclophosphamide, doxorubicin, and 5-fluorouracil
    (b) Sequential epirubicin followed by CMF
    (c) Docetaxel plus cyclophosphamide
3. Third-generation chemotherapy regimens
    (a) Docetaxel, doxorubicin, and cyclophosphamide
    (b) Sequential FEC-taxane therapy
    (c) Dose dense sequential doxorubicin/cyclophosphamide-paclitaxel
    (d) Sequential AC-weekly paclitaxel

Choosing the best treatment course for breast cancer is not an easy task. It requires the physician to consider a range of factors to select a treatment regimen that will destroy the cancer cells to prevent recurrence and potential metastasis. In recent years, survival rates have increased following advancements in the treatment of breast cancer, and therefore, attention has turned to the side effects related to the treatment of breast cancer and other comorbid conditions.

2.2 Breast Cancer and Preexisting Cognitive Impairment

2.2.1 Overview of Cognitive Impairment

Cognition is a term that refers to brain-based processes, including communication, concentration, memory, reasoning, and decision making, which are important for daily activity.[84] A vast amount of research has been conducted on the processes related to cognitive function.[10,12,19,45,50,85-101] Cognitive impairment, or cognitive deficit, occurs as a result of an error in one or more cognitive

domains, such as attention, visual function, language, memory, executive function, and motor function.[50]

2.2.2 Incidence of Preexisting Cognitive Impairment in Breast Cancer

Evidence suggests that breast cancer patients experience cognitive impairment more often than the general population, particularly in the domains of attention, memory, and executive function.[49,102] The prevalence of cognitive impairment in breast cancer patients ranges from 11% to 35%.[12-16] As discussed earlier, cognition encompasses mental actions that are important to execute both simple and complex tasks and are fundamental to daily life. For this reason, cognitive impairment can have a negative effect on the quality of life and health outcomes of cancer patients.

2.2.3 Impact of Preexisting Cognitive Impairment on Survival

The development of effective chemotherapy and endocrine therapy, in addition to early screening, led to a substantial improvement in survival among breast cancer patients.[103] As survival increases, physicians will increasingly be confronted with breast cancer occurring in elderly patients with cognitive related illnesses. Dementia is one of the leading causes of death in older adults. Dementia has been identified as a predictor of a shorter life expectancy among older cancer patients.[17] The results from two studies have shown that there is an association between dementia and later-stage cancer at diagnosis.[104,105]

Cognitive impairment without dementia in older breast cancer patients could potentially shorten life expectancy.[106] It has been estimated that 11% to 35% of breast cancer patients show

evidence of cognitive impairment prior to cancer treatment.[15,16] One study found that older adult cancer patients with cognitive impairment were six times more likely to die compared to older patients without cancer.[21] Sachs et al. reported that patients 60 years or older with mild to moderate cognitive impairment were associated with an increased risk of mortality after 13 years of follow-up.[95] Cognitive impairment is associated with certain risk factors at multiple levels. At the biological level, cognitive impairment is associated with biomarkers that are known to reduce life expectancy. These biomarkers indicate changes such as an increase in inflammation, reduction of DNA repair, and oxidative stress.[107,108] At the medical level, cognitive impairment is associated with late diagnosis of cancer.[17] Cognitive impairment may be associated with delirium, which is a complication that occurs during treatment and has been recognized as a risk factor for a shorter life.[109] Also, cognitive impairment is associated with poor cardiovascular and diabetes outcomes, and thus shortens life-expectancy.[92] At the psychological level, cognitive impairment has been associated with depression, anxiety, and fatigue which all are strong predictors of a shorter life expectancy.[87,110]

Although previous studies identified various conditions that could shorten survival of older breast cancer patients, few have examined the degree to which cognitive impairment impacts the survival of cancer patients.[21] Understanding how cognitive impairment affects death from cancer and non-cancer causes could guide cancer healthcare decisions and answer some important questions. For example, is screening for cognitive impairment appropriate in patients with breast cancer? What is the best level of care (e.g., palliative vs. aggressive treatment) for breast cancer in the context of preexisting cognitive impairment? This dissertation examined the effect of a preexisting diagnosis of cognitive impairment on mortality from cancer and other causes in older

adults diagnosed with breast cancer. Breast cancer was chosen because of the high prevalence and survival among breast cancer patients.[17]

2.2.4 Impact of Preexisting Cognitive Impairment on Chronic Medication Adherence

More than 1.3 million breast cancer survivors are over the age of 65 years in the United States,[22,33] and the number of older people with cancer is increasing, mainly as a result of the success of breast cancer screening and treatment. Therefore, improving the management of common chronic conditions becomes a high priority for survivors of breast cancer.[111] In the United States, two studies used SEER data and found that 24% of patients with breast cancer had comorbid conditions, and among patients over the age of 65 years, 9.8% were reported to have two or more comorbid conditions.[25,26] Chronic conditions such as diabetes and cardiovascular diseases are common among breast cancer patients. According to the CDC, approximately 14% of breast cancer patients have diabetes, which is above the national average of 9.3%.[26,27] Also, around 40% of older breast cancer patients have hypertension, and the risk of hypertension in this population is 1.48 times higher than the risk in non-cancer patients.[28,29 28,29] Furthermore, around 6.9%, 2.7%, and 1% of older breast cancer patients have congestive heart failure, peripheral vascular disease, and a history of myocardial infarction, respectively.[30] Both diabetes and hypertension are leading causes of death in the United States.

The number of comorbidities at the time of early-stage breast cancer diagnosis was highly associated with non-cancer mortality compared with advanced-stage breast cancer without comorbidities.[112-116] One study that examined the impact of comorbidities on survival reported that patients with stage I cancer and a comorbid condition had similar or poorer survival than

patients with stage II and no comorbid condition.[36] Consequently, given the high rate of breast cancer survival, the management of comorbid conditions, such as hypertension and diabetes, is important for overall survival especially in elderly survivors with cognitive impairment.[36]

In general, older adults experience age-related declines in the cognitive functions necessary for medication adherence[117]; therefore, they may be at higher risk for nonadherence to prescribed medications. This risk is accentuated for individuals diagnosed with cancer and chronic disease. One study reported that one-third of breast cancer patients have cognitive decline before the initiation of treatment.[12] Thus, those most in need of adhering to prescribed medicines are also more likely to experience a decrease in medication-taking behavior.

Adherence is referred to as taking prescribed medication as recommended by physicians. Prefrontal cortex theory provided a theoretical model to predict the type of cognitive processes that are important to adhere to prescribed medication.[118] According to this model, two types of cognitive processes are necessary for daily function—one requires executive function and working memory, and one requires memory storage and retrieval.[119] Adhering to medicines requires the involvement of executive function because taking medicines requires developing and implementing a plan to take the medication; remembering to adhere, which may require remembering the time (e.g., at 8:00 a.m.); and remembering whether the medication was taken as prescribed (monitoring). The task of monitoring is more difficult when taking medication is repetitive.[120] Taking medication for chronic disease is repetitive because the same medication is taken in the same manner every day. Medication adherence involves working memory. For example, a patient must maintain the intention to take the medication active in working memory

while doing the usual daily tasks. Researchers reported that patients often have to delay the task until the conditions are suitable to take the medication.[121,122] They found memory decline in older adults compared to young adults and reported that maintaining the intention over short delays is not easy for older adults.[121,122]

Although the evidence is insufficient, the literature suggests that cognitive impairment is associated with medication nonadherence.[123] In fact, in older adults taking antihypertensive medication, those with cognitive impairment had twice the risk of medication nonadherence compared to those without cognitive impairment.[124] Knowing that elderly breast cancer patients are suffering from comorbid conditions and cognitive impairment and are at high risk of mortality from non-cancer causes, raises an important question. Namely, what is the impact of cognitive impairment on chronic medication adherence and its association with non-cancer related mortality? In this dissertation, we used SEER-Medicare data to examine the impact of cognitive impairment on chronic medication adherence (i.e., cardiovascular and diabetes medications) and its consequence on mortality from non-cancer causes in patients with breast cancer.

2.3 Chemotherapy and Cognitive Impairment

The systematic toxic effects of cancer therapy have been extensively investigated; however, their effects on cognitive function are less understood.[125,126] The currently available evidence shows that some cancer treatments or combinations may lead to deterioration of cognitive function.[86,88]

Neuropsychological studies have shown evidence of cognitive impairment in cancer patients that have been attributed mainly to the neurotoxic effects of chemotherapy.[12,99,127-130] Although the association between the use of chemotherapy for central nervous system (CNS) tumors and neurological adverse effects such as cognitive impairment is known,[131] the effect of chemotherapy for treatment of non-CNS cancer, such as breast cancer, on cognitive function as well the mechanisms that may be responsible for this decline remain unclear. Some researchers have explained chemotherapy-related cognitive impairments as a result of neuronal damage caused by multiple risk factors such as neurotoxic side effects. Furthermore, the increased blood-brain barrier permeability, DNA damage, and consequently increased aging, modification of cytokine regulation, reduction in neural repair, and oxidative stress may play significant roles in the effects of chemotherapy on CNS function, particularly cognitive function.[132-136]

It is challenging to make sense of the heterogeneous evidence across studies. A number of studies involving breast cancer patients have found a decline in cognitive function after chemotherapy.[12,99,127,129,130,137] However, other studies reported conflicting results.[51,138,139] Heterogeneous results were also found regarding the length of cognitive impairment; while some studies found a sustained cognitive impairment years after the treatment,[129,140] others showed a recovery of cognitive function soon after completion of chemotherapy.[141,142] These discrepant results could be explained by the methodological differences across the studies. First, the timing of patients' cognitive function assessments was different. Second, different measures were used to evaluate the same domain, because of differences in measure sensitivity. Third, the definition used to determine the cognitive impairment varied. Fourth, patients' characteristics, such as cancer stage, type of treatments, and age, were different. Finally, the type of comparison groups

differed; results may vary based on whether patients are compared to non-cancer patients or cancer patients who did not receive chemotherapy.

Hence, the overall estimated incidence of cognitive impairment varies between 16% and 75%.[12,85,143] Results of a recent meta-analysis of cognitive impairment in women with breast cancer showed that different methodological approaches could lead to different findings.[144] Differences were found when cross-sectional and prospective studies were compared, with a significant association between chemotherapy and cognitive impairment in cross-sectional studies. In contrast, prospective studies showed a slightly improvement in cognitive functioning after to chemotherapy compared to prior chemotherapy.

It has been proposed that certain combinations of drugs and doses are responsible for cognitive decline. A study examined the correlation between different treatments and doses in patients with breast cancer.[96] The study compared four groups of patients, two with patients with breast cancer who were treated with different chemotherapy combinations (high doses vs. standard doses), one with breast cancer patients who did not receive systematic chemotherapy, and one healthy control group.[96] A significantly higher risk of cognitive impairment was observed in patients on high-dose chemotherapy (cyclophosphamide, thiotepa, and carboplatin) than in the patients who did not receive chemotherapy, but not in the other groups.[96] This suggests that differences in chemotherapy combinations and doses affect cognitive function,[145,146] and higher doses are associated with worse cognitive performance.[147] Another randomized study found that patients who received standard-dose chemotherapy consisting of 5-fluorouracil, epirubicin, and cyclophosphamide showed no increased risk for cognitive decline compared with the control

group.[140] However, breast cancer patients who received conventional adjuvant chemotherapy, such as cyclophosphamide, methotrexate, and 5-fluorouracil, showed a higher risk of cognitive impairment than the control group of breast cancer patients who were not treated with chemotherapy.[140]

Recent evidence that includes brain imaging showed the impact of chemotherapy on brain tissue and structure. Researchers found changes in the cortical and subcortical regions in patients who received chemotherapy compared to the healthy control group or patients who did not receive chemotherapy.[93,119,148-150] Multiple studies showed that chemotherapy-associated brain structural and functional changes are associated with a decline in cognitive function.[91,151]

Recently, radiotherapy and endocrine therapy have also been proposed as causes of cognitive impairment.[44,45,152-155] In a longitudinal study, cognitive impairment was found in 34% of patients who underwent radiotherapy, and this persisted in 50% of them after one year of follow-up.[156] Some studies have suggested that cognitive impairment persisted for months or years after radiotherapy,[130,153-156] while others showed that patients recovered shortly after radiotherapy.[157-159] Estrogens have been shown to regulate mental status, mood, and cognitive function.[157-162] Hormone therapy (tamoxifen) works by binding to the estrogen receptor and tamoxifen is the drug of choice for endocrine therapy in breast cancer patients. Controversy exists regarding the adverse effects of tamoxifen in cerebral tissues. Evidence suggests that tamoxifen can cause neurotoxicity and its use might negatively impact cognitive function; however, its effects are reversible after treatment is completed.[100,163,164] For instance, several studies have shown that

tamoxifen plus chemotherapy may cause additional cognitive decline compared to chemotherapy alone.[44,45,147]

There are other risk factors for cognitive impairment, besides treatment, in cancer patients that potentially have a negative effect on the cognitive function of these patients. These factors include the psychological burden of cancer and cancer-related biological factors such as elevated cytokines levels. Patients with cognitive impairment usually have a more advanced cancer stage, with a high psychological burden and worse prognosis. Breast cancer alone might increase cognitive impairment as shown in patients presenting with cognitive decline even before treatment.[50,97,165] However, this risk increases with systemic treatment, especially chemotherapy.[12,99,101,127,129,130] Cognitive impairment in breast cancer patients may be caused by an accumulation of some of these factors. Furthermore, the presence of chronic diseases, low education level, aging,[144,166] menopause,[90] anxiety, and depression have also been explored as possible risk factors.[7,89,90] However, the validity or importance of these predictors is not well established.

Overall, existing evidence is inconsistent regarding the effect of breast cancer chemotherapy on cognitive impairment. The existing evidence suggests that chemotherapy-related cognitive impairment exists; however, further investigation is needed. Population-based studies could be important to understand this issue and to find a better way to minimize the adverse effect of chemotherapy on cognitive function in breast cancer patients.

2.3.1 Mechanisms of Action of Chemotherapy-Related Cognitive Impairment

The mechanisms underlying chemotherapy-related cognitive impairment are still unknown; however, multiple mechanisms have been proposed. The most notable is oxidative damage.[43,167,168] It is well-understood that a significant number of chemotherapeutics agents exert their therapeutic action through oxidative stress which generates reactive oxygen species (ROS) that damage malignant cells as well as normal cells. The cognitive decline in breast cancer patients may be directly associated with the ROS generated when patients undergo chemotherapy. The possible mechanism of how ROS can bypass the blood brain barrier and inflict damage to the brain was described by Butterfield (2014).[169] The author reported that doxorubicin, one of the most commonly used chemotherapy agents, generates ROS in the body which can alter a key plasma protein called apolipoprotein A1 (ApoA1) through an oxidative reaction. Oxidized ApoA1 leads to increased levels of tumor necrosis factor (TNF)-α which bypasses the blood brain barrier causing cell apoptosis.[169,170]

Similar results were found for other antineoplastic agents commonly used in breast cancer, such as methotrexate, cyclophosphamide, 5-fluorouracil, epirubicin, and docetaxel. For example, methotrexate is a dihydrofolate reductase inhibitor used in the treatment of many cancers, including breast cancer. Methotrexate was found to cause nephrotoxicity subsequent to ROS formation.[171] In animal models, researchers found that methotrexate had significant effects on memory tests. This decline in cognitive function could be attributed to the changes induced by methotrexate in the brain, especially the frontal lobes and hippocampus.[172] Other clinical evidence suggested that cognitive changes could be explained by the oxidative stress in CNS membrane phospholipids in children with acute lymphoblastic leukemia.[173] Interestingly, the

oxidative stress markers could be found in the cerebral spinal fluid of patients with cognitive impairment.[174] Also, cyclophosphamide increases the oxidative stress reaction in the CNS. This was quantified by the presence of malondialdehyde, a product of lipid and fatty acid peroxidation and oxidation.[175] It has been shown that the damage caused by cyclophosphamide results from the increased production of inflammatory cytokines (e.g., TNF-α and interleukin 6).[176]

2.4 Antidepressants and Cognitive Impairment

Antidepressants are considered among the most commonly prescribed medications in the US.[62] It has been estimated that around 15% of older adults (over the age of 50 years) use antidepressants.[62,63] The association of antidepressants and cognitive impairment risk is of particular interest, as depression is a known risk factor for cognitive decline.[58-61] To date the association between depression and cognitive impairment remains unclear; nonetheless, several mechanisms have been hypothesized. These mechanisms include depression as a factor in inflammatory changes, increased deposition of B-amyloid plaques, vascular disease, and nerve growth factor deficits.[60] At this time, it is unclear whether antidepressants can alter the risk for developing cognitive impairment. It is possible that antidepressants might alter the risk for cognitive impairment in patients with depression by virtue of altering the pathological pathway between depression and cognitive impairment. However, this might not be the case in patients who use antidepressants for reasons other than depression.

A number of preclinical and clinical studies suggest that antidepressants might have neurogenic and/or neuroprotective effects through the antioxidant properties of antidepressants. In vitro studies have shown that both amitriptyline and fluoxetine protect rat pheochromocytoma (PC12)

cells from damage by oxidative stress.[177] Also, pretreatment with these antidepressants was associated with reduced cell death and increased superoxide dismutase (SOD), an enzyme that neutralizes free radicals.[177] Another study explored the effects of multiple antidepressants, such as desipramine, imipramine, and maprotiline, on the messenger ribonucleic acid (mRNA) levels of many endogenous antioxidants in human cells.[178] They found that long-term treatment increases the mRNA levels of major endogenous antioxidants, such as SOD.[178] Curti et al. (1999) examined the effects of fluoxetine on the rat brain.[179] The results showed that fluoxetine inhibits oxidative phosphorylation through its effect on electron transport and ATP synthase activity.[179]

Animal model studies have been developed to investigate antioxidant properties of antidepressant drugs. For example, R´eus et al. reported increased SOD and catalase (CAT) and decreased protein and lipid oxidation in the rat brain.[180] However, other studies showed that imipramine might increase ATP synthesis and may potentially increase cells' ROS production. Xu et al. (2003) investigated amitriptyline and venlafaxine and found them to be neuroprotective to hippocampal neurons which play a major role in short and long memory.[181] Abdel Wahab and Salama (2011) investigated amitriptyline and venlafaxine and found them to be neuroprotective to hippocampal neurons which play a major role in short- and long-term memory.[182] Similarly, fluoxetine was found to increase the level of some endogenous antioxidants, such as SOD and CAT, in the rat brain.[182]

A number of studies have examined the effect of antidepressant drugs on oxidative stress and potential antioxidant activities in humans. The majority of these studies showed that

antidepressant drugs have antioxidant properties when used to treat depression. In a cohort of 62 patients diagnosed with major depression, it was found they had high levels of the oxidative stress markers SOD and malondialdehyde (MDA).[183] The level of oxidative markers reduced significantly after the administration of fluoxetine and citalopram.[183] These results showed an effective reduction in oxidative stress with fluoxetine and citalopram due to their antioxidant activities. Bilici et al. (2001) investigated four SSRI drugs (fluoxetine, sertraline, fluvoxamine, and citalopram) administered for 12 weeks in patients with major depression. Antioxidant enzyme activities were restored, and SOD level decreased.[184] In another study, the levels of oxidative stress markers, such as SOD, CAT, and MDA, were compared before and after treatment with 20 mg fluoxetine in fifty patients with major depressive disorder (MDD).[185] Before treatment, all the oxidative stress markers were high, and this was reversed after three months of treatment.[185]

Cumurcu et al. (2009) explored whether 3 different oxidant/antioxidant markers, total antioxidant capacity (TAC), oxidative stress index (OSI), and total oxidant status (TOS), were associated with MDD. They evaluated the effects of three antidepressant drugs on these markers in a group of 57 patients.[186] At baseline, the levels of OSI and TOS were higher and TAC was lower in the treatment group than in the control group. After treatment with escitalopram, paroxetine, or sertraline, OSI and TOS were decreased and TAC was increased from the baseline.[186] Another 24-week study investigated the long-term effects of nine antidepressants on oxidative/antioxidant markers in a group of MDD patients.[187] MDA and SOD were high at baseline. After treatment, MDA and SOD levels were significantly decreased. In addition, TAC,

which indicates the oxidative stress observed in the patients, was improved after 24 weeks of treatment with antidepressant drugs.[187]

These studies indicate that antidepressants might have neuroprotective effects through their antioxidant properties. However, there is increasing evidence that contradicts these findings and highlights the possible negative role of antidepressants on cognitive function. In a retrospective cohort study, researchers found an increased risk of dementia associated with many antidepressants, with the highest risk seen among those who used SSRIs and non-SSRIs.[64] The Women's Health Initiative Memory study examined antidepressant use, depression, and the development of cognitive impairment in in a large cohort of postmenopausal women.[65] They found that SSRIs and TCAs were associated with an increased risk of developing mild cognitive impairment.[65] A number of studies have demonstrated that TCAs negatively affect cognitive function compared to placebo or SSRIs.[188,189] Previous studies have found that dose, time of administration, and plasma concentration of the drug are factors that determine the level of cognitive decline in patients using TCAs.[189-192]

It has been suggested that the anticholinergic properties of TCAs may affect the long-term memory because these drugs block acetylcholine-receptors in the hippocampus.[192,193] Additionally, one study showed that the adverse anticholinergic effect was associated with a deterioration in neurocognitive function over time.[194] Furthermore, short-term use of paroxetine (an SSRI drug) was associated with a decline in cognitive function.[195,196] This decline in cognitive function may be due to its anticholinergic properties.[195] Furthermore, one study found that administration of SSRI is associated with upregulation of GPR39 Zn2+-sensing receptor

protein.[197] A possible link between SSRI use and cognitive impairment is through low or high zinc which may cause neurofibrillary tangles, a known marker for cognitive impairment and Alzheimer disease.[198,199]

Considering these conflicting results regarding the effects of antidepressants on the risk for developing cognitive impairment, there is a need for research investigating the effects of these drugs on cognitive impairment among older adults with breast cancer.

Chapter Three | Methods

3.1 Data Source and Aims

This was a retrospective cohort study that used the SEER-Medicare database (January 1, 2006 and December 31, 2014). The SEER program is a cancer registry covering 28% of cancer patients in the United States.[200] The SEER program includes clinical data (e.g., cancer type, stage, grade, tumor size, diagnosis date, and comorbidities), demographic information, and cause of death. Ninety-three percent of cancer patients who were 65 years or older were matched with their Medicare claims records. The Medicare records provide insurance claims data from the date of enrollment until death. These include hospital claims (Part A), outpatient claims (Part B), and pharmacy claims (Part D). The database was used to address the following aims.

<u>Aim 1:</u> To assess the impact of preexisting cognitive impairment on survival and chronic medication adherence among older adults with breast cancer.

<u>Aim 2:</u> To assess the association between chemotherapy and the risk for cognitive impairment among older adults with breast cancer.

<u>Aim 3:</u> To assess the association between antidepressants and the risk for cognitive impairment in breast cancer patients.

Study Population

We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT), and Health Care Financing Administration Revenue Center (HCPCS) codes from Medicare inpatient, outpatient, and pharmacy claims data to apply the following inclusion and exclusion criteria and define the covariates.

Inclusion criteria

Patients were eligible for the study if they met the following criteria:

1. They were diagnosed with breast cancer (ICD-9-CM 174) and started reporting to the SEER program.
2. The breast cancer diagnosis date was available in the SEER data.
3. The breast cancer stage was available in the SEER data.
4. Breast cancer was the primary tumor diagnosis.
5. Patients were continuously enrolled in Medicare fee-for-service Parts A and B.

Exclusion criteria

1. Patients who were enrolled in Health Maintenance Organization (HMO) plans, because the payments for HMO plans are not tied to healthcare services.
2. Patients who had the same date for breast cancer diagnosis and death.

Inclusion criteria specific to aim 1

1. Female patients' ≥ 67 years of age at the first breast cancer diagnosis. We included patients who were at least 67 years old to ensure an adequate period to identify cognitive impairment.
2. For the diseased group: Patients were diagnosed with cognitive impairment before cancer diagnosis coded as dementia (ICD-9-CM 290.0-290.43, 291.2, 291.82, 294.10, 294.11, 294.20, 294.21, 33.1, 331.19, and 331.82), mild cognitive impairment (ICD-9-CM 331.83), and Alzheimer disease (331.0).[104,201]
3. Pre-index eligibility: Patients were continuously enrolled in Medicare for at least 24 months before the breast cancer diagnosis date to ensure an adequate period to capture the cognitive impairment diagnosis. They had at least 12 months of data prior to the cognitive impairment diagnosis date to define the confounding factors. We used the 12 months prior to the index date to define the preexisting confounding factors and chronic medication adherence rate.
4. Post-index eligibility: Patients were enrolled in Medicare for at least one month after the diagnosis for sub-aim 1.1 and at least 18 months for sub-aim 1.2.
5. For sub-aim 1.2, patients were included if they had at least two pharmacy claims for chronic medications 12 months prior to and post index-date (**Appendix A**).[111] We required at least 18 months of follow-up to estimate the adherence to chronic medications. We used a six-month washout period after the date of the initial diagnosis to control for adherence during potential surgery periods and during the initiation of chemotherapy.

Inclusion criteria specific to aim 2

1. Female patients' ≥ 67 years of age at the first breast cancer diagnosis.
2. Pre-index eligibility: Patients were continuously enrolled in Medicare for at least 24 months before the date of breast cancer diagnosis to ensure an adequate period to exclude patients with a cognitive impairment diagnosis. The 12-month period prior to the index date was used to define the confounding factors.
3. Patients were included if they received a breast cancer treatment (i.e., surgery, chemotherapy, radiotherapy, and/or hormone therapy). Treatments were identified using ICD-9-CM, CPT, and HCPCS codes (**Appendix B)**.[202]

Exclusion criteria specific to aim 2

1. Patients with a cognitive impairment diagnosis in the 24 months prior to the breast cancer diagnosis.

Inclusion criteria specific to aim 3

1. Female patients' ≥ 67 years of age at the first breast cancer diagnosis.
2. Pre-index eligibility: Patients were continuously enrolled in Medicare for at least 24 months before the date of breast cancer diagnosis to ensure an adequate period to exclude patients with a cognitive impairment diagnosis. The 12-month period prior to the index date was used to define the confounding factors.
3. For the exposure group, patients were included if they had at least two pharmacy claims for any antidepressants before and after the breast cancer diagnosis date.[203]

Exclusion criteria specific to aim 3

1. Patients with a cognitive impairment diagnosis in the 24 months prior to the breast cancer diagnosis.

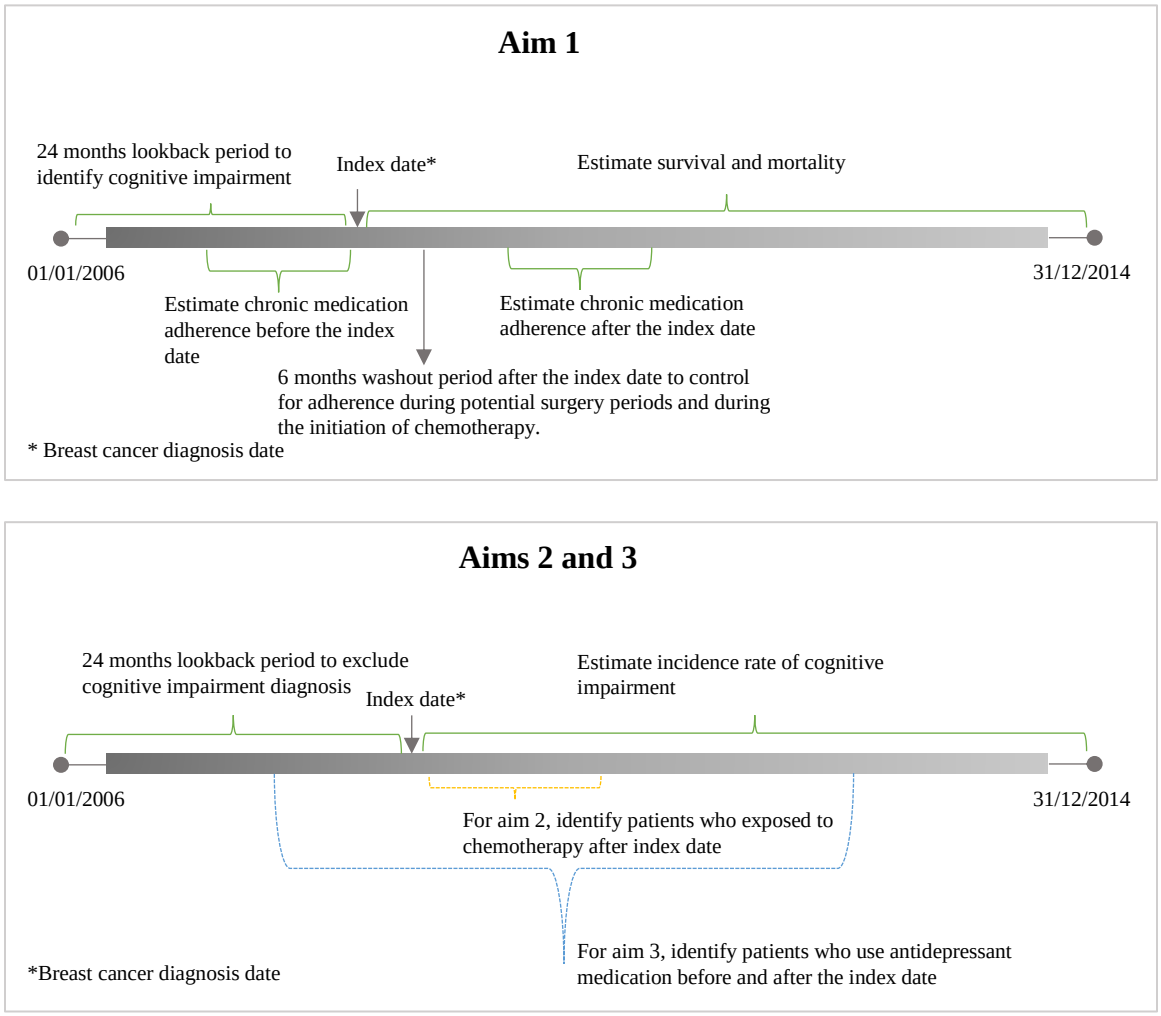

Figure 1. Study Timeline

3.2 Outcome Measures

For sub-aim 1.1, cancer-specific, non-cancer, and all-cause mortality were the primary outcomes of interest. Survival time and mortality were estimated from the date of breast cancer diagnosis until the death date or the censor date of December 31, 2014. For aim 1.2, chronic medication

adherence was assessed using the proportion of days covered (PDC). PDC was estimated as the number of days in the period covered by prescription claims divided by the number of days in the period. The pre- and post-index date PDC for chronic medication were estimated for each patient. Patients were not counted twice if they filled a prescription for any drug in the same class. We used a washout period of six months to control for adherence during surgery and chemotherapy as has been done in a previous study.[111] Adherence was defined as a PDC $\geq$ 0.8. For aims 2 and 3, the incidence of cognitive impairment after breast cancer diagnosis was the primary outcome Cognitive impairment was defined as dementia (ICD-9-CM 290.0-290.43, 291.2, 291.82, 294.10, 294.11, 294.20, 294.21, 33.1, 331.19, and 331.82), mild cognitive impairment (ICD-9 331.83), and Alzheimer disease (331.0).[104,201]

3.3 Covariates

1. Patients' baseline characteristics and comorbidities were obtained from SEER-Medicare as follows:
    1.1. Patients' demographic information and geographical location, including age, ethnicity, marital status, and region (northeast, north central, south, or west).
    1.2. Since socioeconomic status at patient-level is not available in SEER, we used census tract variables to define income, education, and poverty level. The census tract variables are based on where the patient lived at the time of cancer diagnosis.
    1.3. Tumor characteristics, including stage, grade, tumor size, number of positive lymph nodes, and estrogen receptor status, were identified from the SEER data.
    1.4. Charlson Comorbidity Index (CCI) using an application that was developed by the National Cancer Institute based on the approach of Klabunde et al.[204] Comorbidities were identified using specific ICD-9-CM codes from claims that were submitted for

hospital, outpatient care, or physician treatment within a one-year period before the breast cancer diagnosis. However, comorbidities were restricted to codes that appeared on two physician and/or outpatient claims that were made >30 days apart.

1.5. The number of chronic medications (i.e., cardiovascular and diabetes drugs) was added as a confounding factor (aim 1).

1.6. Depression was considered as an independent confounding factor, because of its association with cognitive disorders in elderly patients.[47]

1.7. Anxiety, schizophrenia, and bipolar disorder were considered as independent confounding factors because of their association with cognitive disorder and antidepressant use in older adults (aim 3).

2. Breast cancer treatments, including surgery, hormone therapy, radiotherapy, and chemotherapy were identified using ICD-9-CM, CPT, and HCPCS codes in the SEER-Medicare database (**Appendix B)**.

3.4 Matching

Propensity score methods were used to reduce the potential bias of confounding factors that could affect the outcomes of interest. The propensity score first proposed by Rosenbaum and Rubin (1983) was the probability of treatment assignment based on observed baseline covariates. We used a logistic regression model to estimate the propensity score. Further, we used the propensity score matching method to create one-to-one matching, with the nearest neighbor matching without replacement with a caliper width of 0.2.[205] This allowed for a direct comparison of the outcomes of interest between the comparison groups.

For aim 1, we estimated the propensity scores for each patient based on the probability of receiving a cognitive impairment diagnosis (0 = no cognitive impairment, 1 = cognitive impairment). The confounding factors for the propensity scores were patients' demographic variables (i.e., age, sex, ethnicity, socioeconomic status, marital status, region), comorbidities (i.e., CCI). For aim 2, we estimated the propensity scores for each patient based on the probability of receiving chemotherapy (0 = no chemotherapy, 1 = chemotherapy). For aim 3, we estimated the propensity scores for each patient based on the probability of receiving antidepressants (0 = antidepressant, 1 = antidepressant). The confounding factors for the propensity scores were patients' demographic variables (i.e., age, sex, ethnicity, socioeconomic status, marital status, and region), tumor characteristics (i.e., stage, grade, estrogen receptor status, diagnosis year, tumor size, and number of positive lymph nodes), and comorbidities.

3.5 Statistical Analysis

Means and proportions were used to report the patients' baseline characteristics across cohorts, including demographic information (i.e., age, sex, ethnicity, marital status, education, income, and region), comorbidities (i.e., CCI), tumor characteristics (i.e., stage, grade, estrogen receptor status, diagnosis year, tumor size, and number of positive lymph nodes), relevant treatments, and number of chronic medications (for aim 1). Baseline characteristics were compared across cohorts using t tests for continuous variables and chi-square tests for categorical variables.

For aim 1.1, a survival curve of patients with or without cognitive impairment was generated using the Kaplan-Meier method. Cox proportional hazard models were used to test the effect of

the pre-existing cognitive impairment on overall mortality and cancer-specific mortality. The models were adjusted for tumor characteristics (i.e., stage, grade, estrogen receptor status, diagnosis year, tumor size, and number of positive lymph nodes), cancer treatments, number of chronic medications, depression diagnosis, and unbalanced covariates.

For sub aim 1.2, we compared adherence (PDC $\geq$ 80%) to chronic medication overall, pre- and post-index date, and with or without using a difference-in-differences approach. To this end, we used a generalized linear model with log link and binomial distribution. To examine whether cognitive impairment is a mediator of the relationship between medication adherence and non-cancer mortality, we followed the method described by Baron et al.[206] Here, we conducted a series of logistic regression and Cox proportional hazard analyses (Figure 2). The primary outcome was non-cancer mortality, calculated as the time from the initial breast cancer diagnosis to death from non-cancer causes. The first model tested whether cognitive impairment was a predictor of adherence. The second model tested whether medication adherence might be a predictor of non-cancer mortality. The third model tested whether cognitive impairment was a predictor of non-cancer mortality. The fourth model included both cognitive impairment and medication adherence as predictors of non-cancer mortality. Each regression model was adjusted for tumor characteristics, cancer treatments, number of chronic medications, depression diagnosis, and unbalanced covariates from the propensity score methods mentioned above. To conclude, if the mediator effect is present, the following conditions must be met: a) the first, second, and third models must be significant, and b) in the fourth model, the p-value of the coefficient associated with the cognitive impairment model must be non-significant compared to the p-value in the third model. We also examined if adherence moderated the relationship

between cognitive impairment and non-cancer mortality using an interaction term in the Cox model.

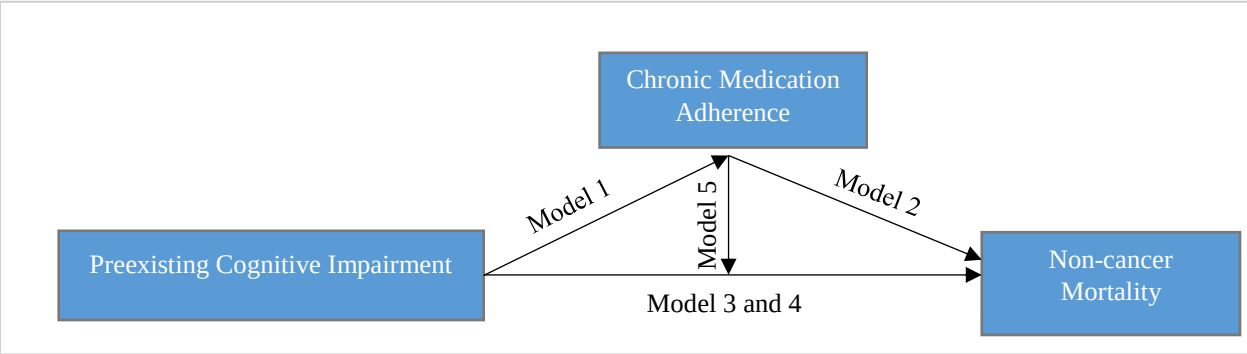

Figure 2. Mediation and Moderation Models Predicting Non-Cancer Mortality.
Model 1: Test of whether cognitive impairment is a predictor of medication adherence.
Model 2: Test of whether medication adherence is a predictor of non-cancer mortality.
Model 3: Test of whether cognitive impairment is a predictor of non-cancer mortality.
Model 4: Test of whether cognitive impairment and medication adherence together are predictors of non-cancer mortality.
Model 5: Test whether medication adherence moderate the relationship between cognitive impairment and mortality.

For aim 2, curves for the incidences of cognitive impairment were created using the Kaplan-Meier method, and Cox proportional hazard models were also created to test the association of chemotherapy with the development of cognitive impairment. These models were adjusted for unbalanced baseline covariates, depression, and other cancer treatments (surgery, hormone therapy, radiation therapy, and targeted therapy). The primary analysis estimated the incidence of cognitive impairment after one year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy, which can take up to a year.

For aim 3, curves for the incidences of cognitive impairment were created using the Kaplan-Meier method stratified by antidepressant use and depression diagnosis. To test the association between antidepressant use and the development of cognitive impairment, we adjusted for age as well as depression, anxiety, schizophrenia, and bipolar disorder diagnosis. These conditions were

included as independent confounding factors to adjust for confounding by indication bias. These conditions are associated with cognitive disorders and antidepressant use among older adult patients. We also examined the interaction between antidepressants, depression, and anxiety. In this analysis, we compared the risk of developing cognitive impairment between patients who had or did not have a diagnosis of depression or anxiety by their antidepressant use. In a separate analysis, we also examined if there was an interaction between chemotherapy and hormone therapy and antidepressants. This was done because there is some evidence that the use of chemotherapy and hormone therapy might increase the risk for a cognitive impairment diagnosis after a breast cancer diagnosis.

3.6 Sample Size Feasibility

Observational studies using SEER-Medicare for studying high prevalence diseases usually yield a large sample size. The statistical analyses conducted using such a database usually have sufficient analytical power. We performed a feasibility assessment of the sample size prior to accessing the SEER-Medicare database. We used previously published studies that utilized SEER-Medicare that have similar inclusion and exclusion criteria to get a rough estimate of the expected sample size for the diseased and exposure group for each aim (Figure 3).[17,105,207] We used the proportion of the population included in the original cohort in these studies (after applying the inclusion and exclusion criteria) and applied it to the total number of breast cancer cases between 2006 and 2013. The estimated sample sizes for each aim were large enough to perform the proposed statistical analyses (Table 1).

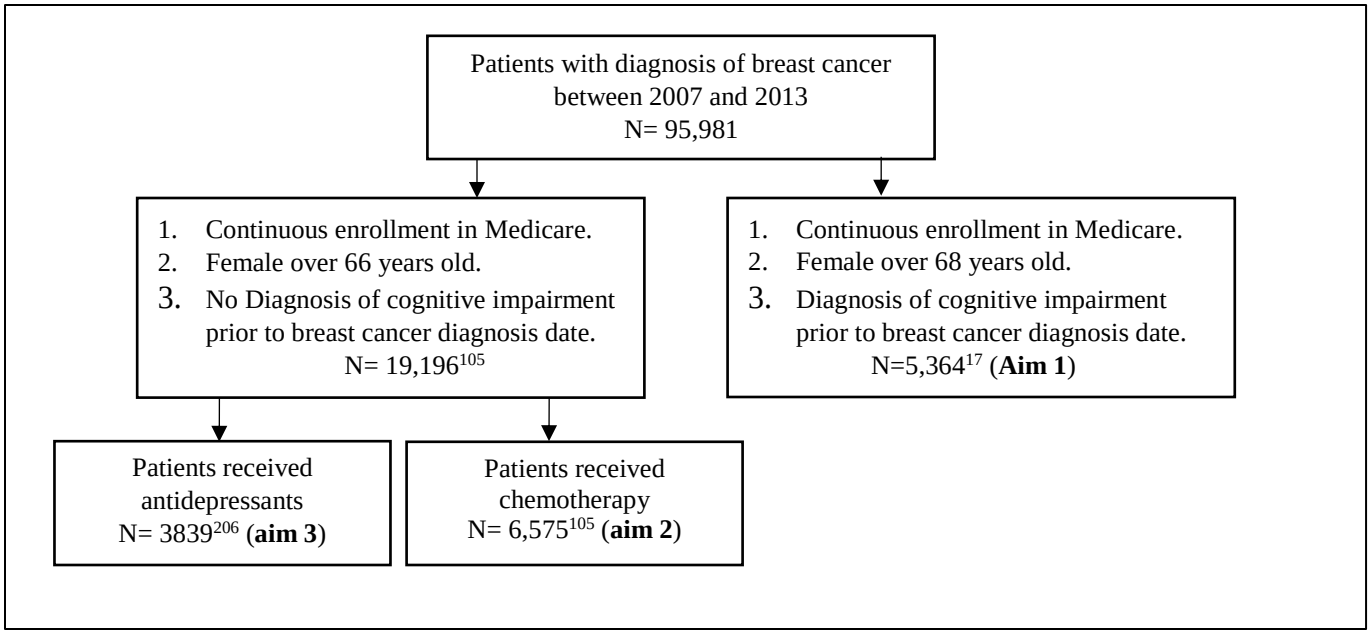

Figure 3. Sample Size Feasibility

Table 1. Summary of outcome variable, measures, and statistical analysis by aim

Aim	**Outcome variables**	**Measures**	**Statistical analysis**
Aim 1	Binary variable: Mortality (1 vs 0)	The incidence of cancer specific, non-cancer, and all-cause mortality were estimated for breast cancer patients who have been diagnosed with cognitive impairment compared to those without cognitive impairment diagnosis.	Descriptive analysis was performed to examine proportion of patients with or without preexisting cognitive impairment before breast cancer diagnosis across baseline characteristics. The Kaplan-Meier method was used to generate the survival curves for breast cancer patients with or without cognitive impairment. A Cox proportional hazard model was used to estimate the risk of mortality in breast cancer patients with or without cognitive impairment, controlling for confounding factors.
	Binary variable: Adherence defined as Proportion of days covered (PDC) ≥ 0.8 (1 vs 0)	PDC and adherence were estimated for breast cancer patients with or without cognitive impairment.	Descriptive analysis was performed to examine the proportion of adherence to chronic medication pre and post cancer diagnosis. A series of logistic regression and Cox proportional hazard moles were

			used to examine the association between cognitive impairment, chronic medication adherence and non-cancer mortality, controlling for confounding factors.
Aim 2	Binary variable: Cognitive impairment (1 vs 0)	The incidence of cognitive impairment after breast cancer diagnosis was compared between patients who received and did not receive chemotherapy.	Descriptive analysis was performed to examine proportion of patients who received or did not receive chemotherapy across baseline characteristics. Cox proportional hazard model was used to examine the likelihood of cognitive impairment between the two groups, controlling for confounding factors.
Aim 3	Binary variable: Cognitive impairment (1 vs 0)	The incidence of cognitive after breast cancer diagnosis was compared between patients who used and did not use antidepressant.	Descriptive analysis was performed to examine proportion of patients Who used or did not use antidepressants across baseline characteristics. Cox proportional hazard model was used to examine the risk of cognitive impairment between the two groups, controlling for confounding factors.

Chapter Four | Results

4.1 Aim 1

Abstract

Objective: The purpose of this study was to examine the impact of preexisting cognitive impairments on survival and medication adherence, and whether chronic medication adherence mediates or moderates the association between cognitive impairments and mortality in patients with breast cancer.

Methods: This retrospective cohort study of female patients aged 67 years or older diagnosed with breast cancer was performed using the SEER- (Surveillance, Epidemiology, and End Results) Medicare Linked Database of the National Cancer Institute. We examined the risk of mortality from cancer and non-cancer causes in patients with and without a history of cognitive impairment. In addition, we examined if chronic medication adherence rates differ between these groups of patients and if medication adherence mediates or moderates the association between cognitive impairments and non-cancer mortality. Difference-in-differences, logistic, and Cox proportional hazards regression models were used to adjust for confounding factors.

Results: Around 8.38% of eligible patients had a history of cognitive impairment prior to breast cancer diagnosis.

Mortality from cancer-specific and non-cancer causes as well as all-cause mortality was markedly higher in patients with cognitive impairments compared to those without cognitive impairment. Both groups showed low adherence levels to chronic medication before and after the breast cancer diagnosis, but the differences between the groups were not significant. Further analysis did not show that medication adherence mediates or moderates the relationship between cognitive impairment and non-cancer mortality.

Conclusion: The results of this study indicate that female patients aged 67 and older with cognitive impairments and a breast cancer diagnosis have a heightened risk of cancer-specific and non-cancer mortality. Our findings do not indicate that adherence plays a role in the association between a history of cognitive impairment and mortality. In order to fully understand which factors associated with cognitive impairment may impact cancer survival, further investigation is necessary**.**

Introduction

The incidence of cancer and cognitive impairment has been shown to increase with age. The pervasiveness of cognitive impairment among people aged 65 or older with breast cancer ranges from 11% to 35%.[1-4] There are approximately 5.5 million people in this age group who are diagnosed with Alzheimer's disease. Of these, 3.4 million are women.[5] This number will further increase in the near future, as the size of the older population (65 years and older) in the US continues to increase. It has been estimated that the number of people aged 65 and older will increase from 53 million in 2018 to 88 million by 2050.[6,7] When one considers that cognitive impairment and cancer are both more frequent in older adults, it becomes obvious that a significant overlap between these conditions will occur.

Evidence suggests that the decline of cognitive functions might interfere with the diagnosis and treatment of cancer in elderly patients. One study investigated 50,460 cases of breast cancer and showed that a history of dementia was linked to an advanced stage of cancer at the time of the primary diagnosis.[8] Another study reported that patients with dementia were less likely to undergo an invasive procedure (i.e., a biopsy) for the diagnosis of cancer, and more likely to show late unstaged cancer.[9] This might explain the increase in mortality from cancer-specific causes, but not that from non-cancer causes, as one study pointed out.[10]

This could be because older adults with breast cancer typically have multiple chronic conditions. Two studies that used SEER (Surveillance, Epidemiology, and End Results-Medicare) data came to similar conclusions. They found that 24% of patients with breast cancer also had comorbid conditions. They further noticed that among patients over the age of 65, 9.8% had two or more

comorbid conditions.[11,12] For instance, according to the Center Of Disease Control and Prevention (CDC), about 14% of patients with breast cancer also suffer from diabetes, which is above the national average of 9.3%. Another factor corroborating the multi-condition conclusion is the fact that approximately 40% of older patients with breast cancer have hypertension, and their overall hypertension risk is 1.48 times higher than that of non-cancer patients.[13] Moreover, around 6.9% of older patients with cancer have congestive heart failure, 2.7% have peripheral vascular disease, and 1% have a history of myocardial infarction.[14] The number of comorbidities at the time of an early-stage breast cancer diagnosis has been shown to be highly associated with non-cancer mortality, compared to advanced-stage breast cancer without comorbidities.[15-18]

As a consequence, and given the high breast cancer survival rate, management of comorbid conditions (e.g., diabetes, hypertension) is important for overall breast cancer survival, especially in the elderly with cognitive impairments.[19] Although the evidence is limited, the literature suggests that cognitive impairments might be associated with medication nonadherence.[20 21] A decline in cognitive functions can be an important predictor of medication nonadherence in elderly patients with breast cancer. Cognitive impairments will decrease the patient's ability to plan, organize, and carry out medication-taking behavior.[21-24] Medication nonadherence plays a potentially significant role in non-cancer mortality. Medication nonadherence is a major issue in older populations, and an even greater concern in patients with breast cancer diagnosed with cognitive impairment.

Health care decisions related to cognitive impairment in patients with breast cancer require a deeper understanding of risks that are uniquely important for this population. The literature

regarding the effects of cognitive impairment on survival and medication adherence is limited, which is why there is a need for real-world research that will help guide treatment of these patients. The main objectives of the current study were: 1) to compare cancer-specific, non-cancer, and all-cause mortality among patients with breast cancer with and without cognitive impairment; 2) to examine if chronic medication adherence differs before and after cancer diagnosis in patients with and without cognitive impairment; 3) to examine if chronic medication adherence mediates or moderates the association between cognitive impairments and non-cancer mortality.

Methods

Data sources and study population

The National Cancer Institute's SEER program is a population-based cancer registry covering 28% of the US population.[25] This program collects cancer incidence information from 18 SEER areas. Information collected by the SEER program includes cancer-specific variables (e.g., type of cancer, month and year of diagnosis, stage, grade, cancer treatment) as well as patient-specific variables (age, sex, insurance, cause of death).

For 97% of elderly patients with cancer aged 65 or older, Medicare is the primary healthcare insurance. This insurance program collects information on all healthcare services provided to Medicare beneficiaries. The information is classified into three different segments: hospital (Part A), physician (Part B), and drug (Part D) plans.

Female patients were included in the study if: 1) they were diagnosed with primary breast cancer between January 1, 2008, and December 31, 2013; 2) they showed no previous history of cancer in their SEER records. Patients who were included in this study had to be enrolled in the Medicare Part A and Part B benefit programs for 24 months before their breast cancer diagnosis and for at least 12 month after the diagnosis date and had to be 67 years of age or older at the time of the initial diagnosis. The age of 67 was selected instead of 65 to allow for the adequate identification of patients with a preexisting cognitive impairment diagnosis and defined comorbidities. Patients were excluded from the study if: 1) they were enrolled in HMO (Health Maintenance Organization) plans, because HMO plan payments are not tied to healthcare services; 2) they were missing diagnosis and cancer stage data, were diagnosed at autopsy, or had the same date for breast cancer diagnosis and death; 3) they had no records of receiving breast cancer treatment. In order to investigate the association between cognitive impairment and chronic medication adherence, patients had to have been enrolled in the Medicare Part D program for at least 12 months prior and 18 months after their breast cancer diagnosis date. We used a 6-month washout period after the date of the initial diagnosis to control for adherence during potential periods of surgery and chemotherapy initiation.

Cohort selection and matching

Patients were considered to be cognitively impaired if, before their breast cancer diagnosis date (index date), they had one claim of the following ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes in any Medicare file: dementia (ICD-9-CM 290.0-290.43, 291.2, 291.82, 294.10, 294.11, 294.20, 294.21, 33.1, 331.19, 331.82), mild cognitive impairment (ICD-9-CM 331.83), or Alzheimer's disease (331.0). To minimize the

possibility for selection bias, we took the following precautionary measures: 1) we estimated the propensity of receiving a cognitive impairment diagnosis for all patients; 2) we matched patients with a cognitive impairment diagnosis with those who had the same or similar propensity but did not have a cognitive impairment diagnosis. We implemented a nearest neighbor matching method to yield one-to-one matching without replacement with a caliper width of 0.2. We estimated the propensity score using a logistic regression model on the patients' demographic variables (i.e., age at breast cancer diagnosis, sex, ethnicity, socioeconomic status, marital status, region), census tract variables (e.g., median income, poverty level, and high school education level), and Charlson comorbidities index variables, as well as on their hypertension, hyperlipidemia, and depression data. Comorbidities included were ascertained from Medicare claims 1 year before the initial breast cancer diagnosis.

Measures

We estimated overall survival rates, as well as cancer-specific, non-cancer, and all-cause mortality rates, based on the period between breast cancer diagnosis and death or censor date of December 31, 2014. Chronic medication (i.e., cardiovascular and diabetes medications) adherence was assessed for patients with two prescription records pre- and post-cancer diagnosis date (Appendix A). In order to estimate adherence, we used the proportion of days covered (PDC) method: the number of days in the period covered by prescription claims was divided by the total number of days in the period. For each patient, pre- and post-cancer diagnosis date PDC was estimated separately. Furthermore, patients with several prescriptions for any drug in the same class were not counted twice. As had been done in another study, to control for adherence during the surgery and chemotherapy periods, we used a washout period of 6 months.[26] Overall

adherence was estimated as the average PDC for all drugs, and adherence was defined as a PDC ≥ 0.8 Further, we examined the impact of changing the definition of adherence to either PDC ≥ 0.9 or ≥ 0.7

Statistical analyses

We used means and proportions to report baseline characteristics for patients across cohorts. This included: 1) demographic information (i.e., age, gender, ethnicity, marital status, education, income, and region); 2) comorbidities; 3) tumor characteristics (i.e., tumor size, stage, grade, estrogen receptor status, diagnosis year, number of positive lymph nodes); 4) relevant cancer treatments; 5) number of chronic medications. Baseline characteristics were compared across cohorts using t tests for continuous variables and chi-square tests for categorical variables.

Survival rates of patients who did or did not have cognitive impairments were generated using the Kaplan-Meier method. To test the associations between preexisting cognitive impairments and cancer-specific, non-cancer, and all-cause mortality, we used the Cox proportional hazard method. The model was appropriately adjusted for: 1) tumor characteristics (i.e., tumor size, stage, grade, estrogen receptor status, diagnosis year, number of positive lymph nodes); 2) cancer treatments; 3) number of chronic medications; 4) depression diagnosis; and 5) unbalanced covariates from the propensity score methods mentioned above.

We compared adherence (PDC ≥ 0.8) to chronic medication overall, pre- and post-cancer diagnosis date, among patients with and without cognitive impairment using a difference-in-differences approach. To this end, we used a generalized linear model with log link and binomial

distribution. In order to determine whether post-index date chronic medication adherence is a mediator of the relationship between cognitive impairments and non-cancer mortality, we used the method described by Baron et al.[27] Here, we conducted a series of logistic regression and Cox proportional hazard analyses (Figure 7). The primary outcome was non-cancer mortality, calculated as the time from the initial breast cancer diagnosis to death from non-cancer causes. The first model tested whether cognitive impairment is a predictor of adherence. The second model tested whether medication adherence might be a predictor of non-cancer mortality. The third model tested whether cognitive impairment is a predictor of non-cancer mortality. The fourth model included both cognitive impairment and medication adherence as predictors of non-cancer mortality. Each regression model was adjusted for tumor characteristics, cancer treatments, number of chronic medications, depression diagnosis, and unbalanced covariates from the propensity score methods mentioned above. To conclude, if the mediator effect is present, the following condition must be met: a) the first, second, and third models must be significant, and b) in the fourth, the p-value of the coefficient associated with the cognitive impairment model must be non-significant compared to the p-value in the third model. We also examined if adherence moderates the relationship between cognitive impairment and non-cancer mortality using an interaction term in the Cox model.

Results

Figure 4 shows the sample flow diagram of the 67,565 female patients aged 67 years and older who were eligible for the study. The prevalence of a preexisting diagnosis of cognitive impairment was 8.38% for all patients. A total of 5,542 females with cognitive impairment were matched with 5,542 females without cognitive impairment, for a total sample size of 11,084.

Table 2 shows the distribution of baseline characteristics among patients with breast cancer according to their cognitive impairment status, and the comparisons for the one-to-one matched cohort based on propensity scores of receiving a cognitive impairment diagnosis. All differences in the prevalence of cognitive impairment according to baseline characteristics were significant at a p-value < 0.05. Nevertheless, in the matched cohort, only age shows significant differences between the two groups.

Table 3 shows breast cancer characteristics of the cohort matched according to the cognitive impairment diagnosis. Patients with a preexisting diagnosis of cognitive impairment were less likely to be diagnosed with early stages of cancer. For instance, 31.83% of the patients with breast cancer with cognitive impairment were diagnosed at stage 1, compared with 38.94% of those without cognitive impairment. Furthermore, 39.91 % of patients with breast cancer with cognitive impairment were diagnosed with a tumor size of less than 2 cm, compared with 48.05% of those without cognitive impairment. Patients with a preexisting diagnosis of cognitive impairment were significantly less likely to receive cancer treatment than those without a history of cognitive impairment. For example, only 42.37%, 23.33%, 7.89%, 37.50%, and 3.37% of the patients with cognitive impairment compared to 49.60%, 34.75%, 12.29%, 41.68%, and 4.11% of those without cognitive impairment received conservative surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy, respectively.

Figure 5 shows the Kaplan-Meier survival curves for patients with breast cancer stratified by their preexisting cognitive impairment diagnosis. Around 22.12% of patients with cognitive impairments compared to 17.95% of those without such a diagnosis died within the first year

after their breast cancer diagnosis. Table 4 shows unadjusted and adjusted Cox model analyses, adjusted for breast cancer characteristics and treatment, examining the association between a cognitive impairment diagnosis and cancer-specific, non-cancer, and all-cause mortality. Model 1 shows the unadjusted and model 2 the adjusted estimate of the hazard ratio. Both models show that a preexisting cognitive impairment diagnosis was significantly associated with increased risk of cancer-specific, non-cancer, and all-cause mortality. For instance, cognitive impairment was associated with a high risk of cancer-specific mortality (hazard ratio (HR) 1.13, 95% CI 1.04-1.23), non-cancer mortality (HR 1.16, 95% CI 1.11-1.21), and all-cause mortality (HR 1.30, 95% CI 1.23-1.38).

Figure 6 shows the matched 2,430 patients with/without cognitive impairments who received at least two prescriptions of cardiovascular or/and diabetes medications pre- and post-index date. Of those, 2,384 and 548 received cardiovascular and diabetes medications, respectively. The adherence level was noticeably low in both groups. For example, prior to cancer diagnosis, overall medication adherence rates were roughly similar for patients with and without cognitive impairments, at 56.05% and 55.56% (at PDC $\geq$ 0.8), respectively. There was a slight increase in adherence rates after diagnosis for patients with and without cognitive impairments, at 60.25% and 61.23% (at PDC $\geq$ 0.8), respectively. Further, there was a significant difference in adherence levels between pre- and post-index date within the group of patients with cognitive impairments (adjusted relative risk (aRR) 1.08, 95% CI 1.02-1.14) and within the group without impairments (aRR 1.10, 95% CI 1.05-1.16) (Table 4). However, there was no significant difference in adherence levels pre and post-cancer diagnosis date between the two groups (aRR 1.00, 95% CI 0.94-1.05). Furthermore, the two additional sensitivity analyses using a PDC $\geq$ 0.9 and $\geq$ 0.7

showed similar results, with the exception that there was no significant difference between pre- and post-index date adherence for patients with cognitive impairments at a PDC $\geq$ 0.9.

We further explored if overall post-index date adherence mediates the relationship between cognitive impairment and non-cancer mortality (Figure 7). Model 1 explored if a cognitive impairment diagnosis is a predictor of medication adherence. There was no association between cognitive impairment and post-index date adherence (odd ratio 1.06, 95% CI 0.90-1.26). Model 2 explored if adherence was associated with mortality from non-cancer causes (HR 1.10, 95% CI 1.01-1.20). Patients who showed medication nonadherence had a higher risk of mortality from non-cancer causes (HR 1.10, 95% CI 1.01-1.20). In model 3, cognitive impairment was associated with a higher risk of non-cancer mortality (HR 1.22, 95% CI 1.12-1.33). In model 4, we included both cognitive impairment and adherence, and both were strong predictors of an increased risk of non-cancer mortality. In model 5, we examined if adherence moderates the relationship between a cognitive impairment diagnosis and non-cancer mortality, and found that adherence levels do not moderate the relationship between cognitive impairment and mortality.

Discussion

This study examined the impact of cognitive impairment on cancer-specific, non-cancer, and all-cause mortality. We found that a preexisting cognitive impairment diagnosis was associated with lower survival and increased cancer-specific, non-cancer, and all-cause mortality risk. Such a diagnosis was also associated with the increased likelihood of cancer being diagnosed at a late stage, and with patients not receiving cancer treatment.

Similarly, an earlier study found that dementia was associated with late-stage and unstaged cancer diagnoses.[10] Another study reported that patients with dementia were less likely to have an invasive procedure (i.e., a biopsy) to diagnose cancer and more likely to show late unstaged cancer.[9] It has also been reported that physicians are less likely to recommend a mammogram to women with dementia than to women without dementia.[28] This evidence of delaying diagnosis and of less access to treatment might explain the increased risk of mortality in this population. However, one study found that excess mortality is not associated with cancer but rather with non-cancer causes of mortality led us to the hypothesis that medication adherence might play a role in the excess mortality linked to cognitive impairment in patients with a cancer diagnosis.[10] We compared medication adherence pre- and post-cancer and investigated whether medication adherence mediates the association between cognitive impairments and non-cancer mortality. We found that there is a low adherence level to chronic medication in patients with and without cognitive impairments before and after their cancer diagnosis. When comparing the adherence levels (PDC $\geq$ 0.8) for each group, we observed a significant increase in adherence after the breast cancer diagnosis. However, there was no significant difference between patients with and without cognitive impairments regarding adherence before and after their cancer diagnosis. Further analysis showed that while medication adherence is an independent predictor of non-cancer mortality, it does not mediate or moderate the relationship between cognitive impairment and non-cancer mortality.

Similarly, a study that examined the effect of Alzheimer-related disorders on chronic heart disease medication adherence found noticeable but non-significant differences between patients with and without such disorders.[29] In contradiction to our results, one study that examined factors

associated with low adherence to antihypertensive medications of Medicare beneficiaries found that dementia was associated with lower medication adherence compared to those without dementia (aRR 0.73, 95% CI 0.69–0.78).[30] A study that examined chronic medication adherence among women over 18 years covered by private insurance before and after an early-stage breast cancer diagnosis found a decline in chronic medication adherence.[26] Our findings differ from these earlier reports, in part due to the fact that our population consisted of elderly patients who were more likely to have a caregiver or reside in a long-term care facility, as Rattinger and colleagues point out.[29] However, our study did not find a difference in medication adherence between patients with and without cognitive impairments. The two groups show low adherence overall, which may be due to a variety of factors, such as age and/or polypharmacy. Chronic disease management in patients with cognitive impairments is associated with higher rates of hospitalization and higher costs when compared to those who do not have cognitive impairments.[31-33] Therefore, interventions targeting an improvement of adherence, even among elderly patients without cognitive impairments, may help. These interventions might lead to a reduction in non-cancer hospitalizations, especially since we found adherence to chronic medications in this population to be low.

One of the main strengths of this study is that the study population covers a large cohort of Medicare beneficiaries, which leads to high generalizability of our findings with regard to patients above the age of 65. Moreover, the 24 months we took to identify patients with cognitive impairments prior to their breast cancer diagnosis provides a solid diagnosis of cognitive impairment. Selection bias was reduced by basing the matched cohort analyses on the probability of receiving a cognitive impairment diagnosis. The analyses were also adjusted for cancer

treatments in patients without cognitive impairments. Moreover, we only included patients with a primary breast cancer diagnosis to reduce the probability of confounding mortality causes. Lastly, the 6-month washout period was established to adjust for any variation in medication adherence caused by cancer treatment. This study has however also some limitations. First, the data in the SEER-Medicare database might already contain certain biases. These might include underdiagnosis of cognitive impairment and ascertainment biases. However, our approach to define cognitive impairment and mortality in this study has been described and used in previous studies.[10,34] Secondly, the study's range is limited to Medicare beneficiaries over the age of 65 as well as those in SEER areas, which might lead to difficulties in the generalization of the results of the study to younger population.

In conclusion, this study indicates that female patients, aged 67 and older, with cognitive impairments and a breast cancer diagnosis, have a heightened risk of cancer-specific and non-cancer mortality. We explored if medication adherence plays a role in mediating the connection between cognitive impairment and non-cancer mortality. Our findings do not indicate that such a mediation exists. However, we found that medication adherence is a strong independent predictor of mortality. In order to fully understand which factors associated with cognitive impairment may impact cancer survival, further investigation is necessary.

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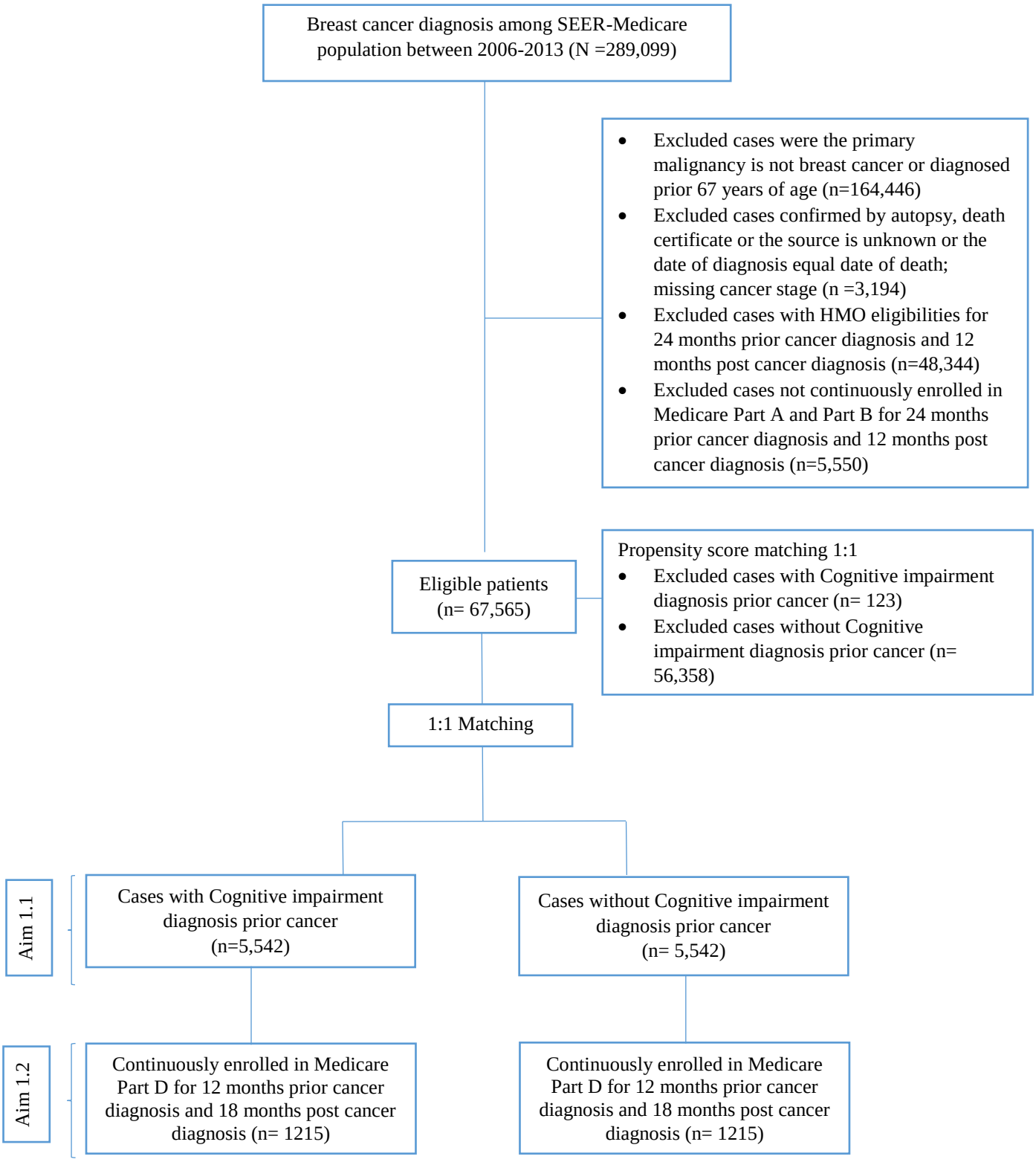


Figure 4. Sample Flow Diagram for Aim 1.

Table 2. Baseline Characteristics of Older Patients with Breast Cancer by Cognitive Impairment Status

	Pre-matched cohort			Matched cohort		
	With Cognitive Impairment (n=5665)	**Without Cognitive Impairment (n=61900)**	**P-value**	**With Cognitive Impairment (n=5542)**	**Without Cognitive Impairment (n=5542)**	**P-value**
Age						
Mean ± SD	82.37 ± 7.23	76.31 ± 6.91	<.0001	82.23 ± 7.20	82.52 ± 7.51	0.0370
Median	83.00	75.00		83.00	83.00	
Ethnicity						
White	4427 (78.15)	51342 (82.94)	<.0001	4341 (78.33)	4327 (78.08)	0.7240
Black	738 (13.03)	4702 (7.60)		706 (12.74)	688 (12.41)	
Hispanic	263 (4.64)	2706 (4.01)		260 (4.69)	281 (5.07)	
Other	237 (4.18)	3150 (5.09)		235 (4.24)	246 (4.44)	
Married status						
single	531 (9.37)	5130 (8.29)	<.0001	521 (9.40)	516 (9.31)	0.9209
Married/domestic partner	1316 (23.23)	26475 (42.77)		1310 (23.64)	1300 (23.46)	
Divorced/window	3393 (59.89)	26945 (43.53)		3297 (59.49)	3293 (59.42)	
Unknown	425 (7.50)	3350 (5.41)		414 (7.47)	433 (7.81)	
Median income						
Mean ± SD	53911.94 ±					
Median	25165.52	56535.31 ± 26304	<.0001	53958.59 ± 25171.04	53836.01 ± 26575.00	0.8031
High school education	49191.50	51262.33		49269.00	48240.50	
Mean ± SD						
Median	27.07±9.48	26.50 ± 9.84	<.0001	27.06±9.51	26.96±9.70	0.6022
Below poverty	27.48	26.63		27.45	27.22	
Mean ± SD						
Median	12.78±10.09	11.67±9.41	<.0001	12.77±10.10	12.90 ±10.40	0.4995
Region	9.82	8.69		9.9.81	9.64	
Midwest	606 (10.70)	6639 (10.73)		587 (10.59)	561 (10.12)	0.7695
Northeast	1282 (22.63)	12782 (20.65)	<.0001	1249 (22.54)	1226 (22.12)	
South	1511 (26.67)	15028 (24.28)		1473 (26.58)	1496 (26.99)	
West	2266 (40.00)	27451 (44.35)		2233 (40.29)	2259 (40.76)	
Medicaid enrollment	3125 (55.16)	51170 (82.67)	<.0001	3118 (56.26)	3142 (56.69)	0.3368

Chronic condition						
Congestive Heart Failure	1104 (19.49)	4007 (6.47)	<.0001	1037 (18.71)	1002 (18.08)	0. 3909
Peripheral Vascular Disease	1280 (22.59)	4320 (6.98)	<.0001	1198 (21.62)	1122 (20.25)	0.0760
Cerebrovascular Disease	1043 (18.41)	2991 (4.83)	<.0001	971 (17.52)	929 (16.76)	0.2898
Chronic Obstructive Pulmonary Disease	1089 (19.38)	7214 (11.65)	<.0001	1057 (19.07)	1000 (18.04)	0.1637
Hypertension	255 (4.50)	1072 (1.73)	<.0001	241 (4.35)	235 (4.24)	0.7786
Hemiplegia or Paraplegia	708 (12.50)	3334 (5.39)	<.0001	677 (6.11)	662 (11.95)	0.6620
Moderate-Severe Renal Disease	4372 (77.18)	37107 (59.95)	<.0001	4257 (76.81)	4214 (76.04)	0.3359
Peptic Ulcer Disease	2629 (46.41)	29573 (47.78)	0.0485	2584 (46.63)	2616 (47.20)	0.5425
Rheumatologic Disease	1795 (31.69)	13807 (22.31)	<.0001	1739 (31.38)	1753 (31.63)	0.7747
Liver disease	90 (0.016)	229 (0.37)	<.0001	85 (1.53)	79 (1.43)	0.6369
Myocardial infarction	91 (0.13)	386 (0.62)	<.0001	84 (1.52)	86 (1.52)	0.8772
Diabetes and diabetes complications	172 (3.04)	1695 (2.74)	0.1904	166 (3.00)	161 (2.91)	0.7790
Aids	NR	NR	0.2341	NR	NR	0.6546
Depression	43 (0.76)	323 (0.52)	0.0199	43 (0.78)	37 (0.67)	0.5008
Hyperlipidemia	1218 (21.50)	3318 (5.36)	<.0001	1110 (20.03)	1015 (18.31)	0.0219

Abbreviation: NR, not reportable (cell sizes less than 11 are not reported per the SEER-Medicare data use agreement)

Table 3. Cancer Characteristics of Older Patients with Breast Cancer by Cognitive Impairment Status

	With Cognitive Impairment	Without Cognitive Impairment	P-value
Year of diagnosis n (%)			
2008	940 (16.96)	969 (17.87)	0.2972
2009	942 (17.00)	1005 (18.13)	
2010	967 (17.45)	936 (16.89)	
2011	933 (16.84)	890 (16.06)	
2012	913 (16.47)	862 (15.55)	
2013	847 (15.28)	880 (15.88)	
Cancer stage n (%)			
I	1764 (31.83)	2158 (38.94)	<.0001
II	1823 (32.89)	1744 (31.47)	
III	701 (12.65)	565 (10.19)	
IV	410 (7.40)	484 (8.73)	
Unknown	844 (15.23)	591 (10.66)	
Grade n (%)			
I	1005 (9.07)	1139 (20.55)	<.0001
II	2024 (36.52)	2240 (40.42)	
III	1589 (28.67)	1422 (25.66)	
IV	32 (0.58)	22 (0.40)	
Unknown	892 (16.10)	719 (12.97)	
Tumor size n (%)			
< 2 cm	2212 (39.91)	2663 (48.05)	<.0001
2-5 cm	2034 (36.70)	1829 (33.00)	
> 5 cm	581 (10.48)	483 (8.72)	
Diffuse/Metastasis	20 (0.36)	27 (0.24)	
Unknown	695 (12.54)	540 (9.74)	
Number of lymph nodes n (%)			
Negative	1755 (31.67)	2271 (40.98)	<.0001
Positive	987 (17.81)	1051 (18.96)	
Unknown	2800 (50.52)	2220 (40.06)	
Estrogen receptor status n (%)			
Negative	3930 (70.91)	4206 (75.89)	<.0001
Positive/Borderline	865 (15.62)	786 (14.19)	
Unknown	747 (13.48)	550 (9.92)	
Progesterone receptor status n (%)			
Negative	3326 (60.01)	3566 (64.35)	<.0001
Borderline	17 (0.31)	21 (0.38)	
Positive	1454 (26.24)	1406 (25.37)	
Unknown	745 (13.44)	549 (9.91)	
Cancer treatments n (%)			
Conservative surgery	2348 (42.37)	2749(49.60)	<.0001
Mastectomy	1936 (34.93))	1973(35.60)	0.4620
Radiation therapy	1293 (23.33)	1926(34.75)	<.0001
Chemotherapy	437(7.89)	681(12.29)	<.0001
Hormone therapy	2078 (37.50)	2310(41.68)	<.0001
Targeted therapy	187(3.37)	228(4.11)	0.0402

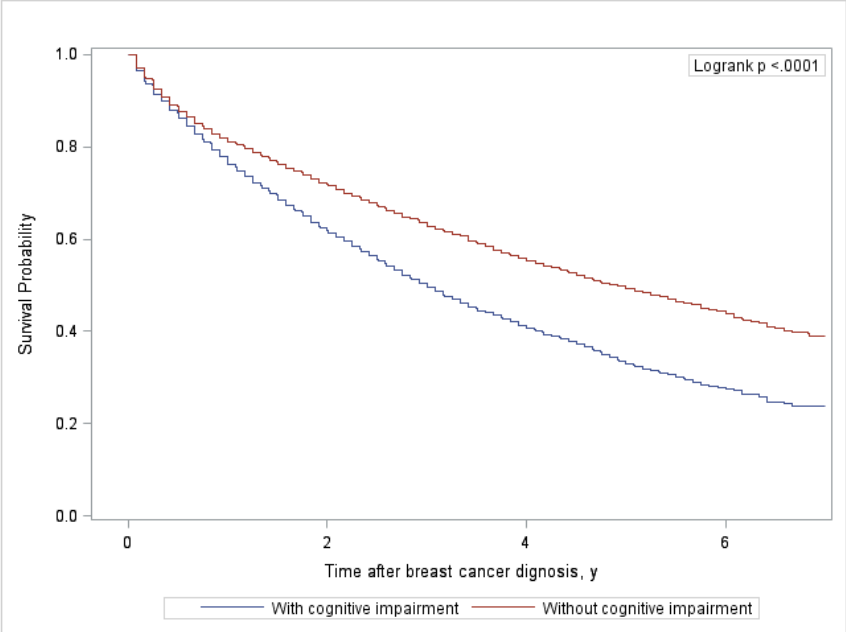


Figure 5. Survival for Breast Cancer Patients by Cognitive Impairment Status.
Kaplan-Meier curve for years survived since breast cancer diagnosis in patients with and without cognitive impairment.

Table 4. Unadjusted and Adjusted Hazard ratios of Cancer-Specific, Non-Cancer, and All-cause Mortality

	HR [a] (95% CI)		
Main Analysis	**Cancer-Specific Mortality**	**Non-Cancer Mortality**	**All-Cause Mortality**
Model 1 [b]	1.33 (1.22-1.44) [d]	1.22 (1.17-1.28) [d]	1.49 (1.41-1.57) [d]
Model 2 [c]	1.13 (1.04-1.23) [d]	1.16 (1.11-1.21) [d]	1.30 (1.23-1.38) [d]

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Reference group was patients without cognitive impairment.

[b] Model 1: unadjusted hazard ratio, [c] Model 2: Adjusted hazard ratio for age, cancer characteristics, and cancer treatment.

[d] P-value < 0.05

	With Cognitive Impairment	Without Cognitive Impairment
Adherence (PDC ≥ 0.8)		
Prior BC overall Medications Adherence	56.05%	55.56%
Post BC overall Medications Adherence	60.25%	61.23%
Prior BC Cardiovascular Medications Adherence	58.38%	58.48%
Post BC Cardiovascular Medications Adherence	61.42%	62.07%
Prior BC Diabetes Medications Adherence	49.81%	49.82%
Post BC Diabetes Medications Adherence	58.56%	56.49%
Adherence (PDC ≥ 0.9) rate		
Prior BC overall Medications Adherence	38.60%	36.38%
Post BC overall Medications Adherence	41.56%	41.65%
Prior BC Cardiovascular Medications Adherence	39.85%	43.61%
Post BC Cardiovascular Medications Adherence	43.05%	39.68%
Prior BC Diabetes Medications Adherence	38.40%	38.25%
Post BC Diabetes Medications Adherence	45.63%	41.40%
Adherence (PDC ≥ 0.7) rate		
Prior BC overall Medications Adherence	70.29%	72.02%
Post BC overall Medications Adherence	76.38%	75.72%
Prior BC Cardiovascular Medications Adherence	71.44%	73.68%
Post BC Cardiovascular Medications Adherence	77.09%	76.19%
Prior BC Diabetes Medications Adherence	61.60%	62.81%
Post BC Diabetes Medications Adherence	69.96%	69.82%

Figure 6 Percent of Adherent to Chronic Medications Adherence Prior and Post Breast Cancer Diagnosis by Cognitive Impairment Status.

Abbreviations: BC, breast cancer; PDC, proportion of days covered. We used a 6-month washout period after the date of the cancer diagnosis to control for adherence during potential periods of surgery and chemotherapy initiation

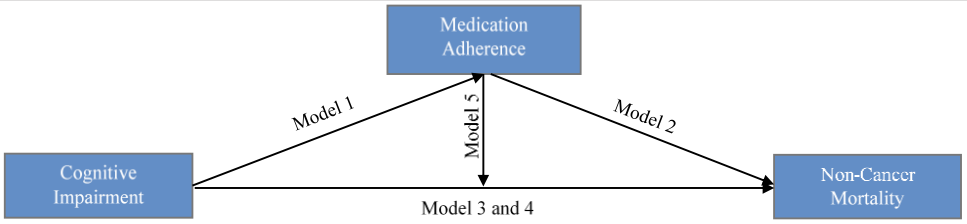
Table 5. Chronic Medications Adherence Prior and Post Breast Cancer Diagnosis by Cognitive Impairment Status

	Prior cancer	Post cancer	aRR [b] (95%CI)	P-value
Adherence [a] (PDC ≥ 0.8) rate n (%)				
Without cognitive impairment	675 (55.56)	744 (61.23)	1.10 (1.05-1.16)	0.0003
With cognitive impairment	681 (56.05)	732 (60.25)	1.08 (1.02-1.14)	0.0145
Without cognitive impairment	675 (55.56)	744 (61.23)	REF	
With cognitive impairment	681 (56.05)	732 (60.25)	1.00 (0.94-1.05)	0.9308
Adherence [a] (PDC ≥ 0.9) rate n (%)				
Without cognitive impairment	442 (36.38)	506 (41.65)	1.14 (1.06--1.24)	0.0010
With cognitive impairment	469 (38.60)	505 (41.56)	1.08 (0.99-1.17)	0.0765
Without cognitive impairment	442 (36.38)	506 (41.65)	REF	
With cognitive impairment	469 (38.60)	505 (41.56)	1.02 (0.94-1.11)	0.6118
Adherence [a] (PDC ≥ 0.7) rate n (%)				
Without cognitive impairment	875 (72.02)	920 (75.72)	1.05 (1.01-1.09)	0.0089
With cognitive impairment	854 (70.29)	928 (76.38)	1.09 (1.04-1.14)	0.0001
Without cognitive impairment	875 (72.02)	920 (75.72)	REF	
With cognitive impairment	854 (70.29)	928 (76.38)	1.00 (0.96-1.04)	0.8539

Abbreviations: PDC, proportion of days covered; aRR, adjusted relative risk.

[a] Medication adherence was measured using PDC in both 1 year prior and 1 year post cancer diagnosis. We used a 6-month washout period after the date of the cancer diagnosis to control for adherence during potential periods of surgery and chemotherapy initiation.

[b] aRR comparing adherence prior and post cancer diagnosis in patients with and without cognitive impairments.



	HR or OR (95%CI)	P-Value
Model 1: Test of whether cognitive impairment is a predictor of medication adherence		
Cognitive impairment	1.06 (0.90-1.26) [b]	0.4792
Model 2: Test of whether medication adherence is a predictor of mortality		
Medication adherence	1.10 (1.01-1.20) [a]	0.0274
Model 3: Test of whether cognitive impairment is a predictor mortality		
Cognitive impairment	1.22 (1.12-1.33) [a]	< 0.0001
Model 4: Test of whether cognitive impairment and medication adherence together are predictors of mortality		
Cognitive impairment	1.22 (1.12-1.33) [a]	< 0.0001
Medication adherence	1.10 (1.01-1.20) [a]	0.0362
Model 5: Test whether medication adherence moderate the relationship between cognitive impairment and mortality		
Adherence vs non-adherence in patients with cognitive impairment	1.06 (1 0.94-1.20) [a]	0.3644
Adherence vs non-adherence in patients without cognitive impairment	1.11 (0.98- 1.25) [a]	0.1702

Figure 7. Mediation and Moderation Models Predicting Non-Cancer Mortality.

Abbreviations: [a] HR, hazard ratio; [b] OR, Odd ratio; CI, confidence interval.
Reference group for cognitive impairment status is patients without cognitive impairment diagnosis.
Medication adherence refer to adherence to cardiovascular or/and diabetes medications after breast cancer diagnosis.
Reference group for Medication adherence status is patients with proportion of days covered more than 0.8.

4.2 Aim 2

Abstract

Objective: This study aimed to evaluate the association between the development of cognitive impairment and exposure to chemotherapy among older patients with breast cancer.

Methods: This retrospective cohort study identified women who were ≥67 years old and had breast cancer between 2008 and 2013 using the National Cancer Institute's Surveillance, Epidemiology, and End Results-Medicare database. Propensity scoring was used to account for pre-treatment confounding factors, and Cox proportional hazards modeling was used to examine the risks of developing cognitive impairment among patients who were or were not exposed to chemotherapy.

Results: The only significant differences in the two groups' post-matching characteristic was age. Chemotherapy was not associated with a statistically significant risk of cognitive impairment (hazard ratio: 0.96, 95% confidence interval: 0.86–1.09). However, patients who received hormone therapy had a 16% higher risk of developing cognitive impairment (hazard ratio: 1.16, 95% confidence interval: 1.04–1.31) compared with patients who did not receive hormone therapy.

Conclusion: These findings suggest that there was no increase in the risk of developing cognitive impairment among older patients with breast cancer after they were exposed to

chemotherapy. However, there appears to be an association between the risk of developing cognitive impairment and the exposure to hormone therapy.

Introduction

Early screening measures and the development of effective chemotherapy and endocrine therapy has led to a substantial improvement in survival among breast cancer patients. Recent statistics indicate that the 5-year survival rate among these patients has increased from 75% during 1975–1977 to 91% during 2004–2010.[1] Therefore, increased attention is being focused on comorbid conditions and side effects of cancer treatment that may adversely affect health outcomes among patients with breast cancer.

Accumulating evidence indicates that breast cancer patients experience a post-treatment decline in cognitive function that is worse than that among the general population.[2-4] Patients commonly refer to this condition as "chemo brain" or "chemo fog", which reflects a chemotherapy-related decline in cognitive function that is experienced by 15–61% of breast cancer survivors each year.[5,6] Researchers have found that this cognitive impairment, which is associated with cancer treatment and specifically chemotherapy, can last for years after treatment completion.[7,8] Other researchers have found that chemotherapy and endocrine therapy, or endocrine therapy alone, are associated with cognitive impairment,[9,10] although most existing research has focused on chemotherapy as the causal factor.[11-13]

Cross-sectional studies have found that breast cancer patients experience cognitive impairment,[14-16] although the absence of pre-treatment cognitive function assessments has limited the inferences that can be drawn from these studies. Thus, an increasing number of longitudinal neuropsychological studies have included pre-treatment and post-treatment assessments of cognitive function. Many studies revealed a quantitative decline in cognitive

function among breast cancer patients who have received chemotherapy relative to disease-free or non-chemotherapy control groups.[3,4,6,7] However, other studies failed to detect associations between cancer treatment and cognitive function.[17-19]

Only a small portion of chemotherapy-related cognitive decline can be attributed to age, education, depression, anxiety, or surgery/anesthesia.[20] In addition, there is no explanation for why breast cancer patients have an elevated risk of cognitive impairment relative to the general population. However, two hypotheses have circulated in the literature. First, the biology of cancer cells may trigger an inflammatory response that releases neurotoxic cytokines and/or poor DNA repair may result in neurodegenerative diseases. Second, exposure to chemotherapy or endocrine therapy may affect cognitive function through various mechanisms.[21-23] For example, adjuvant chemotherapy (e.g., using doxorubicin) may increase the levels of free radicals in the brain, which could damage the brain cells and negatively affect cognitive function.[21,22]

Regardless of the precise underlying mechanism, chemotherapy-related cognitive impairment can seriously and negatively affect health outcomes and quality of life.[24] Therefore, given the mixed results from prior studies, the present study aimed to examine the incidences of cognitive impairment among breast cancer patients who did and did not receive chemotherapy, and to evaluate the potential risk of developing cognitive impairment in this setting.

Methods

Data sources and study population

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program maintains a population-based cancer registry that covers 28% of the American population.[25] This database includes information regarding cancer incidence in 18 SEER areas, as well as information regarding cancer-specific variables (e.g., type of cancer, month and year of diagnosis, stage, grade, cancer treatment) and patient-specific variables (age, sex, insurance, cause of death). Medicare is the primary healthcare insurance for 97% of the population who are ≥65 years old, and the Medicare program collects information regarding all healthcare services provided to beneficiaries under its hospital (Part A), medical (Part B), and drug (Part D) benefits.

Women were included in the present study if they were diagnosed with primary breast cancer between January 1, 2008 and December 31, 2013 and had no previous history of cancer in the SEER records. Furthermore, these patients were required to have been continuously enrolled in Medicare Part A and Part B for 24 months, and Part D for 12 months before their cancer diagnosis, and for at least 12 months after the cancer diagnosis. If patients died in the first year, they had to have had coverage for at least 1 month. This ensured that all patients had comparable coverage and similar access to health services. The age cut-off was defined as ≥67 years at the first diagnosis, rather than 65 years, to adequately exclude patients with a diagnosed history of cognitive impairment. Patients were excluded if: 1) they were enrolled in Health Maintenance Organization (HMO) plans because payments for those plans are not linked to healthcare services; 2) they had missing data regarding their diagnosis date, cancer stage, autopsy diagnosis,

or had the same date for breast cancer diagnosis and death; and 3) they had no record of receiving breast cancer treatment.

Cohort selection and matching

Exposure to chemotherapy was identified using Medicare claims within 12 months after the breast cancer diagnosis based on Healthcare Common Procedure Coding System codes (HCPCS) and Common Procedural Terminology (CPT) (Appendix B). To reduce selection bias based on factors that might have influenced the physician's decision to provide chemotherapy, or the patient's decision to undergo treatment, we estimated the propensity scores for receiving chemotherapy among all patients and then matched patients who did or did not receive chemotherapy according to their propensity scores. The one-to-one matching was performed using the nearest neighbor method without replacement and with a caliper width of 0.2. The propensity score was estimated using a logistic regression model that controlled for the patients' demographic variables (age, sex, ethnicity, socioeconomic status, marital status, and region), tumor characteristics (stage, grade, estrogen receptor status, diagnosis year, tumor size, and number of positive lymph nodes), Charlson comorbidity index variables, and depression status. Depression was included as an independent confounding factor because of its association with cognitive disorders among elderly patients.[12]

Development of cognitive impairment

Cognitive impairment was considered present in cases with at least one claim after the breast cancer diagnosis that involved International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for dementia (ICD-9-CM 290.0–290.43, 291.2, 291.82, 294.10,

294.11, 294.20, 294.21, 33.1, 331.19, 331.82), mild cognitive impairment (ICD-9-CM 331.83), or Alzheimer's disease (ICD-9-CM 331.0). The patients were followed until the first instance of cognitive impairment development, death, or the censoring date (December 31, 2014).

Covariates

The SEER data were searched to obtain the eligible patients' demographics characteristics, including age, sex, ethnicity/race, and marital status. However, because the SEER data do not include patient-level socioeconomic information, we used census tract variables to estimate income, education, and poverty levels based on the patient's area of residence at their cancer diagnosis. Comorbidities were identified to calculate each patient's Charlson comorbidity index using an application that was developed by the National Cancer Institute based on the approach of Klabunde et al.[26] Comorbidities were identified using specific ICD-9-CM codes from claims that were submitted for MEDPAR, outpatient care, or physician treatment within a 1-year period before the breast cancer diagnosis. However, comorbidities were restricted to codes that appeared on two physician and/or outpatient claims that were made >30 days apart. The SEER data were also searched using the ICD-9-CM, CPT, and HCPCS codes to determine the patients' tumor and treatment characteristics, including stage, grade, tumor size, number of positive lymph nodes, estrogen receptor status, surgery, hormone therapy, and radiotherapy (Appendix B).

Statistical analyses

Descriptive statistics were used to report the patients' baseline demographic characteristics (age, sex, ethnicity, marital status, education, income, and region) and comorbidities, as well as their tumor characteristics (stage, grade, estrogen receptor status, diagnosis year, tumor size, number

of positive lymph nodes), and relevant treatment. These characteristics were compared between the groups of patients who did and did not receive chemotherapy using the t test for continuous variables and the chi-square test for categorical variables. Curves for the incidences of cognitive impairment were created using the Kaplan-Meier method, and Cox proportional hazard models were also created to test the association of chemotherapy with the development of cognitive impairment. These models were adjusted for unbalanced baseline covariates, depression, and other cancer treatments (surgery, hormone therapy, radiation therapy, and targeted therapy). The primary analysis estimated the risk of cognitive impairment after 1 year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy (Model 1), which can take up to a year. Further, we categorized chemotherapy regimens into taxane-based and non-taxane-based chemotherapy and estimated the risk of cognitive impairment after 1 year for each regimens (Model 2). A sensitivity analysis was also performed in which we included the incidence of cognitive impairment occurred during the year after the breast cancer diagnosis.

Results

Figure 8 shows the sample flow diagram for the present study, which ultimately included 9,910 women who were ≥67 years old. Table 6 shows the included patients' baseline characteristics according to chemotherapy status and a comparison of the propensity score-matched cohorts. Before the matching, patients who received chemotherapy were more likely to be younger and married, relative to patients who did not receive chemotherapy. A slightly lower percentage of dual Medicare-Medicaid enrollees received chemotherapy. However, the propensity score matching process eliminated most significant inter-group differences, with the exception of age.

Figure 9 shows the Kaplan-Meier curves for the development of cognitive impairment, which failed to reveal a significant difference according to chemotherapy status. Table 7 shows the results of the time-to-event analysis for the development of cognitive impairment after the cancer diagnosis, chemotherapy was not associated with a risk of developing cognitive impairment (hazard ratio [HR]: 0.94, 95% confidence interval [CI]: 0.83–1.07) (Model 1). However, after accounting for cognitive impairment incidence during the year after the breast cancer diagnosis, chemotherapy was associated with a significantly reduced risk of developing cognitive impairment (HR: 0.85, 95%CI: 0.76–0.95).

We also performed subgroup analyses according to whether the patients received taxane-based or non-taxane-based chemotherapy (Model 2). These analyses revealed no significant differences in the risks of developing cognitive impairment relative to the group that did not receive chemotherapy among patients who received taxane-based chemotherapy (HR: 0.88, 95% CI: 0.76–1.02) or among patients who received non-taxane-based chemotherapy (HR: 1.09, 95% CI: 0.90–1.32). In the sensitivity analysis, only taxane-based chemotherapy was associated with a reduction in cognitive impairment relative to the group that did not receive chemotherapy (HR: 0.78, 95% CI: 0.69–0.89). Table 8 shows the results of the time-to-event analyses for mild cognitive impairment, dementia, and Alzheimer's disease, which failed to detect significant differences according to whether the patients did or did not receive chemotherapy.
Relative to patients who did not receive hormone therapy, patients who received hormone therapy had an increased risk of developing cognitive impairment (HR: 1.16, 95% CI: 1.02–1.31) (Table 9). In addition, relative to patients who did not receive hormone therapy, patients who received taxane-based chemotherapy plus hormone therapy had an increased risk of developing

cognitive impairment (HR: 1.28, 95% CI: 1.03–1.58), although similar results were not observed among patients who received non-taxane-based chemotherapy plus hormone therapy (HR: 0.89, 95% CI: 0.63–1.25) or patients who did not receive chemotherapy plus hormone therapy (HR: 1.15, 95% CI: 0.95–1.37). Older age and a history of depression were all associated with increased risks of developing cognitive impairment.

Discussion

The present study failed to detect an increased risk of developing cognitive impairment after exposure to chemotherapy among older women with breast cancer. Two studies that used the SEER-Medicare database (1991–1999) have revealed conflicting findings regarding the same issue, with one indicating that chemotherapy exposure increased the risk of developing cognitive impairment by 20%,[12] while the other revealed no association between chemotherapy exposure and the subsequent diagnosis of cognitive impairment.[27] Another study examined this association among patients with colorectal cancer and revealed that chemotherapy was only associated with drug-induced dementia among patients with no history of mood disorders, although chemotherapy was also associated with decreased risks of Alzheimer's disease and other dementias.[13] The present study adds to the existing data because we had access to information regarding drug treatment (e.g., hormone therapy and some oral chemotherapy agents) through Medicare Part D data, which started being collected in 2007. Thus, we were able to control for hormone therapy, which accumulating evidence indicates is associated with an increased risk of developing cognitive impairment among elderly breast cancer patients.

The present study revealed that hormone therapy was associated with a 16% increase in the risk of developing cognitive impairment after 1 year of breast cancer diagnosis. In this context, the existing evidence indicates that hormone therapy can have an adverse effect on cognition function. For example, among patients who received tamoxifen or raloxifene for breast cancer, hormone therapy was associated with a decline in cognitive function (vs. patients who received a placebo), although the absolute decline was small and the long-term outcomes remain unclear.[28] Another study revealed that, among breast cancer patients who were 55–75 years old, exposure to tamoxifen was associated with greater cognitive difficulties, especially regarding memory function.[29] In addition, long-term tamoxifen treatment appears to be associated with reduced verbal cognitive function.[30] Furthermore, postmenopausal women with early-stage breast cancer who received anastrozole exhibited declines in memory and concentration.[31] However, other studies have reported conflicting data regarding the association of tamoxifen use with cognitive impairment. One recent population-based study of 24,197 patients with breast cancer revealed that long-term tamoxifen use was associated with a reduced risk of cognitive impairment,[32] and another cross-sectional study revealed a lower prevalence of Alzheimer's disease among patients who were exposed to tamoxifen.[33]

The nature of these data may lead to residual selection bias, which could confound these results. For example, breast cancer patients who have cognitive impairment, or who have an increased risk of developing it, are less likely to receive chemotherapy.[34] This may explain the lower incidence of cognitive impairment in the chemotherapy group (vs. the non-chemotherapy group) when we included all cases of cognitive impairment after breast cancer diagnosis. However, when we censored the cases during the first year after the breast cancer diagnosis, the difference

between the two groups diminished. In addition, underdiagnosis of cognitive impairment is common, with one study indicating that physicians did not diagnose cognitive impairment in >40% of their patients[35] and another study indicating that >50% of patients with dementia did not complete an appropriate cognitive function evaluation.[36] Thus, the failure to detect cognitive impairment may limit the usefulness of administrative databases for evaluating the association between chemotherapy and cognitive impairment. All of the retrospective studies, including this study, have used ICD-9 for dementia, Alzheimer's disease, and mild cognitive impairment to identify chemotherapy-related cognitive impairment.[12,27] However, it may not be an accurate measure to identify early stages of cognitive impairment associated with chemotherapy as identified in previous clinical studies.[6,37-41] Other non-cancer-related factors can affect the use of chemotherapy among elderly patients, such as race, age, and comorbidities.[42,43] Thus, the present study may have been prone to selection bias, although we took two steps to address this issue. First, we excluded patients with a history of cognitive impairment before the breast cancer diagnosis. Second, we used propensity score matching to balance the baseline characteristics of the chemotherapy and non-chemotherapy groups. Nevertheless, it was not possible to control for all possible confounders, although we did adjust the multivariable analysis for imbalanced characteristic (age) and depression, which is associated with cognitive impairment.

In conclusion, the present study failed to detect a significant relationship between chemotherapy exposure and subsequent cognitive impairment among older women with breast cancer. However, we did find that exposure to hormone therapy was associated with the development of cognitive impairment within the first year after the breast cancer diagnosis. Nevertheless, these findings should be interpreted with caution, given the conflicting results regarding exposure to

chemotherapy and hormone therapy in the literature. Further well-designed longitudinal studies with appropriate neurocognitive testing are needed, especially if chemotherapy or hormone therapy is associated with acute or subtle cognitive impairment.

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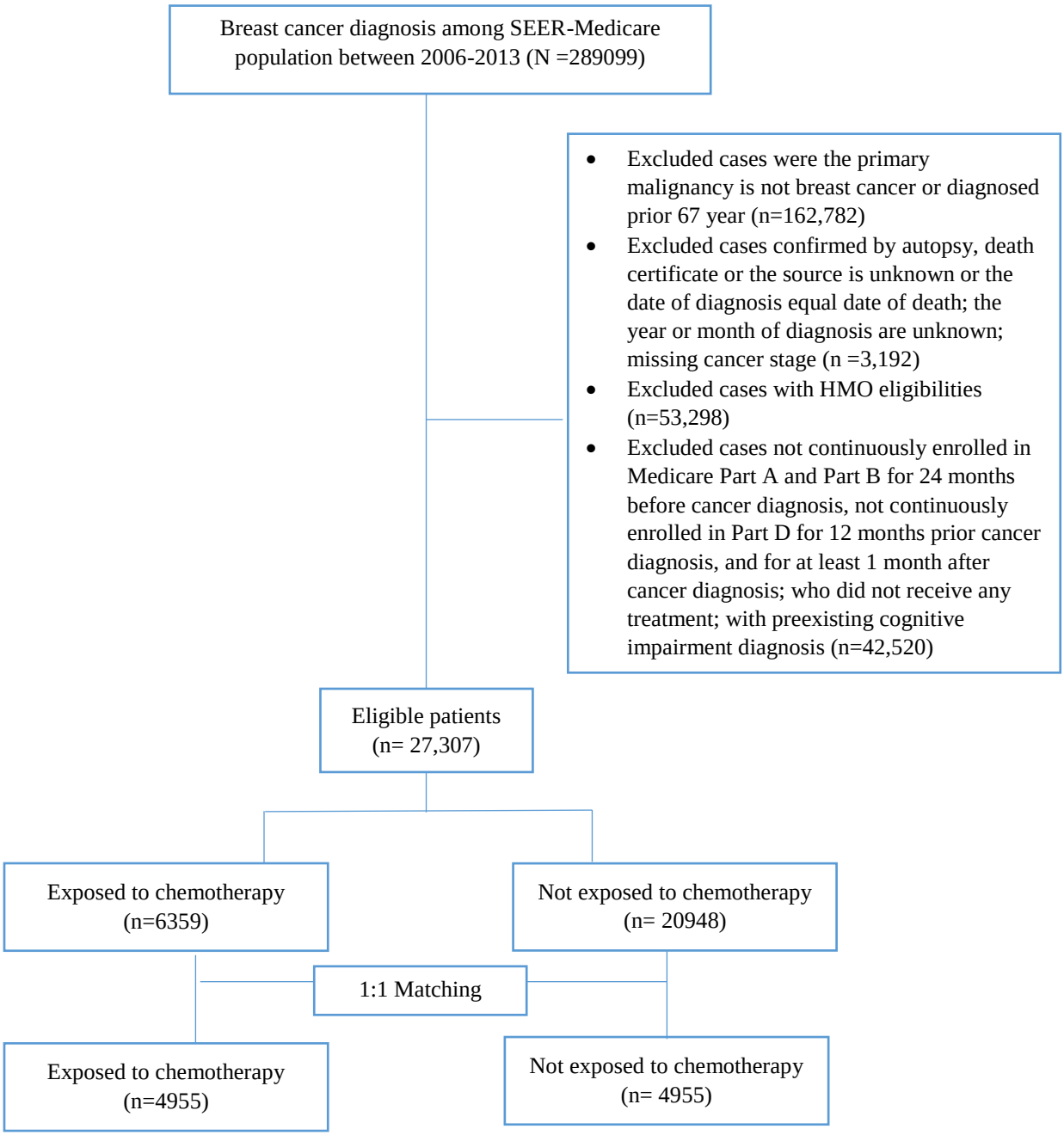

Figure 8. Sample Flow Diagram for Aim 2.

Table 6. Comparison of Baseline Characteristics among Older Adults with Breast Cancer by Chemotherapy Exposure in both Eligible Cohort and Propensity-Matched Cohort.

	Eligible cohort			Matched cohort		
Variables	**Chemotherapy (n=6359)**	**No chemotherapy (n=20948)**	**p-value**	**Chemotherapy (n=4955)**	**No chemotherapy (n=4955)**	
Age						
Mean ± SD	72.89 ± 5.09	76.71 ± 6.75	<.0001	73.41 ± 5.33	74.20 ± 6.12	0.0001
Median	72.00	76.00		72.00	73.00	
Age groups						
67-70	2605 (40.97)	4671 (22.20)	<.0001	1829 (36.91)	1731 (34.93)	0.0120
71-75	2060 (32.40)	5324 (25.42)		1598 (32.25)	1557 (31.42)	
76-79	970 (15.25)	3911 (18.13)		826 (16.67)	863 (17.42)	
≤ 80	724 (11.39)	7042 (33.62)		702 (14.17)	804 (16.23)	
Ethnicity n (%)						
White	5157 (22.28)	17986 (85.72)	<.0001	4081 (82.36)	4065 (82.04)	0.9465
Black	547 (8.60)	1239 (5.91)		391 (7.87)	406 (8.19)	
Hispanic	350 (5.50)	756 (3.61)		251 (5.07)	249 (5.03)	
Other	305 (4.80)	967 (4.62)		233 (4.70)	235 (4.74)	
Married status n (%)						
Single	561 (8.82)	1766 (8.43)	<.0001	428 (8.16)	467 (9.42)	0.0658
Married/domestic partner	3058 (48.09)	8614 (41.12)		2311 (46.64)	2182 (44.04)	
Divorced/ widowed	2413 (37.95)	9509 (45.39)		1958 (39.52)	2039 (41.15)	
Unknown	327 (5.14)	1059 (5.06)		258 (4.98)	267 (5.39)	
Median income						
Mean ± SD	55512.88± 26302	57235.91±27178	<.0001	55720.00± 26260	55296.79± 27136	0.4302
Median	50048.00	51424.75		50345.00	49303.00	
High school education						
Mean ± SD	27.17 ± 9.85	26.59±10.11	<.0001	26.13 ± 9.79	26.98 ± 9.84	0.4323
Median	27.53	26.89		27.40	27.38	
Below poverty						
Mean ± SD	12.33 ± 9.93	11.37 ± 9.24	<.0001	12.23 ±9.91	12.48 ±10.02	0.9923
Median	9.35	8.45		9.20	9.39	
Region n (%)						
Midwest	671 (10.35)	2638 (12.52)	<.0001	540 (10.90)	537 (10.84)	0.5685

Northeast	1446 (22.61)	4949 (23.63)		1123 (22.66)	1112 (22.44)	
South	1671 (25.75)	4819 (23.00)		1284 (25.96)	1287 (25.97)	
West	2568 (40.38)	8542 (40.78)		2008 (40.52)	2019 (40.75)	
Medicaid enrollment n (%)	4953 (77.89)	17018 (81.24)	<.0001	3872 (78.14)	3822 (77.13)	0.2280
Chronic condition n (%)						
Congestive heart failure	306 (4.81)	1443 (6.89)	<.0001	269 (5.43)	287 (5.79)	0.4320
Peripheral vascular disease	319 (5.02)	1704 (8.13)	<.0001	275 (5.55)	299 (6.03)	0.3020
Cerebrovascular disease	266 (4.18)	1097 (5.24)	0.0007	224 (4.52)	234 (4.72)	0.6323
Chronic obstructive pulmonary Disease	703 (11.06)	2604 (12.43)	0.0032	563 (11.36)	568 (11.46)	0.8745
Myocardial infarction	103 (1.62)	376 (1.79)	0.3514	85 (1.72)	88 (1.78)	0.8180
Moderate-severe renal disease	258 (4.06)	1149 (5.49)	<.0001	216 (4.36)	249 (5.03)	0.1170
Diabetes and diabetes complications	1538 (24.19)	4840 (23.10)	0.0742	1214 (24.50)	1286 (25.95)	0.0959
Hemiplegia or Paraplegia	18 (0.28)	68 (0.32)	0.6045	17 (0.34)	17 (0.34)	1.00
Peptic ulcer disease	44 (0.69)	125 (0.60)	0.3964	29 (0.59)	30 (0.61)	0.8961
Rheumatologic disease	306 (4.81)	493 (2.35)	<.0001	200 (4.04)	206 (4.16)	0.7611
Liver disease	29 (0.46)	115 (0.55)	0.3702	24 (0.48)	29 (0.59)	0.4910
Aids	NR	NR	0.3712	NR	NR	0.3750
Depression	340 (5.66)	1186 (5.66)	0.3383	283 (5.71)	260 (5.25)	0.3100
Year of diagnosis n (%)						
2008	1239 (19.48)	4078 (19.47)	0.0006	965 (19.48)	977 (19.72)	0.9731
2009	1186 (18.65)	4272 (20.39)		952 (19.21)	960 (19.37)	
2010	1223 (19.23)	4046 (19.31)		976 (19.70)	949 (19.15)	
2011	1240 (19.50)	4045 (19.31)		939 (18.95)	959 (19.35)	
2012	1259 (19.80)	3948 (19.02)		965 (19.48)	949 (19.15)	
2013	212 (3.33)	523 (2.50)		158 (3.19)	161 (3.25)	
Cancer stage n (%)						
I	1527 (24.01)	13106 (62.56)	<.0001	1498 (30.23)	1496 (30.19)	0.1234
II	2561 (40.27)	5523 (26.37)		2028 (40.93)	2114 (42.66)	
III	1399 (22.00)	954 (4.55)		760 (15.34)	676 (13.64)	
IV	591 (79.29)	688 (3.28)		853 (8.74)	420 (8.48)	
Unknown	281 (4.42)	677 (3.23)		236 (4.76)	249 (5.03)	
Grade n (%)						
I	569 (8.95)	6220 (29.69)	<.0001	554 (11.18)	581 (11.73)	0.7200
II	2262 (35.57)	9661 (46.12)		1987 (40.10)	2006 (40.48)	

III	2996 (47.11)	3764 (17.97)		1982 (40.00)	1927 (38.89)	
IV	56 (0.88)	81 (0.39)		40 (0.81)	35 (0.71)	
Unknown	476 (7.49)	1222 (5.83)		329 (7.91)	406 (8.19)	
Tumor size n (%)						
< 2 cm	2625 (41.28)	14722 (70.28)	<.0001	2300 (46.42)	2342 (47.27)	0.8619
2-5 cm	2642 (41.28)	4812 (22.97)		1917 (38.69)	1887 (38.08)	
> 5 cm	685 (10.77)	916 (4.37)		453 (9.14)	452 (9.12)	
Diffuse/Metastasis	49 (0.77)	22 (0.11)		23 (0.46)	18 (0.36)	
Unknown	358 (5.63)	476 (2.27)		262 (5.29)	256 (5.17)	
Lymph nodes status n (%)						
Negative	2526 (39.72)	14471 (69.08)	<.0001	2271 (45.83)	2271 (45.83)	0.5708
Positive	2820 (44.35)	3083 (14.72)		1860 (37.54)	1824 (36.81)	
Unknown	1013 (15.93)	3394 (16.20)		824 (16.63)	860 (17.36)	
Estrogen receptor status n (%)						
Negative	1910 (30.04)	1774 (8.47)	<.0001	1164 (23.49)	1122 (22.64)	0.5994
Positive/Borderline	4165 (65.50)	18307 (87.39)		3535 (71.34)	3571 (72.07)	
Unknown	284 (4.47)	867 (4.14)		256 (5.17)	262 (5.29)	
Progesterone receptor status n (%)						
Negative	3254 (51.17)	16036 (76.55)	<.0001	2848 (57.48)	2897 (58.47)	0.7237
Borderline	27 (0.42)	56 (0.27)		14 (0.28)	14 (0.28)	
Positive	2795 (43.95)	3996 (19.08)		2848 (37.09)	1783 (35.98)	
Unknown	283 (4.45)	860 (4.11)		255 (5.15)	261 (5.27)	

Abbreviation: NR, not reportable (cell sizes less than 11 are not reported per the SEER-Medicare data use agreement)

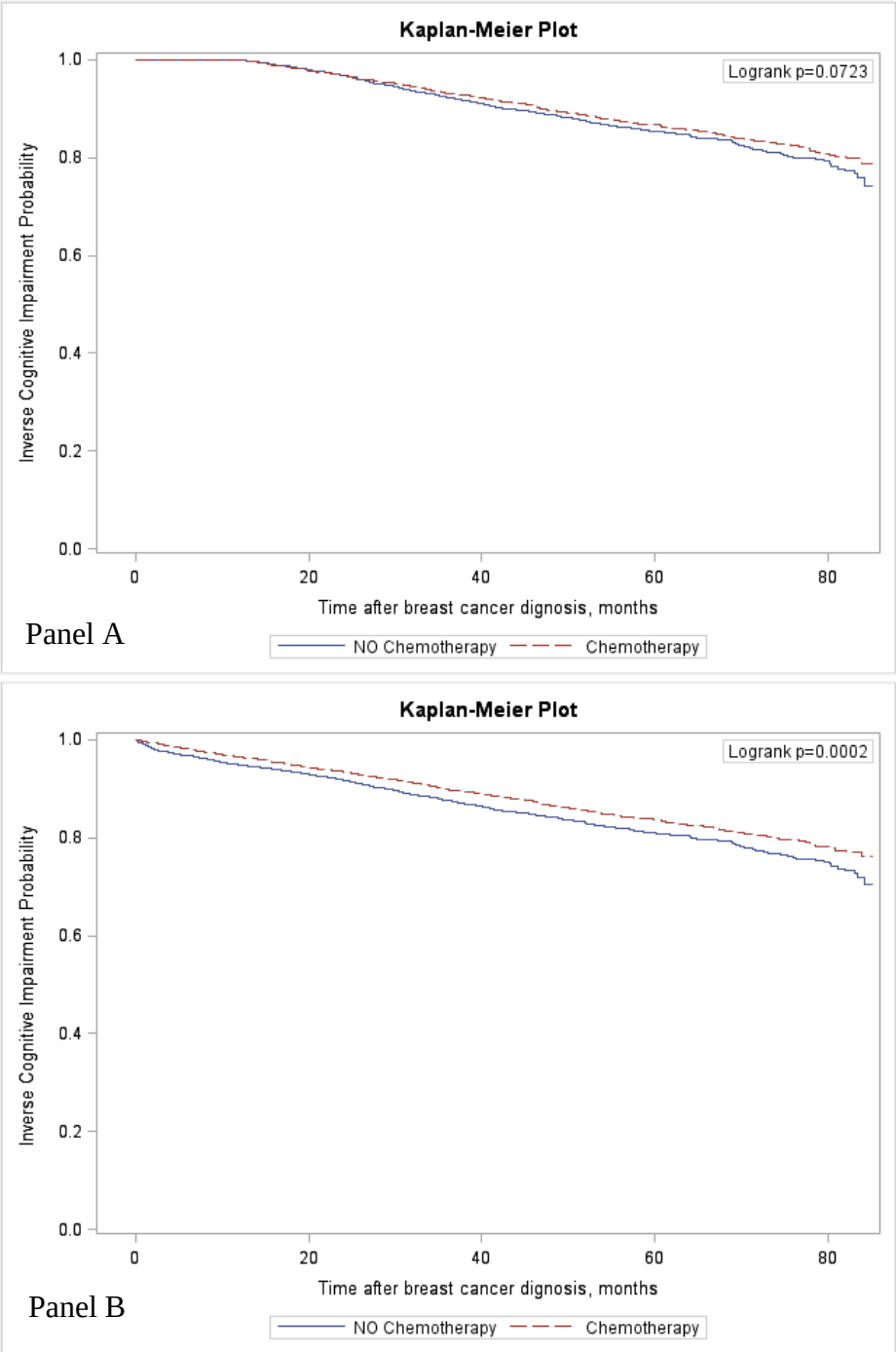

Figure 9. Inverse Probability of Cognitive Impairment in Patients with Breast Cancer, by Chemotherapy Exposure.

Panel A: Kaplan-Meier curve shows the inverse probability of cognitive impairment after 1 year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy, which can take up to a year. Panel B: Kaplan-Meier curve shows the inverse probability of cognitive impairment in which we included the incidence of cognitive impairment occurred during the year after the breast cancer diagnosis.

Table 7. Adjusted Hazard Ratios of Breast Cancer Chemotherapy-Related Cognitive Impairment

	Hazard ratio [a] (95% confidence interval)	
	Main analysis [b]	**Sensitivity analysis [c]**
Model 1		
Cancer Treatment		
No chemotherapy	REF	REF
Chemotherapy	0.94 (0.83-1.07)	0.85 (0.76-0.95)
No Hormone	REF	REF
Hormone	1.16 (1.02-1.31)	1.02 (0.92-1.13)
No surgery	REF	REF
Conservative surgery	0.69 (0.50-0.94)	0.51 (0.41-0.63)
Non-conservative surgery	0.72 (0.53-0.98)	0.62 (0.50-0.76)
No radiation therapy	REF	REF
Radiation therapy	0.76 (0.65-0.88)	0.76 (0.67-0.86)
No targeted therapy	REF	REF
Targeted therapy	1.00 (0.82-1.22)	0.98 (0.83-1.17)
Age groups		
67-70	REF	REF
71-75	1.37 (1.52-1.63)	1.39 (1.19-1.61)
76-79	2.28 (1.90-2.74)	2.27 (1.94-2.65)
≤ 80	4.21 (3.54-5.02)	4.11 (3.55-4.77)
Depression history		
without depression history	REF	REF
With depression history	1.89 (1.49-2.39)	1.99 (1.65-2.41)
Model 2		
Cancer Treatment		
No chemotherapy	REF	REF
Non-taxane-based chemotherapy	1.09 (0.90-1.32)	1.01 (0.85-1.18)
Taxane-based chemotherapy	0.88 (0.76-1.02)	0.78 (0.69-0.89)
No Hormone	REF	REF
Hormone	1.15 (1.02-1.31)	1.01 (0.91-1.23)
No surgery	REF	REF
Conservative surgery	0.69 (0.50-0.94)	0.51 (0.41-0.64)
Non-conservative surgery	0.74 (0.54-1.01)	0.63 (0.51-0.78)
No radiation therapy	REF	REF
Radiation therapy	0.77 (0.68-0.90)	0.77 (0.69-0.87)
No targeted therapy	REF	REF
Targeted therapy	1.05 (0.85-1.28)	1.03 (0.87-1.23)
Age groups		
67-70	REF	REF
71-75	1.37 (1.15-1.62)	1.38 (1.19-1.60)
76-79	2.24 (1.86-2.69)	2.22 (1.90-2.60)
≤ 80	4.10 (3.43 -4.90)	3.99 (3.43-4.63)
Age groups		
Depression history		
without depression history	REF	REF
With depression history	1.88 (1.49-2.38)	1.98 (1.64-2.40)

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, and depression. [b] Main analysis: Cox models estimate the risk of cognitive impairment after 1 year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy, which can take up to a year. [c] Sensitivity analysis: Cox models estimate the risk of cognitive impairment in which we included the incidence of cognitive impairment occurred during the year after the breast cancer diagnosis.

Table 8. Adjusted Hazard Ratios of Breast Cancer Chemotherapy-Related Cognitive Impairment by Cognitive Impairment Diagnosis

	Hazard ratio [a] (95% confidence interval)		
	Dementia	**Mild cognitive Impairment**	**Alzheimer's disease**
Main Analysis [b]			
No chemotherapy	REF	REF	REF
Chemotherapy	0.97 (0.84-1.12)	1.27 (0.83-1.52)	0.81 (0.64-1.02)
No Hormone	REF	REF	REF
Hormone	1.24 (1.08-1.42)	0.71 (0.53-0.95)	1.99 (0.80-1.24)
Surgery			
No surgery	REF	REF	REF
Conservative surgery	0.67 (0.47-0.94)	0.61 (0.31-1.19)	0.72 (0.40-1.28)
Non-conservative surgery	0.78 (0.56-1.09)	0.50 (0.26-0.97)	0.68 (0.38-1.19)
No radiation therapy	REF	REF	REF
Radiation therapy	0.79 (0.67-0.92)	0.91 (0.64-1.28)	0.75 (0.57-0.97)
No targeted therapy	REF	REF	REF
Targeted therapy	0.95 (0.76-1.18)	0.99 (0.64-1.54)	0.68 (0.45-1.04)
Sensitivity analysis [c]			
No chemotherapy	REF	REF	REF
Chemotherapy	0.83 (0.74-0.94)	1.08 (0.81-1.44)	0.76 (0.62-0.94)
No Hormone	REF	REF	REF
Hormone	1.08 (0.96-1.21)	0.74 (0.56-0.97)	0.96 (0.79-1.17)
Surgery			
No surgery	REF	REF	REF
Conservative surgery	0.52 (0.41-0.67)	0.73 (0.38-1.38)	0.47 (0.31-0.70)
Non-conservative surgery	0.67 (0.53-0.85)	0.63 (0.33-1.19)	0.49 (0.33-0.72)
No radiation therapy	REF	REF	REF
Radiation therapy	0.74 (0.65-0.84)	0.84 (0.61-1.61)	0.74 (0.59-0.92)
No targeted therapy	REF	REF	REF
Targeted therapy	0.95 (0.79-1.15)	1.07 (0.71-1.61)	0.75 (0.53-1.07)

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, and depression. The results of age and depression are not shown in the table. [b] Main analysis: Cox models estimate the risk of cognitive impairment after 1 year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy, which can take up to a year. [c] Sensitivity analysis: Cox models estimate the risk of cognitive impairment in which we included the incidence of cognitive impairment occurred during the year after the breast cancer diagnosis.

Table 9. Adjusted Hazard Ratios of Breast Cancer Chemotherapy-Related Cognitive Impairment by Treatment Regimens

	Hazard ratio [a] (95% confidence interval)	
	Main analysis [b]	**Sensitivity analysis [c]**
Taxane-based chemotherapy	REF	REF
Non-taxane-based chemotherapy	1.23 (1.00-1.52)	1.28 (1.07-1.53)
No chemotherapy	REF	REF
No chemotherapy plus hormone	1.15 (0.95-1.37)	0.96 (0.83-1.11)
Taxane-based chemotherapy	REF	REF
Taxane-based chemotherapy plus hormone therapy	1.28 (1.03-1.58)	1.13 (1.94-1.36)
Non-taxane-based chemotherapy	REF	REF
Non-taxane-based chemotherapy plus hormone therapy	0.89 (0.63-1.25)	0.95 (0.70-1.26)

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, and depression. [b] Main analysis: Cox models estimate the risk of cognitive impairment after 1 year of the breast cancer diagnosis to allow patients to be exposed to chemotherapy, which can take up to a year. [c] Sensitivity analysis: Cox models estimate the risk of cognitive impairment in which we included the incidence of cognitive impairment occurred during the year after the breast cancer diagnosis.

4.3 Aim 3

Abstract

Objective: This study aimed to evaluate the association between the development of cognitive impairment and the use of antidepressants among older patients with breast cancer.

Methods: This retrospective cohort study used the National Cancer Institute's Surveillance, Epidemiology, and End Results-Medicare database to identify women who were ≥67 years old and had breast cancer between 2008 and 2013. Propensity scoring was used to account for confounding pre-treatment factors, and Cox proportional hazards modeling was used to examine the risk of developing cognitive impairment among patients based on whether they used antidepressants.

Results: Antidepressant use was associated with a significantly increased risk of cognitive impairment (hazard ratio [HR]: 1.33, 95%; confidence interval [CI]: 1.18–1.48). Additionally, we found that patients without a history of depression or anxiety who use antidepressants have a higher risk of developing cognitive impairment than those who did not use antidepressants (HR: 1.53, 95%; CI: 1.34–1.75 and HR: 1.39, 95%; CI: 1.23–1.56, respectively). Subgroup analysis showed that the use of non-tricyclic antidepressants (TCAs) was associated with a higher risk of cognitive impairment.

Conclusion: We found that non-TCA antidepressant use in older adults with breast cancer was associated with a higher risk of cognitive impairment. This association was also observed among patients without depression or anxiety who used antidepressants.

Introduction

Early cancer screenings and the availability of effective cancer treatments have led to a substantial improvement in survival rates among older patients with breast cancer. Therefore, increased attention is being directed to comorbid conditions, particularly those associated with age, such as cognitive impairment. Evidence suggests that breast cancer patients experience cognitive impairment more often than the general population, particularly in the domains of attention, memory, and executive function.[1,2] It has been estimated that 11% to 35% of older adults with breast cancer show cognitive decline.[3,4] The prevalence of cognitive impairment in the general population is higher in women than in men. Nearly 60% of the 5.5 million older adults diagnosed with Alzheimer's disease were women.[5] The number of older women living with cognitive impairment will increase as the population of older adults in the United States continues to increase. By 2050, the number of older adults will be around 88 million compared to 55 million in 2018.[6,7] The health care costs associated with dementia and Alzheimer's disease were estimated to be around $287,000 compared to $183,000 for other conditions among Medicare beneficiaries.[8]

Research to understand modifiable factors for cognitive impairment, particularly the severe forms such as dementia and Alzheimer's disease, is currently underway. Depression is a well-known predisposing factor for dementia and Alzheimer disease.[9] It has been reported as one of the mental conditions that could be a prodrome of cognitive impairment.[10,11] It increases the risk of cognitive impairment twofold, even if a depression diagnosis precedes cognitive impairment by 25 years.[12-15] Depression is a common mood disorder among older adults with breast cancer with prevalence rates of up to 25%.[16-18] Antidepressants are considered to be one of the most

commonly used drugs in the United States. It has been estimated that around 20% of patients with breast cancer use antidepressants to treat depression, anxiety, and/or chronic pain.[19]

It has been suggested that antidepressants might have neuroprotective effects.[20,21] Evidence from animal models have pointed out that selective serotonin reuptake inhibitors (SSRIs) might reduce the incidence of cognitive impairment through various mechanisms.[20-24] However, evidence from clinical studies has been contradictive. Several randomized studies have investigated the effect of antidepressants, mainly SSRIs, on cognitive functioning in patients with dementia, and their findings have not been consistent. Some studies have found that SSRIs reduce cognitive impairment,[25,26] whereas other studies found no effect[27,28] or negative effects.[29,30] The majority of these studies had small sample sizes and short follow-up times. A retrospective analysis of patients with depression and no history for cognitive impairment showed that patients who received first-generation antidepressants had a lower risk for developing dementia compared to those who received the newer generation of antidepressants, such as SSRIs or serotonin-norepinephrine reuptake inhibitors.[31] Another study of patients with depression found that antidepressant use was associated with a higher risk of cognitive impairment over 4 years.[32] A Women's Health Initiative Memory Study found that there was a 70% increased risk of cognitive impairment in women who used antidepressant medications.[33] Another study of 3,714 adults over the age of 50 years old found, after a 6 year follow up, that exposure to antidepressants did not alter the risk of cognitive impairment.[34]

Little and conflicting evidence exists on the association between long-term antidepressant use and cognitive impairment. To the best of our knowledge, there has been no large population-

based study evaluating the association between antidepressants and cognitive impairment among patients with breast cancer. Thus, in this study, we aimed to examine the effect of antidepressant use on cognitive impairment in older patients diagnosed with breast cancer.

Methods

Data sources and study population

This study used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims between January 1, 2006 and December 31, 2014. The SEER program is a cancer registry that covers 28% of the population of the United States. It contains information regarding the incidence of cancer in 18 areas. It collects information regarding cancer characteristics (e.g., cancer type, diagnosis date, stage, grade, cancer treatment) and patient characteristics (e.g., age, sex, insurance, cause of death). Medicare is the primary health care insurance for 97% of older adults (≥65 years old), and the Medicare program collects information regarding all health care services provided to beneficiaries under its hospital (Part A), medical (Part B), and drug (Part D) plans.

Women were included in the present study if they were diagnosed with primary breast cancer between January 1, 2008 and December 31, 2013 and had no previous history of cancer as per the SEER records. Furthermore, these patients were required to have been continuously enrolled in Medicare Part A and Part B for 24 months and Part D for 12 months before their cancer diagnosis, and for at least 12 after the cancer diagnosis. If patients died in the first year, they had to have had coverage for at least 1 month. This was to ensure that all patients had similar coverage and access to health care services. The age cut-off was defined as ≥67 years at the first

diagnosis, rather than 65 years, to adequately exclude patients with a diagnosed history of cognitive impairment. Patients were excluded if: 1) they were enrolled in Health Maintenance Organization (HMO) plans, because payments for those plans are not linked to health care services; 2) data on diagnosis date, cancer stage, and autopsy diagnosis were missing; or 3) the date of breast cancer diagnosis and death were the same.

Cohort selection and matching

Prevalent use of antidepressants was identified using Medicare Part D claims 12 months before and after the date of breast cancer diagnosis. The patients were considered prevalent users if they had two prescriptions of antidepressants before and after their date of breast cancer diagnosis. Antidepressants users were further classified into three groups: 1) SSRIs, 2) Tricyclic antidepressants (TCAs), and 3) other antidepressants (defined as other antidepressants or combinations of antidepressants). To minimize selection bias based on factors that might have influenced the physician's decision to prescribe antidepressants, we calculated the propensity scores for receiving antidepressants among all patients, and then matched patients who did or did not receive antidepressants according to their propensity scores. The one-to-one matching was performed using the nearest neighbor method without replacement and with a caliper width of 0.2. The propensity score was estimated using a logistic regression model that controlled for the patients' demographic variables (age, sex, ethnicity, socioeconomic status, marital status, and region), tumor characteristics (stage, grade, estrogen receptor status, diagnosis year, tumor size, and number of positive lymph nodes), cancer treatment, Charlson comorbidity index variables, and the presence of depression, anxiety, schizophrenia, and bipolar disorder.

Development of cognitive impairment

Cognitive impairment was considered present in cases with at least one claim after the breast cancer diagnosis that involved the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for dementia (ICD-9-CM 290.0–290.43, 291.2, 291.82, 294.10, 294.11, 294.20, 294.21, 33.1, 331.19, 331.82), mild cognitive impairment (ICD-9-CM 331.83), or Alzheimer's disease (ICD-9-CM 331.0). The patients were followed until the first instance of cognitive impairment development, death, or the censoring date (December 31, 2014).

Covariates

The SEER data were searched to obtain the eligible patients' demographic characteristics, including age, sex, ethnicity/race, and marital status. Because the SEER data lacks patient-level socioeconomic information, we used census tract variables to estimate income, education, and poverty levels based on the patient's area of residence at their cancer diagnosis. The SEER data were also searched to determine the patients' tumor and treatment characteristics, including stage, grade, tumor size, number of positive lymph nodes, and estrogen receptor status. Comorbidities were identified to calculate each patient's Charlson comorbidity index using an application that was developed by the National Cancer Institute based on the approach of Klabunde et al.[35] Comorbidities were identified using specific ICD-9-CM codes from claims that were submitted for MEDPAR, outpatient care, or physician treatment within a 1-year period before the breast cancer diagnosis. However, comorbidities were restricted to codes that appeared on two physician and/or outpatient claims that were made >30 days apart. The Medicare data were also searched using the ICD-9-CM, Current Procedural Terminology, and

the Healthcare Common Procedure Coding System codes to determine if the patients received surgery, hormone therapy, chemotherapy, and radiotherapy (Appendix B).

Statistical analyses

Descriptive statistics were used to report the patients' baseline demographic characteristics (age, sex, ethnicity, marital status, education, income, and region) and comorbidities, as well as their tumor characteristics (stage, grade, estrogen receptor status, diagnosis year, tumor size, number of positive lymph nodes), and cancer treatments. These characteristics were compared between the groups of patients who did and did not receive antidepressant treatment, using the t-test for continuous variables and the chi-square test for categorical variables. Curves for the incidences of cognitive impairment were created using the Kaplan-Meier method stratified by antidepressant use and depression diagnosis. To test the association between antidepressant use and the development of cognitive impairment, we used Cox proportional hazard model adjusted for age as well as depression, anxiety, schizophrenia, and bipolar disorder diagnosis. These conditions were included as independent confounding factors to adjust for confounding by indication bias. These conditions are associated with cognitive disorders and antidepressant use among older adult patients. We also examined the interaction between antidepressants, depression, and anxiety. In this analysis, we compared the risk of developing cognitive impairment between patients who have or do not have a diagnosis of depression or anxiety by their antidepressant use. In a separate analysis, we also examined if there was an interaction between chemotherapy and hormone therapy and antidepressants. This was done because there is some evidence that the use of chemotherapy and hormone therapy might increase the risk of cognitive impairment diagnosis after breast cancer diagnosis.

Results

Figure 10 shows the sample flow diagram for the current study, which identifies 29,842 eligible women with breast cancer. A total of 3,174 females taking antidepressants were matched with 3,174 females not taking antidepressants, for a total sample size of 6,348 female patients taking/not taking cognitive antidepressants. Table 10 shows the distribution of baseline characteristics among eligible patients according to their use of antidepressants and a comparison of the matched cohorts. Prior to matching, patients who used antidepressants were more likely to be younger, white, and divorced/widowed. Additionally, the prevalence of depression, anxiety, and other mental disorders were higher among those taking antidepressants. However, the propensity matching methods eliminated all significant inter-group differences.

Figure 11 shows the Kaplan-Meier curves for the incidence of cognitive impairment, which indicate significant differences according to antidepressant use and depression status (log-rank test p-value <0.0001). Figure 12 shows the incidence of cognitive impairment in patients among patients taking SSRIs, TCAs, and other antidepressants. The results show that a higher percentage of patients on SSRIs or other antidepressants develop cognitive impairment compared to patients on TCAs, 24%, 26%, and 18%, respectively (Figure 12).

Table 11 shows the results of the time-to-event analysis for the development of cognitive impairment after cancer diagnosis, which indicates that patients who use antidepressants have a significantly higher risk of cognitive impairment after the cancer diagnosis (hazard ratio [HR]: 1.33, 95%; confidence interval [CI]: 1.18–1.48) (Model 1). We also examined the three types of conditions included in the cognitive impairment definition (mild cognitive impairment, dementia,

Alzheimer's disease). Antidepressant use was associated with a higher risk of impairment, ranging from 37% to 45% in all conditions. Additionally, we found that age and diagnosis with a mental disorder were associated with a higher risk in patients using antidepressants. We also performed subgroup analysis according to whether the patients received SSRIs, TCAs, or other antidepressants (Model 2). This analysis showed a significant difference in the risk of incidence of cognitive impairment between the patients who did not use antidepressants and patients who used SSRI (HR: 1.28, 95%; CI: 1.13–1.46) or other antidepressants (HR: 1.54, 95%; CI: 0.33–1.73), but not with those who used TCA (HR: 0.97, 95%; CI: 0.74–1.26).

Furthermore, we compared the risk of developing cognitive impairment based on a history of depression and anxiety to antidepressant use (Table 12). We found that patients diagnosed with depression who used antidepressants did not significantly differ from those diagnosed with depression who do not use antidepressants (HR: 0.92, 95%; CI: 0.74–1.13). In contrast, patients without depression who took antidepressants had a higher risk of cognitive impairment than those without depression who did not take antidepressants (HR: 1.53, 95%; CI: 1.34–1.75). In the subgroup analysis, SSRIs and other antidepressant groups yielded similar results. Patients who used antidepressants had a higher risk of developing cognitive impairment than patients who did not have anxiety and did not use antidepressants, (HR: 1.39, 95%; CI: 1.23–1.56). The results were similar in the subgroup analysis for SSRIs (HR: 1.36, 95%; CI: 1.19–1.56) and other antidepressants (HR: 1.58, 95%; CI: 1.35–1.85).

We also examined if an interaction exists between antidepressant use paired with chemotherapy or hormone therapy and the development of cognitive impairment (Table 13). Patients who

received or did not receive chemotherapy and used antidepressants were at a higher risk of cognitive impairment relative to those that did not use antidepressants (HR: 1.47, 95%; CI: 1.12–1.92 and HR: 1.30, 95%; CI: 1.15–1.47, respectively). When we compared patients based on hormone therapy, the results showed that patients who received hormone therapy and used antidepressants had a higher risk of cognitive impairment than those that received hormone therapy but did not take antidepressants (HR: 1.48, 95%; CI: 1.29–1.71). However, among those who did not receive hormone therapy, the use of antidepressants was not associated with increased risk of cognitive impairment relative to those who did not use antidepressants (HR: 1.09, 95%; CI: 0.91–1.31).

Discussion

In this study of older adults with breast cancer, we found that antidepressant use was associated with a higher risk cognitive impairment. We compared cognitive function between those who took antidepressants and those who did not. Among the patients without depression or anxiety disorder, we observed a significant increase in cognitive impairment incidence in those who used antidepressants. However, among those with depression or anxiety, we did not find a significant difference based on the use of antidepressants.

Few published studies have examined the association between antidepressant use and the development of cognitive impairment, and none have examined this within the cancer population. The findings of these studies were not consistent, due to varying study design, population, comparison group, length of treatment, and type of antidepressants. One study found that there was no association between the use of antidepressants and the decline in cognitive

function among older adults.[34] Other studies examined the association between cognitive function and whether or not patients responded to treatment with antidepressants. They found that patients who responded to treatment showed improvement in cognitive function, while patients who did not respond showed a decline or no improvement.[36-38] Another study found that antidepressant use was associated with a lower risk of dementia, but only among those with mild cognitive function at baseline.[39]

In contrast, a study of older adults in a primary care setting found that the use of SSRIs or non-SSRIs was associated with a higher risk of dementia than non-users among patients without depression. Additionally, they found that there was no significant difference in the risk of dementia between antidepressant users and non-users among patients with depression.[40] These findings are consistent with our results. However, we found that TCAs were not associated with an increased risk of cognitive impairment compared to those who did not use antidepressants in both patients with and without depression.

Also, we found that among those who received hormone therapy, antidepressant use was associated with higher risk of cognitive impairment compared to those that did not use antidepressants. However, we did not find similar results among those who did not receive hormone therapy. Both antidepressants and hormone therapy have been linked to an increased risk of cognitive impairment.[40,41] It is possible that the concomitant use of these two drugs can result in an increased risk of cognitive decline, especially when both drugs are commonly used among breast cancer patients.

The association between cognitive decline and anticholinergic activity, which is present to varying degrees in antidepressants (low in SSRIs and high in TCAs), has been established.[42] Several studies have found that anticholinergic activity was not associated with cognitive decline, while others found a significant association.[42-46] One study that examined the effect of anticholinergic activity on cognitive impairment among the elderly found that anticholinergic activity had a small effect on cognitive function at baseline and at the end of the study.[34] Our results showed that SSRIs (with low anticholinergic activity) yielded a significant increase in risk of cognitive impairment compared to TCAs (with high anticholinergic activity). A possible explanation for this effect is that physicians might avoid prescribing TCA to older adults or to those who show signs of cognitive decline.

The pharmacological mechanism that could explain the associated risk of cognitive impairment with SSRIs is still unclear. One in vitro study has shown that administration of SSRIs is associated with the upregulation of GPR39 Zn2+-sensing receptor protein.[47] A possible link between SSRI use and cognitive impairment involves low or high Zinc levels, which may cause neurofibrillary tangles, a known marker of cognitive impairment and Alzheimer's disease.[48,49]

One of the main strengths of this study is that the study population covers a large cohort of Medicare beneficiaries, which leads to a high generalizability of our findings with regard to patients above the age of 65 years. Additionally, we used the propensity score to balance baseline characteristic to minimize selection bias. We included only patients with breast cancer and controlled for mood and mental disorders as confounding factors to ensure that we had two groups with comparable risk of developing cognitive impairment.

However, this study also has some limitations. First, the data in the SEER-Medicare database might already contain certain biases. For instance, physicians may be more likely to prescribe SSRIs over TCAs to older adults with cognitive impairment as it is known that TCAs have higher anticholinergic activity, which is associated with memory decline and confusion. Although we excluded patients who showed signs of cognitive impairment before cancer diagnosis, it is possible that we included patients with cognitive impairment who were undiagnosed during the exclusion period. Another limitation that we did not account for is the duration of antidepressant use, which could have had an impact on the findings. However, we included patients with two prescriptions before and after breast cancer diagnosis to ensure that patients were prevalent users of antidepressants.

In conclusion, we found that antidepressant (non-TCAs) use in older adults with breast cancer was associated with a higher risk of cognitive impairment. Similarly, among patients without depression or anxiety, the use of antidepressants is associated with an increased risk of cognitive impairment. Additionally, we found that patients who received both hormone therapy and antidepressants had a higher risk of cognitive impairment than did those who received hormone therapy but did not use antidepressants. It is important to further investigate this finding in order to understand the mechanisms underlying the association between antidepressants and development of cognitive impairment in older adults.

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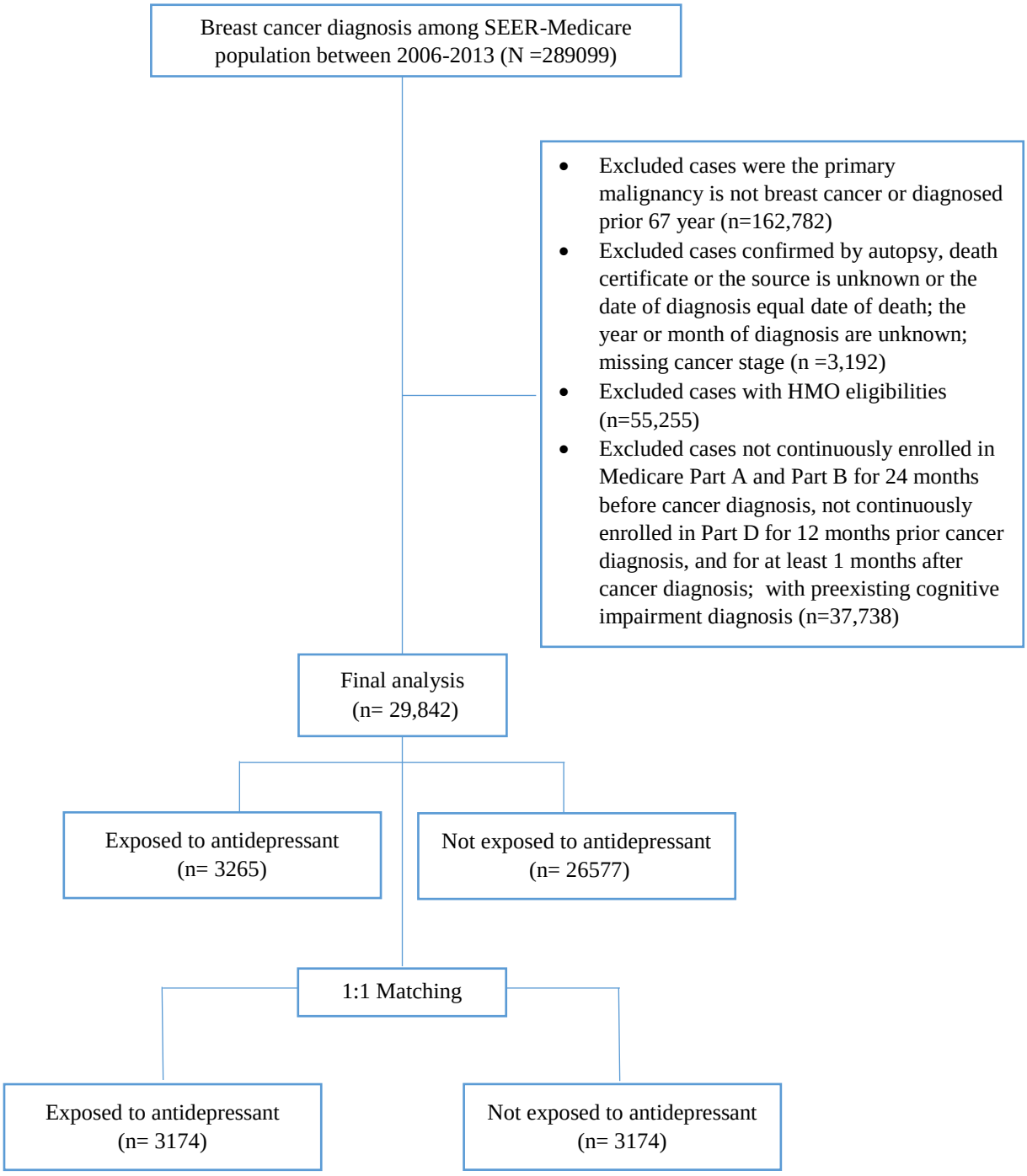


Figure 10. Sample Flow Diagram for Aim 3.

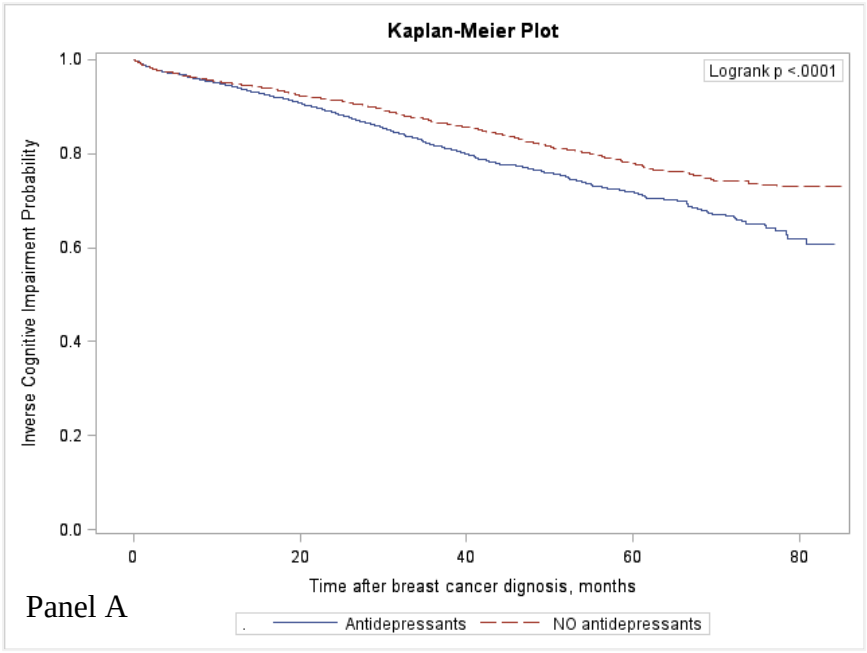
Table 10. Comparison of Baseline Characteristics among Older Adults with Breast Cancer by Antidepressants in both Eligible Cohort and Propensity-Matched Cohort.

	Full cohort			Matched cohort		
Variables	**Antidepressants (n=3265)**	**No Antidepressants (n=26577)**	**P-value**	**Antidepressants (n=3174)**	**No Antidepressants (n=3174)**	**P-value**
Age						
Mean ± SD	75.14 ± 6.41	76.35 ± 6.96	<.0001	75.21 ± 6.41	75.38 ± 6.73	0.2938
Median	74.00	75.00		74.00	74.00	
Age groups						
67-70	1004 (30.75)	6702 (25.22)	<.0001	961 (30.28)	940 (29.62)	0.9119
71-75	905 (27.72)	6879 (25.88)		879 (27.69)	902 (28.42)	
76-79	540 (16.54)	4655 (17.52)		532 (16.76)	532 (16.76)	
≤ 80	816 (24.99)	8341 (31.38)		802 (25.27)	800 (25.20)	
Ethnicity n (%)						
White	2966 (90.94)	22182 (83.46)	<.0001	2879 (90.71)	2907 (91.59)	0.3472
Black	106 (3.25)	1960 (7.37)		105 (3.31)	86 (2.71)	
Hispanic	118 (3.61)	1107 (4.17)		115 (3.62)	100 (3.15)	
Other	75 (2.30)	1328 (5.00)		75 (2.36)	81 (2.55)	
Married status n (%)						
Single	270 (8.27)	2368 (8.91)	0.0048	259 (8.16)	248 (7.81)	0.9426
Married/domestic partner	1270 (38.90)	11017 (41.45)		1244 (39.19)	1260 (39.70)	
Divorced/ Widowed	1550 (47.47)	11750 (44.21)		1501 (47.29)	1493 (47.04)	
Unknown	175 (5.36)	1442 (5.43)		170 (5.36)	173 (5.45	
Median income						
Mean ± SD	54959.60± 26756	56831.36± 26986	0.0002	55161.49±26766	54897.88±25851	0.6898
Median	48804.00	51167.67		48954.33	49074.50	
High school education						
Mean ± SD	26.94±10.30	26.76±9.99	0.3251	26.92±10.33	27.08±10.04	0.5415
Median	27.16	27.08		27.09	27.57	
Below poverty						
Mean ± SD	12.34±9.15	11.61±9.45	<.0001	12.28±9.11	12.16±9.30	0.5938
Median	9..87	8.57		9.80	9.48	
Region n (%)						
Midwest	369 (11.30)	3243 (12.20)	<.0001	364 (11.47)	376 (11.85)	0.9463
Northeast	564 (17.27)	6439 (24.23)		547 (17.23)	544 (17.14)	

South	996 (30.51)	6115 (23.01)		963 (30.34)	972 (30.62)	
West	1336 (40.92)	10780 (40.56)		1300 (40.96)	1282 (40.39)	
Medicaid enrollment n (%)	2415 (73.97)	20806 (78.29)	<.0001	2371 (74.70)	2360 (74.35)	0.7513
Chronic condition n (%)						
Congestive heart failure	295 (9.04)	1813 (6.82)	<.0001	282 (8.88)	285 (8.98)	0.8950
Peripheral vascular disease	319 (9.77)	1982 (7.47)	<.0001	300 (9.45)	309 (9.74)	0.7013
Cerebrovascular disease	220 (6.74)	1306 (4.91)	<.0001	212 (6.68)	216 (6.47)	0.9201
Chronic obstructive pulmonary Disease	559 (17.12)	3139 (11.81)	<.0001	527 (16.60)	521 (16.41)	0.8393
Myocardial infarction	56 (1.72)	498 (1.87)	0.5262	56 (1.76)	55 (1.73)	0.9237
Moderate-severe renal disease	196 (5.36)	1424 (5.36)	0.1247	191 (6.02)	178 (5.61)	0.4856
Diabetes and diabetes complications	898 (27.50)	6057 (22.79)	<.0001	869 (27.38)	891 (28.07)	0.5373
Hemiplegia or Paraplegia	NR	95 (0.36)	0.3642	NR	19 (0.60)	0.4916
Peptic ulcer disease	21 (0.64)	169 (0.64)	0.9605	20 (0.63)	17 (0.54)	0.6209
Rheumatologic disease	112 (3.43)	741 (2.79)	0.0377	105 (3.31)	121 (3.81)	0.2785
Liver disease	21 (0.64)	137 (0.52)	0.0846	19 (0.60)	21 (0.66)	0.7511
Aids	NR	NR	0.3678	NR	NR	N/A
Depression	753 (23.06)	906 (3.41)	<.0001	665 (20.95)	668 (21.05)	0.9263
Anxiety	326 (9.98)	822 (3.09)	<.0001	288 (9.07)	287 (9.04)	0.9651
Bipolar disorder	66 (2.02)	69 (0.26)	<.0001	50 (1.58)	40 (1.26)	0.2884
Schizophrenia	50 (1.53)	98 (0.37)	<.0001	44 (1.39)	39 (1.23)	0.5806
Year of diagnosis n (%)						
2008	347 (11.45)	5414 (20.37)	<.0001	372 (11.72)	409 (12.89)	0.6742
2009	662 (20.28)	5255 (19.77)		647 (20.38)	669 (21.06)	
2010	731 (22.39)	5006 (18.84)		706 (22.24)	698 (21.99)	
2011	724 (22.17)	4987 (18.76)		698 (21.99)	673 (21.20)	
2012	715 (21.90)	4975 (18.72)		693 (21.83)	666 (20.98)	
2013	59 (1.81)	940 (3.54)		58 (1.83)	59 (1.86)	
Cancer stage n (%)						
I	1818 (55.68)	13210 (49.70)	<.0001	1741 (54.85)	1741 (54.85)	0.9121
II	980 (30.02)	7512 (28.27)		950 (29.93)	950 (29.93)	
III	260 (7.96)	2288 (8.61)		266 (8.38)	266 (8.38)	
IV	58 (1.78)	2088 (7.86)		57 (1.80)	57 (1.80)	
Unknown	149 (4.56)	1479 (5.56)		145 (4.57)	145 (4.57)	

Grade n (%)						
I	866 (26.90)	6231 (23.45)	<.0001	839 (26.43)	847 (26.69)	0.6483
II	1412 (43.2588)	11270 (42.41)		1374 (43.29)	1358 (42.79)	
III	771 (23.61)	6413 (24.13)		751 (23.66)	741 (23.35)	
IV	16 (0.49)	138 (0.52)		15 (0.47)	NR	
Unknown	200 (6.13)	2525 (9.50)		195 (6.14)	218 (6.87)	
Tumor size n (%)						
< 2 cm	2150 (65.85)	15802 (59.46)	<.0001	2083 (65.63)	2065 (65.06)	0.9247
2-5 cm	868 (26.58)	7323 (27.55)		847 (26.69)	859 (27.06)	
> 5 cm	141 (4.32)	1793 (6.75)		140 (4.41)	138 (4.35)	
Unknown/ Diffuse/Metastasis	106 (3.22)	1559 (5.84)		104 (3.25)	112 (3.53)	
Lymph nodes n (%)						
Negative	2078 (63.64)	15138 (56.96)	<.0001	2016 (63.52)	2001 (63.04)	0.4607
Positive	678 (20.77)	5343 (20.10)		659 (20.76)	639 (20.13)	
Unknown	509 (15.59)	6096 (22.94)		499 (15.72)	534 (16.82)	
Cancer Treatment						
Surgery			<.0001			0.9289
Conservative	1786 (54.70)	13538 (50.94)		1736 (54.69)	1739 (54.79)	
Non-conservative	1322 (40.49)	9460 (35.59)		1282 (40.39)	1273 (40.11)	
Radiotherapy	1833 (56.14)	14277 (53.72)	0.0088	1783 (56.18)	1765 (55.61)	0.6491
Chemotherapy	1869 (21.78)	5648 (21.25711)	0.4894	686 (21.61)	696 (21.93)	0.7610
Hormone Therapy	2218 (67.93)	13791 (51.89)	<.0001	2319 (67.39)	2072 (65.28)	0.0752
Targeted therapy	198 (6.06)	1508 (5.67)	0.3647	192 (6.05)	180 (5.67)	0.5214

Abbreviation: NR, not reportable (cell sizes less than 11 are not reported per the SEER-Medicare data use agreement); N/A, not applicable.



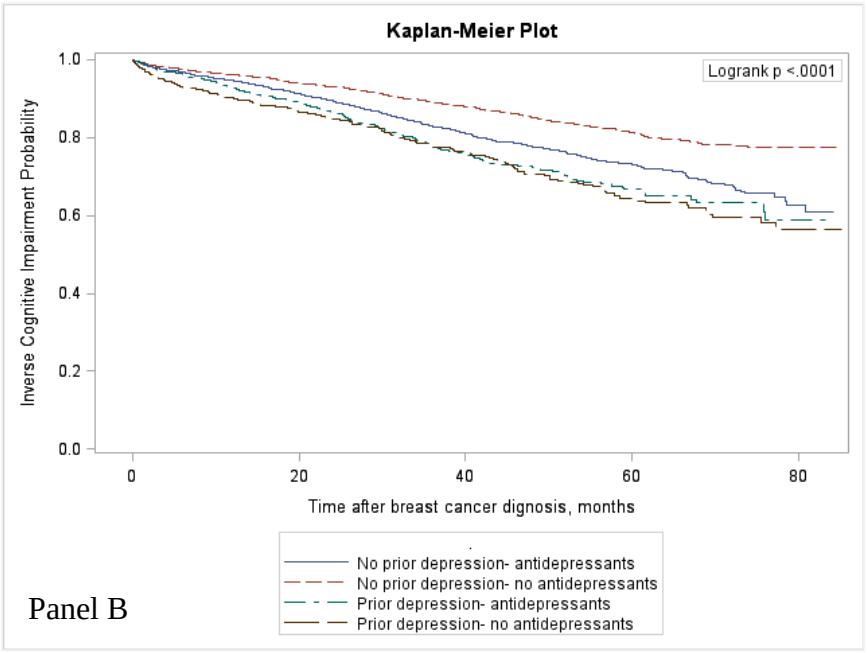


Figure 11. Inverse Probability of Cognitive Impairment in Patients with Breast Cancer by Antidepressants and depression diagnosis.

Panel A: Kaplan-Meier estimated the inverse probability of cognitive impairment after the breast cancer diagnosis stratified by antidepressants. Panel B: Kaplan-Meier estimated the inverse probability of cognitive impairment after the breast cancer diagnosis stratified by antidepressants and prior depression diagnosis.

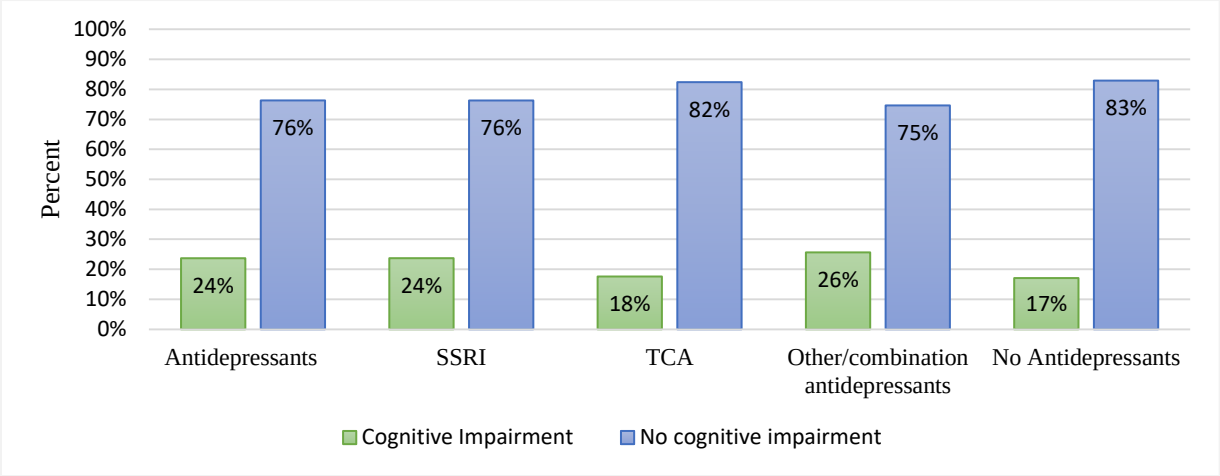


Figure 12. Incidence of Cognitive Impairment after Breast Cancer Diagnosis by Antidepressants
Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic or Tetracyclic Antidepressants

Table 11. Adjusted Hazard Ratios of Cognitive Impairment by Antidepressants

	Hazard ratio [a] (95% confidence interval)			
	Mild cognitive Impairment	**Dementia**	**Alzheimer's**	**Cognitive Impairment**
Model 1				
No Antidepressants	REF	REF	REF	REF
Antidepressants	1.37 (1.06-1.78)	1.34 (1.16-1.51)	1.45 (1.18-1.77)	1.33 (1.18-1.48)
No History of depression	REF	REF	REF	REF
History of depression	1.60 (1.20-2.14)	1.55 (1.35-1.78)	1.26 (0.99-1.59)	1.56 (1.37-1.77)
No History of Anxiety	REF	REF	REF	REF
History of Anxiety	1.03(0.66-1.61)	1.10 (0.89-1.35)	1.06 (0.74-1.50)	1.14 (0.95-1.37)
No History of schizophrenia	REF	REF	REF	REF
History of schizophrenia	1.71(0.63-4.67)	3.35 (2.35-4.86)	2.39 (1.17-4.86)	3.30 (2.36-4.65)
No History of bipolar	REF	REF	REF	REF
History of bipolar	1.20 (0.44-3.26)	2.44 (1.68-3.55)	1.39 (0.65-2.96)	2.19 (1.54-3.11)
Age groups				
67-70	REF	REF	REF	REF
71-75	1.61 (1.09-2.39)	1.31 (1.14-1.60)	1.34 (0.96-1.86)	1.28 (1.07-1.53)
76-79	1.92 (1.26-2.94)	2.42 (1.97-2.98)	2.08 (1.49-2.97)	1.28 (1.07-1.53)
≤ 80	2.95 (2.04-4.27)	4.71 (3.95-5.63)	3.96 (2.97-5.26)	4.01 (3.43-4.69)
Model 2				
No Antidepressants	REF	REF	REF	REF
SSRI	1.21 (0.89-1.65)	1.31 (1.14-1.51)	1.53 (1.22-1.92)	1.28 (1.13-1.46)
TCA	0.63 (0.29-1.36)	0.96 (0.71-1.29)	0.77 (0.44-1.33)	0.97 (0.74-1.26)
Other/combination	1.93 (1.40-2.65)	1.53 (1.30-1.74)	1.56 (1.18-2.03)	1.54 (1.33-1.73)
No History of depression	REF	REF	REF	REF
History of depression	1.55 (1.16-2.06)	1.52 (1.30-1.80)	1.23 (0.97-1.55)	1.53 (1.35-1.73)
No History of Anxiety	REF	REF	REF	REF
History of Anxiety	1.01 (0.65 -1.57)	1.09 (0.89 -1.34)	1.04 (0.73 -1.49)	1.14 (0.95 -1.37)
No History of schizophrenia	REF	REF	REF	REF
History of schizophrenia	1.59 (0.59-4.32)	3.26 (2.24-4.73)	2.33 (1.15-4.75)	3.21 (2.28-4.51)
No History of bipolar	REF	REF	REF	REF
History of bipolar	1.22 (0.44-3.32)	2.44 (1.67-3.55)	1.36 (0.64-2.90)	2.20 (1.55-3.12)
Age groups				
67-70	REF	REF	REF	REF
71-75	1.65 (1.11-2.43)	1.31 (1.06-1.61)	1.35 (0.97-1.87)	1.29 (1.08-1.54)
76-79	1.29 (1.29-3.02)	2.45 (2.00-3.01)	2.11 (1.50-2.96)	2.17 (1.80-2.60)

≤ 80	3.04 (2.09-4.39)	4.77 (4.00-5.69)	3.99 (2.99-5.33)	4.06 (3.47-4.75)

Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic or Tetracyclic Antidepressants.

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, depression, bipolar disorder, and schizophrenia.

Table 12. Hazard ratios of Cognitive Impairment by Antidepressants and Mental disorder.

	Hazard ratio [a] (95% confidence interval)			
	Mild cognitive Impairment	**Dementia**	**Alzheimer's**	**Cognitive Impairment**
Depression Diagnosis				
All Antidepressant				
History of depression	0.84 (0.52-1.35)	1.01 (0.80-1.27)	0.99 (0.66-1.48)	0.92 (0.74-1.13)
No History of depression	1.69 (1.23-2.31)	1.49 (1.29-1.72)	1.64 (1.30-2.08)	1.53 (1.34-1.75)
SSRI				
History of depression	0.55 (0.29-1.04)	1.02 (0.78-1.32)	0.87 (0.54-1.41)	0.89 (0.70-1.13)
No History of depression	1.62 (1.14-2.32)	1.48 (1.26-1.75)	1.82 (1.41-2.37)	1.51 (1.30-1.75)
TCA				
History of depression	-	1.36 (0.71-2.60)	1.59 (0.57-4.41)	1.15 (0.63-2.12)
No History of depression	0.82 (0.38-1.81)	0.91 (0.66-1.28)	0.66 (0.35-1.27)	0.97 (0.72-1.31)
Other Antidepressant				
History of depression	1.45 (0.84-2.51)	1.00 (0.73-2.60)	1.10 (0.65-1.86)	1.45 (0.84-2.51)
No History of depression	2.21 (1.49-3.27)	1.87 (1.54-2.25)	1.76 (1.28-2.42)	1.91 (1.61-2.27)
Anxiety Diagnosis				
All Antidepressant				
History of Anxiety	1.17 (0.50-2.70)	0.97 (0.67-1.45)	0.99 (0.51-1.92)	0.89 (0.63-1.25)
No History of Anxiety	1.40 (1.06-1.83)	1.39 (1.22-1.58)	1.51 (1.22-1.86)	1.39 (1.23-1.56)
SSRI				
History of Anxiety	0.98 (0.36-2.71)	0.83 (0.52-1.31)	0.81(0.36-1.83)	0.73 (0.48-1.11)
No History of Anxiety	1.24 (0.90 -1.71)	1.38 (1.19-1.59)	1.62 (1.28-2.06))	1.36 (1.19-1.56)
TCA				
History of Anxiety	-	0.59 (0.14-2.45)	-	0.43 (0.11-1.77)
No History of Anxiety	0.67 (0.31-1.45)	0.99 (0.73-1.34)	0.83 (0.48-1.43)	1.02 (0.78-1.34)
Other Antidepressant				
History of Anxiety	1.45 (0.84-2.51)	1.34 (0.83-2.17)	1.46 (0.65-3.27)	1.26 (0.82-1.93)
No History of Anxiety	1.96 (1.40-2.75)	1.56 (1.31-1.85)	1.55 (1.16-2.07)	1.58 (1.35-1.85)

Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic or Tetracyclic Antidepressants.

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, depression, bipolar disorder, and schizophrenia.

Reference group is patients without antidepressants.

Table 13. Hazard ratios of Cognitive Impairment by Antidepressants and Cancer Treatment

	Hazard ratio [a] (95% confidence interval)			
	Mild cognitive Impairment	**Dementia**	**Alzheimer's**	**Cognitive Impairment**
Chemotherapy				
All Antidepressant				
Chemotherapy	1.11 (0.59-2.08)	1.57 (1.16-2.13)	1.67 (0.97 -2.89)	1.47 (1.12-1.92)
No chemotherapy	1.43 (1.08-1.91)	1.30 (1.14-1.48)	1.41 (1.13-1.75)	1.30 (1.15-1.47)
SSRI				
Chemotherapy	1.35 (0.67-2.74)	1.28 (0.88-1.86)	1.49 (0.78-2.86)	1.31 (0.94 -1.13)
No chemotherapy	1.19 (0.85 -2.32)	1.31 (1.13-1.53)	1.51 (1.19-1.94)	1.28 (1.11-1.47)
TCA				
Chemotherapy	-	1.86 (1.05-3.30)	0.42 (0.07-3.09)	1.39 (0.79-2.44)
No chemotherapy	0.78 (0.36-1.69)	0.80 (0.57-1.13)	0.83 (0.47-1.46)	0.88 (0.65-1.20)
Other Antidepressant				
Chemotherapy	1.10 (0.46-2.62)	1.91 (1.31-2.79)	2.37 (1.25-4.50)	1.74 (1.23-2.44)
No chemotherapy	2.13 (1.51-3.2017)	1.46 (1.22-1.75)	1.41 (1.04-1.91)	1.50 (1.28-1.77)
Hormone therapy				
All Antidepressant				
Hormone therapy	1.53 (1.10 -2.13)	1.43 (1.23-1.66)	1.57 (1.22-2.01)	1.49 (1.30 -1.71)
No Hormone therapy	1.13 (0.74-1.74)	1.20 (0.98-1.47)	1.21 (0.85-1.73)	1.09 (0.91-1.31)
SSRI				
Hormone therapy	1.31 (0.89 -1.93)	1.34 (1.12-1.60)	1.54 (1.16 -2.03)	1.40 (1.19-1.64)
No Hormone therapy	1.07 (0.64-1.77)	1.27 (1.01-1.60)	1.50 (1.02-1.41)	1.12 (0.91-1.38)
TCA				
Hormone therapy	0.93 (0.40-2.15)	1.07 (0.75-1.54)	0.97 (0.51-1.80)	1.14 (0.82-1.58)
No Hormone therapy	0.21 (0.03-1.56)	0.77 (0.47-1.30)	0.44 (0.13-1.41)	0.72 (0.45-1.15)
Other Antidepressant				
Hormone therapy	2.16 (1.45-3.23)	1.74 (1.43-2.13)	1.86 (35-2.56)	1.79 (1.49-2.15)
No Hormone therapy	1.59 (0.93 -2.71)	1.21 (0.91 -1.60)	0.99 (0.58-1.68)	1.18 (0.92 -1.52)

Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic or Tetracyclic Antidepressants.

[a] Hazard Ratios were adjusted for chemotherapy, hormone therapy, surgery, radiation therapy, targeted therapy, age, depression, bipolar disorder, and schizophrenia.

Reference group is patients without antidepressants.

Chapter Five | Discussion

The overall objectives of this study were to examine the associations between 1) cognitive impairment and health outcomes (i.e., mortality and chronic medication adherence), 2) chemotherapy and cognitive impairment, and 3) antidepressants and cognitive impairment. In addition, we evaluated whether cognitive impairment mediates or moderates the relationship between chronic medication adherence and non-cancer mortality. This chapter summarizes the overall findings and provides insights into clinical practice implications and future directions for research.

5.1 Findings and Implications for Aim 1

In the first step, we investigated the impact of preexisting cognitive impairment diagnosis on cancer-specific, non-cancer, and all-cause mortality. We found that cognitive impairment was associated with lower survival and increased cancer-specific, non-cancer, and all-cause mortality risk. Additionally, cognitive impairment was associated with the increased likelihood of the cancer being diagnosed at a late stage and with the patients receiving less than optimum cancer treatment. Similarly, an earlier study found that dementia was associated with late-stage and unstaged cancer diagnoses.[17] Another study reported that patients with dementia were less likely to have an invasive procedure (i.e., a biopsy) to diagnose cancer and more likely to show late unstaged cancer.[105] One study has also reported that physicians are less likely to recommend a mammogram to women with dementia than to women without dementia.[208] This evidence of

delaying diagnosis and of less access to treatment might explain the increased risk of cancer-specific mortality in this population.

Next, we compared the medication adherence, pre- and post-cancer, and investigated whether cognitive impairments mediate the association between medication adherence and non-cancer mortality. Our results revealed that there was a low level of adherence to chronic medication in older patients with or without cognitive impairments, before and after their cancer diagnosis. We also found a significant increase in adherence after breast cancer compared with adherence before breast cancer in patients, independent of their cognitive impairment. However, there was no significant difference between patients, irrespective of their cognitive impairments, regarding adherence before and after their cancer diagnosis. Furthermore, our results showed that medication adherence does not mediate the relationship between cognitive impairment and non-cancer mortality. Similarly, a study that examined the effect of Alzheimer-related disorders on chronic heart disease medication adherence found noticeable but nonsignificant differences between patients with and without such disorders.[209] In contradiction to our results, one study that examined factors associated with low adherence to antihypertensive medications of Medicare beneficiaries found that dementia was associated with lower medication adherence compared to that of those without dementia.[210] Our findings differ from these earlier reports, in part due to the fact that our population consisted of elderly patients who were more likely to have a caregiver or reside in a long-term care facility, as Rattinger and colleagues pointed out.[209] However, our study did not find a difference in medication adherence between patients with and without cognitive impairments. The two groups showed low adherence overall, which may be due to a variety of factors such as age and/or polypharmacy. Chronic disease management in

patients with cognitive impairments is associated with higher rates of hospitalization and higher costs when compared to that of those who do not have cognitive impairments.[211-213]

Our study has several implications. First, our results support the existing evidence that cognitive impairment is a major issue in older patients with breast cancer.[17] In light of the knowledge that cognitive impairments are common among older adults with breast cancer, cognitive impairment screening should be considered as a routine oncology practice. This may help identify patients with cognitive impairment and determine whether older adults with cognitive impairment are able to participate in the decision-making process for their cancer treatment. Second, low adherence was observed in patients with and without cognitive impairment. Thus, interventions targeting an improvement of adherence, even among elderly patients without cognitive impairments, might lead to a reduction in mortality.

5.2 Findings and Implications for Aim 2

This study examined the association between chemotherapy and incidence of cognitive impairment among older adults with breast cancer. We found that there was no association between exposure to chemotherapy and increased incidence of cognitive impairment when evaluated 12 months from the breast cancer diagnosis. The inclusion of the cognitive impairment diagnosis that occurs in the first 12 months after the cancer diagnosis led to the observation that the chemotherapy group had a lower incidence of cognitive impairment diagnosis compared with the non-chemotherapy group. Two studies that used the SEER-Medicare database (1991–1999) have revealed conflicting findings regarding the same issue, with one indicating that chemotherapy exposure increased the risk of developing cognitive impairment by 20%,[47] while

the other revealed no association between chemotherapy exposure and the subsequent diagnosis of cognitive impairment.[214]

Furthermore, we found that hormone therapy was associated with a 16% increase in the risk of developing cognitive impairment after 1 year of breast cancer diagnosis. In this context, the existing evidence indicates that hormone therapy can have an adverse effect on cognition function. For instance, one study found that breast cancer patients who were 55–75 years old and used tamoxifen had a greater occurrence of cognitive difficulties, especially regarding memory function.[164] Also, postmenopausal women with early-stage breast cancer who received anastrozole exhibited declines in memory and concentration.[215] However, other studies have reported conflicting data regarding the association of tamoxifen use with cognitive impairment. One recent population-based study of 24,197 patients with breast cancer revealed that long-term tamoxifen use was associated with a reduced risk of cognitive impairment.[216]

Findings from this study have multiple ramifications. First, although we did not find any significant association between exposure to chemotherapy and cognitive impairment, an increasing body of evidence supports the association between chemotherapy and the risk of development of cognitive impairment. This growing evidence raises the question whether patients who exhibit a decline in cognitive functions when they are diagnosed with cancer receive the appropriate cancer treatment. This study highlights the need for further investigation of the pattern of care for patients who show a decline in their cognitive function at the time of cancer diagnosis. The second major ramification is that it raises questions regarding the usefulness of administrative database in evaluating chemotherapy-related cognitive impairment.

All of the retrospective studies, including this study, have used ICD-9 for dementia, Alzheimer's disease, and mild cognitive impairment to identify chemotherapy-related cognitive impairment.[47,214] However, it may not be an accurate measure to identify early stages of cognitive impairment associated with chemotherapy as identified in previous clinical studies. The administrative database lacks information regarding the assessment of cognitive functions (such as the decline in attention and memory).

5.3 Findings and Implications for Aim 3

In this study of older adults with breast cancer, we examined the association between antidepressants and cognitive impairments in older adults with breast cancer. We found that antidepressants were associated with a higher risk of cognitive impairment. Additionally, we compared patients without depression or anxiety disorder that used antidepressants with those without these conditions and antidepressants use. The results revealed a significant increase in cognitive impairment among the antidepressants users. However, among those with depression or anxiety, we did not find any significant difference between those that use and did not use antidepressants. We also found that non-TCA use is associated with an increased risk of cognitive impairment. However, we did not find similar results among those who received TCA.

Few published studies have examined the association between antidepressant use and the development of cognitive impairment, and none have examined this within the cancer population. The findings of these studies were not consistent, due to varying study design, population, comparison group, length of treatment, and type of antidepressants. One study found that there was no association between the use of antidepressants and the decline in cognitive

function among older adults.[66] In contrast, a study of older adults in a primary-care setting found that SSRI use or non-SSRI use was associated with a higher risk of dementia than nonuse among patients without depression.[64] These findings are consistent with our results. However, we found that TCA use was not associated with an increased risk of cognitive impairment compared to those who did not use antidepressants in both patients with and without depression.

This is the first study to examine the association between antidepressants and cognitive impairment among older adults with breast cancer. Our study supports the existing evidence of an increased risk of cognitive impairment among those who use antidepressants (non-TCAs). Consequently, our study calls for further research to understand the association between antidepressants and cognitive impairments among older adults, particularly those with cancer. It also emphasizes the need for evidence-based practices regarding prescription of antidepressants for off-label indications. In light of the growing evidence that antidepressants were associated with cognitive impairment in patients without depression or anxiety, it is imperative for health care providers to recognize the risk of cognitive impairment among older adults who use antidepressants and optimize their practice based on the current evidence.

5.4 Limitations

This dissertation has several limitations. This is an observational study that utilized the SEER-Medicare database. The results of this study may not be generalizable to younger populations and older adults living in non-SEER areas. In addition, the results of this study may not be generalizable to HMO enrollees who were excluded from the analyses, because their medical utilization records were not available. Furthermore, because risk factors, survival rates, and

treatment options vary by cancer types, the results from this study may not be generalizable to other patients with other types of cancer.

We required 24 months before breast cancer diagnosis to include (aim 1) or exclude (aim 2 and 3) cognitive impairment. Although the period was sufficient to identify patients with cognitive impairment, it is possible that we did not identify all patients with cognitive impairment diagnosis.

The nature of these data may lead to residual selection bias, which could confound these results. For instance, all of the retrospective studies, including this study, have used ICD-9 for dementia, Alzheimer's disease, and mild cognitive impairment to identify chemotherapy-related cognitive impairment.[47,214] However, it may not be an accurate measure to identify early stages of cognitive impairment associated with chemotherapy (aim 2) as identified in previous clinical studies.[12,127,137] Other non-cancer-related factors can also affect mortality (aim 1) and incidence of cognitive impairment (aim 2 and 3) among older patients with breast cancer.[217,218] For instance, breast cancer patients who have cognitive impairment, or who have an increased risk of developing it, are less likely to receive chemotherapy. Also, providers may be more likely to prescribe SSRIs over TCAs to older adults, as it is known that TCAs have higher anticholinergic activity, which is associated with cognitive decline. Thus, the present study may have been prone to selection bias. We used propensity score matching to balance the baseline characteristics between groups to reduce selection bias. Nevertheless, it was not possible to control for all possible confounders, although we did adjust the multivariable analysis for imbalanced characteristics and other relevant confounders.

5.5 Future Research Directions

These findings and limitations highlight the need for future research. Firstly, it is important that the findings from the current dissertations are validated. For instance, the study could be replicated for other types of cancers that are commonly present in older adults (e.g., prostate and colorectal cancers). This is important because there is limited understanding on how cognitive impairment increases the risk of mortality among older adults with cancer. This is also particularly important for non-cancer mortality because there is evidence that older adults with cancer die from causes other than cancer.[17]

We explored if medication adherence plays a role in mediating the relationship between cognitive impairment and non-cancer mortality. Our findings do not indicate that such a mediation exists. However, further investigation is needed to overcome the limitations for the current study. For instance, we used pharmacy claims to measure medication adherence. This might not be accurate, because we only measured the refill rate, not the actual medication-taking behavior. Primary-data collection studies may be able to accurately measure medication adherence, which could be done using an electronic cap (e.g., Medication Event Monitoring System).

Furthermore, we found that preexisting cognitive impairment was associated with the increased likelihood of cancer being diagnosed at a late stage and with patients not receiving cancer treatment. Further research is needed to understand the underlying factors that might influence the pattern of and access to care for this vulnerable population. This could be done using administrative databases, electronic heath records (EHRs), or primary data collection. The

advantage of administrative databases is their ability to capture health-care services for a large number of people, which could be utilized to compare patterns of care between patients with or without cognitive impairment. However, administrative databases lack information regarding the severity of the conditions and reasons why patients receive or do not receive particular cancer treatment. This could be overcome by using either EHRs or primary data collection. The advantage of using EHRs is that researchers can follow patients for a long period of time at a lower cost compared to the cost of primary data collection.

In addition, more research is required to understand why cancer patients experience cognitive decline after cancer diagnosis. Evidence has suggested that approximately 11%–35% of patients with breast cancer have cognitive impairment prior to treatment and 16%–75% have cognitive impairment post-treatment.[12,41,143] Researchers have examined several factors to understand the increased risk of cognitive impairment among patients with breast cancer. This includes comorbid conditions, chemotherapy, and hormone therapy. Many longitudinal and cross-sectional studies have demonstrated a decline in cognitive functions in breast cancer patients who have been treated with chemotherapy.[12,39,40,42] However, other studies have found no association between chemotherapy and cognitive function.[51-53] We did not find that chemotherapy was associated with increased risk of cognitive impairment. However, we found that hormone therapy and antidepressants are associated with increased risk of cognitive impairment after breast cancer diagnosis. This study does not conclude that cognitive impairment is not associated with chemotherapy, but rather that it is not be differentially diagnosed in the medical record. Further research needs to investigate cognitive impairment among patients with breast cancer. In particular, large longitudinal studies are required to identify the nature of cognitive impairment (incidence, severity, onset, duration) in patients with cancer undergoing

chemotherapy and hormone therapy and taking antidepressants as well as the implication of these agents on the quality of life. This could be done preferably by using primary data collection, as cognitive function assessment is not a routine practice in oncology care. Researchers could use newly developed computerized cognitive assessment tools that have been adapted to assess cognitive function in both research and practice (e.g., Cognitive Drug Research system).[219] Computerized cognitive assessment offers flexibility and economic advantage over traditional pencil-and-paper cognitive tests.

Finally, recent improvements in health technology have substantially increased the availability of data for outcomes research. There is a need to efficiently utilize these data to understand health-care related questions such as the complex association between cancer and cognitive impairment and its impact on health outcomes in older adults. We suggest for future studies to explore the use of machine learning to answer: 1) How does cognitive impairment impact survival of older patients with cancer? What is the pattern of care for older patients with cancer with pretexting cognitive impairment? What risk factors are associated with the increased risk of cognitive impairment among older patients with cancer?

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Appendix A

Table A.1. Cardiovascular and diabetes medication included in the medication adherence analysis

Medication groups	Medication classes
Cardiovascular medications	Diuretics, angiotensin-converting-enzyme inhibitors, calcium channel blockers, angiotensin ii receptor blockers , beta blockers, alpha blockers, alpha-2 receptor agonist, and peripheral adrenergic inhibitors, direct vasodilators, cardiac glycoside, nitrates, HMG-COA reductase, fibric acid derivatives, bile acid sequestrants.
Diabetes medications	Sulfonylureas, biguanides, meglitinide, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, and antidiabetic combination.

Appendix B

Table B.1. Definition of breast cancer surgical code

Conserving Surgery

ICD9 Procedure Codes

Code	*Code Description*
85.2	Excision Or Destruction Of Breast Tissue
85.20	Excision Or Destruction Of Breast Tissue, Not Otherwise Specified
85.21	Local Excision Of Lesion Of Breast
85.22	Resection Of Quadrant Of Breast

CPT Procedure Codes

Code	*Code Description*
19160	Mastectomy, partial (e.g. lumpectomy, tylectomy, quadrantectomy, segmentectomy)
19162	Mastectomy, partial (e.g. lumpectomy, tylectomy, quadrantectomy, segmentectomy; with axillary lymphadenectomy)
19120	Excision of cyst, fibroadenoma, or other benign or malignant tumor, aberrant breast tissue, duct lesion, nipple or areolar lesion, open, male or female, 1 or more lesions

Non-Conserving Surgery

ICD9 Procedure Codes

Code	*Code Description*
85.36	Other Bilateral Subcutaneous Mammectomy
85.35	Bilateral Subcutaneous Mammectomy With Synchronous Implant
85.34	Other Unilateral Subcutaneous Mammectomy
85.33	Unilateral Subcutaneous Mammectomy With Synchronous Implant
85.23	Subtotal Mastectomy
85.4	Mastectomy
85.41	Unilateral Simple Mastectomy
85.42	Bilateral Simple Mastectomy
85.43	Unilateral Extended Simple Mastectomy
85.44	Bilateral Extended Simple Mastectomy
85.45	Unilateral Radical Mastectomy
85.46	Bilateral Radical Mastectomy
85.47	Unilateral Extended Radical Mastectomy
85.48	Bilateral Extended Radical Mastectomy

CPT Procedure Codes

Code	*Code Description*

19120 Excision of cyst, fibroadenoma, or other benign or malignant tumor, aberrant breast tissue, duct lesion, nipple or areolar lesion, open, male or female, 1 or more lesions 19125 Excision of breast lesion identified by preoperative placement of radiological marker, open; single lesion 19126 Excision of breast lesion identified by preoperative placement of radiological marker, open; each each additional lesion separately identified by preoperative radiological marker 19180 Mastectomy, simple, complete 19182 Mastectomy, subcutaneous 19200 Mastectomy, radical, including pectoral muscles, axillary lymph nodes 19220 Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes (urban type operation) 19240 Mastectomy, modified radical, including axillary lymph nodes, with or without pectoralis minor muscle, but excluding pectoralis major muscle 19260 Excision of chest wall tumor including ribs 19271 Excision of chest wall tumor involving ribs, with plastic reconstruction; without mediastinal lymphadenectomy 19272 Excision of chest wall tumor involving ribs, with plastic reconstruction; with mediastinal lymphadenectomy 19301 Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy) 19302 Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy); with axillary axillary lymphadenectomy 19303 Mastectomy, simple, complete 19304 Mastectomy, subcutaneous 19305 Mastectomy, radical, including pectoral muscles, axillary lymph nodes 19306 Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes (urban type operation) 19307 Mastectomy, modified radical, including axillary

Table B.3. Definition of breast cancer radiotherapy code

ICD9 Procedure Codes	
Code	*Code Description*
92.21	Superficial Radiation
92.22	Orthovoltage Radiation
92.23	Radioisotopic Teleradiotherapy

92.24 Teleradiotherapy Using Photons
92.25 Teleradiotherapy Using Electrons
92.26 Teleradiotherapy Of Other Particulate Radiation
92.27 Implantation Or Insertion Of Radioactive Elements
92.28 Injection Or Instillation Of Radioisotopes
92.29 Other Radiotherapeutic Procedure

ICD9 Diagnostic Codes

Code *Code Description*
V580 Encounter for radiotherapy (Radiotherapy encounter)
V661 Convalescence following radiotherapy (Radiotherapy convalescence)
V671 Follow-up examination, following radiotherapy (Radiotherapy follow-up)

CPT Procedure Codes

Code *Code Description*
77261 Therapeutic radiology treatment planning; simple
77262 Therapeutic radiology treatment planning; intermediate
77263 Therapeutic radiology treatment planning; complex
77280 Therapeutic radiology simulation-aided field setting; simple
77285 Therapeutic radiology simulation-aided field setting; intermediate
77290 Therapeutic radiology simulation-aided field setting; complex
77295 Therapeutic radiology simulation-aided field setting; 3-dimensional
77299 Unlisted procedure, therapeutic radiology clinical treatment planning
77300 Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap
calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation
surface and depth dose, as required during course of treatment, only when prescribed by the
treating physician
77301 Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical
structure partial tolerance specifications
77305 Teletherapy, isodose plan (whether hand or computer calculated); simple (1 or 2 parallel
opposed unmodified ports directed to a single area of interest)
77310 Teletherapy, isodose plan (whether hand or computer calculated); intermediate (3 or more
treatment ports directed to a single area of interest)
77315 Teletherapy, isodose plan (whether hand or computer calculated); complex (mantle or inverted
Y, tangential ports, the use of wedges, compensators, complex blocking, rotational beam, or
special beam considerations)
77321 Special teletherapy port plan, particles, hemibody, total body
77331 Special dosimetry (eg, TLD, microdosimetry) (specify), only when prescribed by the treating
physician

77332 Treatment devices, design and construction; simple (simple block, simple bolus)
77333 Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks,
special bolus)
77334 Treatment devices, design and construction; complex (irregular blocks, special shields,
compensators, wedges, molds or casts)
77336 Continuing medical physics consultation, including assessment of treatment parameters, quality
assurance of dose delivery, and review of patient treatment documentation in support of the
radiation oncologist, reported per week of therapy
77338 Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design
and construction per IMRT plan
77370 Special medical radiation physics consultation
77371 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of
cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
CPT Procedure Codes
Code *Code Description*
77373 Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions,
including image guidance, entire course not to exceed 5 fractions
77399 Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special
services
77400 Daily megavoltage treatment management; simple
77401 Radiation treatment delivery, superficial and/or ortho voltage
77402 Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple
blocks or no blocks; up to 5 MeV
77403 Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple
blocks or no blocks; 6-10 MeV
77404 Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple
blocks or no blocks; 11-19 MeV
77405 Daily megavoltage treatment management; intermediate
77406 Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple
blocks or no blocks; 20 MeV or greater
77407 Radiation treatment delivery, two separate treatment areas, three or more ports on a single
treatment area, use of multiple blocks; up to 5 MeV

77408 Radiation treatment delivery, two separate treatment areas, three or more ports on a single
treatment area, use of multiple blocks; 6-10 MeV
77409 Radiation treatment delivery, two separate treatment areas, three or more ports on a single
treatment area, use of multiple blocks; 11-19 MeV
77410 Daily megavoltage treatment management; complex
77411 Radiation treatment delivery, two separate treatment areas, three or more ports on a single
treatment area, use of multiple blocks; 20 MeV or greater
77412 Radiation treatment delivery, three or more separate treatment areas, custom blocking,
tangential ports, wedges, rotational beam, compensators, electron beam; up to 5 MeV
77413 Radiation treatment delivery, three or more separate treatment areas, custom blocking,
tangential ports, wedges, rotational beam, compensators, electron beam; 6-10 MeV
77414 Radiation treatment delivery, three or more separate treatment areas, custom blocking,
tangential ports, wedges, rotational beam, compensators, electron beam; 11-19 MeV
77415 Therapeutic radiology treatment port film interpretation and verification, per treatment course
77416 Radiation treatment delivery, three or more separate treatment areas, custom blocking,
tangential ports, wedges, rotational beam, compensators, electron beam; 20 MeV or greater
77417 Therapeutic radiology port film(s)
77418 Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and
temporally modulated beams, binary, dynamic MLC, per treatment session
77419 Weekly radiation therapy management; conformal
77421 Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation
therapy
77422 High energy neutron radiation treatment delivery; single treatment area using a single port or
parallel-opposed ports with no blocks or simple blocking
77423 High energy neutron radiation treatment delivery; 1 or more isocenter(s) with coplanar or ========= noncoplanar geometry with blocking and/or wedge, and/or compensator(s)
77427 Radiation treatment management, 5 treatments
77435 Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more
lesions, including image guidance, entire course not to exceed 5 fractions

77465 Daily kilovoltage treatment management
77470 Special treatment procedure (eg, total body irradiation, hemibody radiation, per oral,
endocavitary or intraoperative cone irradiation)
77499 Unlisted procedure, therapeutic radiology treatment management
77600 Hyperthermia, externally generated; superficial (ie, heating to a depth of 4 cm or less)
77605 Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77610 Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
77615 Hyperthermia generated by interstitial probe(s); more than 5 interstitial applicators
77260 Hyperthermia generated by intracavitary probe(s)
77750 Infusion or instillation of radioelement solution (includes 3-month follow-up care)
77761 Intracavitary radiation source application; simple
77762 Intracavitary radiation source application; intermediate
77763 Intracavitary radiation source application; complex
77776 Interstitial radiation source application; simple

CPT Procedure Codes

Code *Code Description*

77777 Interstitial radiation source application; intermediate
77778 Interstitial radiation source application; complex
77789 Surface application of radiation source
77790 Supervision, handling, loading of radiation source
G0173 Stereo radiosurgery, complete
G0174 Intensity modulated radiation therapy (imrt) delivery to one or more treatment areas, multiple
couch angles/fields/arc, custom collimated pencil-beams with treatment setup and verification
images, complete course of therapy requiring more than one session, per session
G0178 Intensity modulated radiation therapy (imrt) plan, including dose volume histograms for target and ********** critical structure partial tolerances, inverse plan optimization performed for highly conformal ********** distributions, plan positional accuracy and dose verification, per course of treatment
G0242 Multisource photon stero plan
G0243 Multisource photon stero treat
G0251 Linear acc based stero radio
G0338 Linear accelerator stero plan
G0339 Robot lin-radsurg com, first
G0340 Robot lin-radsurg fractx 2–5
61770 Incise skull for treatment
61793 Focus radiation beam
S8049 Intraoperative radiation therapy (single administration)
G8378 Clinician documentation that patient was not an eligible candidate for radiation therapy measure

G8379	Documentation of radiation therapy recommended within 12 months of first office visit
C9726	Placement and removal (if performed) of applicator into breast for radiation therapy
C9728	Placement of interstitial device(s) for radiation therapy/surgery guidance (eg, fiducial markers, dosimeter), other than prostate (any approach), single or multiple
D5985	Radiation cone locator
D5983	Radiation carrier
D5984	Radiation shield
A4650	Implantable radiation do
Revenue Center Codes	
Radiation Oncology Indicator Switch	
0280	Oncology, general classification
0289	Oncology, other
Therapeutic Radiology Indicator Switch	
0330	General classification
0333	Radiation Therapy
SEER Radiation Delivery Variables and Codes	
Variable Name: rad1-rad10 (Radiation)	
Codes	*Radiation, Yes or No*
1-6	Yes
0, 7-9	No
Variable Name: radsurg1-radsurg10 (Radiation sequence with surgery)	
Codes	*Radiation, Yes or No*
2-6, 9	Yes
0	No

Table B.4. Definition of breast cancer chemotherapy code

Code	*Code Description*
C1167	epirubicin, hcl, 2 mg
C9115	zoledronic acid, 2 mg
C9120	injection, fulvestrant
C9127	paclitaxel, protein bound
C9214	injectino, bevacizumab
C9399	unclassified drugs or biologics
C9411	pamidronate disodium, brand
C9415	doxorubicin hcl, brand
C9420	cyclophosphamide
C9421	cyclophosphamide, lyophilized, brand
C9430	leuprolide acetate inj, brand
C9431	paclitaxel, inj, brand
C9432	mitomycin inj, brand
C9440	vinorelbine tar, brand

G0356	hormonal anti-neoplastic
G8371	chemotherapy not received for stage 3 colon cancer
G8373	chemo plan doc prio che
G8374	chemo plan not doc prior che
J0207	amifostine
J0640	leucovorin calcium
J1950	leuprolide acetate, 3.75 mg
J7150	prescription oral chemo drug
J8520	capecitabine, oral, 150 mg
J8521	capecitabine, oral, 500 mg
J8530	cyclophosphamide oral, 25 mg
J8610	methotrexate oral, 2.5 mg
J8700	temozolomide
J8999	oral prescription drug, chemo
J9000	doxorubicin
J9001	doxorubicin hcl lipsome
J9035	bevacizumab
J9045	carboplatin
J9070	cyclophosphamide, 100 mg
J9080	cyclophosphamide, 200 mg
J9090	cyclophosphamide, 500 mg
J9093	cyclophosphamide, lyophilized
J9094	cyclophosphamide, lyophilized
J9095	cyclophosphamide, lyophilized
J9096	cyclophosphamide, lyophilized
J9097	cyclophosphamide, lyophilized
J9170	docetaxel
J9175	methotrexate (Elliotts b solution per ml)
J9178	epirubicin, hcl
J9180	epirubicin, hcl
J9190	fluorouracil
J9200	floxuridine
J9202	goserelin acetate implant
J9217	leuprolide acetate suspension
J9218	leuprolide acetate injection
J9219	leuprolide acetate implant
J9250	methotrexate sodium
J9260	methotrexate sodium
J9264	paclitaxel, protein bound
J9265	paclitaxel
J9280	mitomycin, 5 mg
J9290	mitomycin, 20 mg
Chemotherapy Agent Codes	
Code	*Code Description*
J9291	mitomycin 40 mg inj
J9293	mitoxantrone hydrochloride

J9295	polyestradiol phosphate inj
J9355	trastuzumab
J9357	valrubicin, 200 mg
J9390	vinorelbine tartrate/10mg
J9395	Fulvestrant, injection
J9999	chemotherapy drug
Chemotherapy Administration Codes	
Code	*Code Description*
C8953	Chemotherapy administration, intravenous; push technique
C8954	Chemotherapy administration, intravenous; infusion technique, up to one hour
C8955	Chemotherapy administration, intravenous; infusion technique, each additional hour
	(list separately in addition to c8954)
G0355	Chemotherapy administration, subcutaneous or intramuscular non-hormonal antineoplastic
G0359	Chemotherapy administration, intravenous infusion technique; up to one hour, single
	or initial substance/drug
G0361	Initiation of prolonged chemotherapy infusion (more than eight hours), requiring use of
	a portable or implantable pump
G8371	Chemotherapy documented as not received or prescribed for stage iii colon cancer
	patients
G8374	chemotherapy plan not documented prior to chemotherapy administration
Q0081	infusion therapy, using other than chemotherapeutic drugs, per visit
Q0083	chemotherapy administration by other than infusion technique only (eg subcutaneous,
	intramuscular, push), per visit
Q0084	chemotherapy administration by infusion technique only, per visit
Q0085	chemotherapy administration by both infusion technique and other techique(s) (eg subcutaneous, intramuscular, push), per visit